DEVELOPMENT AND OPTIMIZATION OF TASTE-MASKING TECHNIQUES FOR SUSPENSION CONTAINING MULTIPLE ACTIVE PHARMACEUTICAL INGREDIENTS (APIs) USING ION EXCHANGE RESINS

Thesis Submitted for the Award of the Degree of

DOCTOR OF PHILOSOPHY

in

Chemistry

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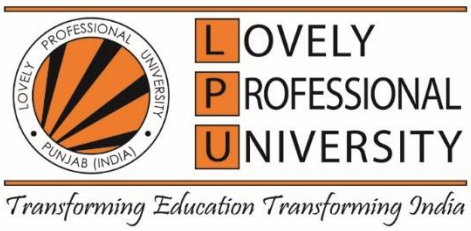

LOVELY PROFESSIONAL UNIVERSITY, PUNJAB

2025

DECLARATION

I, hereby declared that the presented work in the thesis entitled "***Development and Optimization of Taste-Masking Techniques for Oral Suspension Containing Multiple Active Pharmaceutical Ingredients (APIs) using Ion Exchange Resins*.**" in fulfilment of degree of **Doctor of Philosophy (Ph. D.)** is outcome of research work carried out by me under the supervision of Dr. Vivek Pandey, working as Asst. Professor, in the Department of Chemistry, School of Chemical Engineering and Physical Sciences of Lovely Professional University, Punjab, India. In keeping with general practice of reporting scientific observations, due acknowledgements have been made whenever work described here has been based on findings of another investigator. This work has not been submitted in part or full to any other University or Institute for the award of any degree.

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CERTIFICATE

This is to certify that the work reported in the Ph. D. thesis entitled "***Development and Optimization of Taste-Masking Techniques for Oral Suspension Containing Multiple Active Pharmaceutical Ingredients (APIs) using Ion Exchange Resins***" submitted in fulfillment of the requirement for the award of degree of **Doctor of Philosophy (Ph.D.)** in the Department of Chemistry, School of Chemical Engineering and Physical Sciences, is a research work carried out by Mr. Robindra Kumar Pandit, 42200254, is bonafide record of his original work carried out under my supervision and that no part of thesis has been submitted for any other degree, diploma or equivalent course.

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Acknowledgement

First and foremost, I offer my deepest gratitude to the Almighty, whose grace and blessings have guided me through every step of this academic journey. The successful completion of my Ph.D. thesis titled *"**Development and Optimization of Taste-Masking Techniques for Suspension Containing Multiple Active Pharmaceutical Ingredients (APIs) Using Ion Exchange Resins"*** would not have been possible without the support, mentorship, and encouragement of several individuals and institutions to whom I owe my sincerest thanks.

I express my heartfelt gratitude to my first supervisor, Dr. Tausif Altamash Sir, for laying the foundation of this research. His early guidance, critical insights, and encouragement gave me the initial direction and confidence to pursue this challenging but fulfilling project. I am equally grateful to my current supervisor, Dr. Vivek Pandey Sir, for taking over the mentorship with exceptional dedication. His scholarly inputs, constant motivation, and unwavering support were crucial throughout the final phases of my research.

I am truly thankful to Dr. Hamanjit Singh Sir, Head of Department, whose constant encouragement, resource facilitation, and administrative support created a smooth environment for the successful progression of my work. My sincere appreciation also goes to Dr. Kailash Chandra Juglan Sir, Head of the School, for his visionary academic leadership, constructive feedback, and institutional support that contributed immensely to the overall quality of my research journey.

I extend my profound appreciation to the entire Ph.D. evaluation panel who reviewed my work during various academic stages Research Proposal, ETP presentations, Pre-submission Seminar, and Final Viva. Your constructive criticisms, technical suggestions, and encouraging remarks helped sharpen the clarity, accuracy, and scientific depth of this dissertation. Each observation and recommendation, whether regarding methodological rigor, data analysis, or overall research direction, significantly strengthened the academic merit of this work. I remain grateful for the time, effort, and attention you devoted to evaluating and improving my research.

I would also like to thank the faculty and technical staff members of the School of Chemistry and all research laboratories I accessed during this work. Your generous help with instrumentation, data collection, and analysis was invaluable.

I extend my gratitude to my research colleagues and fellow Ph.D. scholars, whose camaraderie, discussions, and shared experiences provided intellectual stimulation and emotional support during times of stress and challenge.

A special note of thanks is due to my family, who stood by me as a pillar of strength throughout this demanding journey. Your patience, sacrifice, and unconditional love have been my source of inspiration and motivation.

Lastly, I thank all the authors, researchers, and institutions whose work has been cited in this thesis. Your contributions provided a solid foundation upon which my research was built.

This thesis is submitted in July 2025, with profound gratitude and humility to all those who have been a part of this scholarly endeavor.

Robindra Kumar Pandit.

Date of Submission: 29-07-2025

Abstract

The oral route remains the most preferred and convenient method for drug administration due to its non-invasiveness, ease of dosing, and high patient acceptability. However, oral pharmaceutical formulations often face the critical challenge of bitterness and unpleasant taste, especially in the case of pediatric and geriatric populations. Taste masking becomes a crucial parameter in determining patient compliance, particularly for multi-drug therapy systems used in over-the-counter (OTC) cold and cough remedies. This research was undertaken to develop and optimize an effective taste-masking strategy using ion exchange resins for an oral suspension containing a fixed-dose combination of three widely used bitter-tasting APIs: Dextromethorphan Hydrobromide (antitussive), Phenylephrine Hydrochloride (nasal decongestant), and Chlorpheniramine Maleate (antihistamine).

The central objective of the study was to formulate a palatable oral suspension with improved taste masking and acceptable drug release characteristics, using a rational ion exchange resin-based approach. The APIs were complexed with a strong cation exchange resin, Indion 234, selected after screening multiple commercial resins including Kyron T-114, Kyron T-314, Indion 204, Indion 214, and Indion 254. Drug-resin complex (DRC) formation was carried out using a systematic approach, evaluating resin activation procedures, pH effects, drug-to-resin ratios, and contact time. Parameters such as filtrate assay, drug loading efficiency, and suspension drug content were evaluated in preliminary trials to select the most appropriate resin.

A Design of Experiments (DoE)-based optimization was carried out for DRC preparation, assessing critical process variables such as drug-resin ratio (ranging from 1:0.25 to 1:3), soaking time (15–180 minutes), and pH (1.2, 4.5, and 6.8). The optimal conditions were established to be a 1:2 drug-to-resin ratio, pH 6.8, and 120 minutes of soaking under magnetic stirring, which yielded the highest drug loading and optimal bitterness suppression.

The DRCs were further incorporated into a paediatric friendly oral suspension formulation using pharmaceutically approved excipients. The suspension was evaluated for key physicochemical properties such as pH, sedimentation volume, viscosity, re-dispersibility, specific gravity, and appearance. Assay and content

uniformity of the APIs were confirmed by a validated High-Performance Liquid Chromatography (HPLC) method, ensuring that all formulations remained within 95–105% of the labelled claim. In-vitro dissolution testing was performed using USP Type II Paddle Apparatus in simulated gastric (pH 1.2), acetate (pH 4.5), and phosphate buffer (pH 6.8) media, with release profiles benchmarked against pure APIs and a marketed syrup formulation. The resin-based suspension exhibited consistent and controlled drug release across all tested pH ranges.

An electronic tongue (E-tongue) instrument was used as an advanced, objective tool for taste evaluation. Sensor readings confirmed a significant reduction in bitterness for all three APIs in the optimized suspension compared to their unmasked forms and the marketed comparator. This technological inclusion provided scientific rigor to the taste-masking claim and minimized human sensory variation.

Advanced characterization studies of the DRCs, including Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), Thermogravimetric Analysis (TGA), and Scanning Electron Microscopy (SEM), confirmed successful complexation of drugs with the resin, loss of crystalline nature, and favourable physicochemical interactions contributing to stability. Stability studies of the final formulation were carried out under refrigerated (2–8°C), room temperature (25°C ± 2°C/60% RH), and accelerated (40°C ± 2°C/75% RH) conditions for six months. Samples were evaluated at 0, 1, 3, and 6 months, and the formulation retained its appearance, drug content, taste, and in-vitro release profile, confirming the product's robustness.

Additional analysis included estimation of related substances via HPLC, preservative content of sodium methyl paraben and sodium propyl paraben, microbial contamination tests, and toxicity evaluation of ethylene glycol and diethylene glycol using gas chromatography. All parameters were found to be within ICH and pharmacopeial limits, confirming the formulation's safety and regulatory compliance.

A price comparison study showed that the developed suspension had a significant cost advantage over marketed products, making it a potential candidate for large-scale paediatric and OTC applications. Moreover, quality risk assessment (QRA) using FMEA tools identified potential formulation and manufacturing risks, which were adequately mitigated through optimized processes and analytical validations.

In conclusion, this research provides a novel and practical approach to overcoming the challenge of taste masking in multi-API oral suspensions using ion exchange resins. The optimized formulation achieved a desirable balance of palatability, bioavailability, and stability. It offers a scalable and cost-effective solution for improving patient compliance in paediatric and adult cold/cough therapy. This work contributes significantly to the domain of formulation science by establishing a framework for designing multi-drug oral suspensions with enhanced acceptability and performance using resin-based technology.

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List of Abbreviation

Abbreviation	Full Form
APIs	Active Pharmaceutical Ingredients
ETP	End Term Presentation
OTC	Over-The-Counter
DRC	Drug-Resin Complex
DoE	Design of Experiments
HPLC	High-Performance Liquid Chromatography
USP	United States Pharmacopeia
FTIR	Fourier Transform Infrared Spectroscopy
DSC	Differential Scanning Calorimetry
XRD	X-ray Diffraction
SEM	Scanning Electron Microscopy
TGA	Thermogravimetric Analysis
ICH	International Council for Harmonisation
QRA	Quality Risk Assessment
FDC	Fixed Dose Combination
WHO	World Health Organization
GRAS)	Generally Recognized as Safe
US FDA	United States Food and Drug Administration
NLT	Not Less Than
NMT	Not More Than
RH	Relative Humidity
ODTs	Orally Disintegrating Tablets
IERs	Ion Exchange Resins
RT	Retention Time
cfu	Colony Forming Units
UV	Ultraviolet
µg	Microgram
mL	Millilitre
°C	Degree Celsius
min	Minute
%	Percentage
RSD	Relative Standard Deviation
IP	Indian Pharmacopoeia
DEG	Diethylene Glycol
EG	Ethylene Glycol

UV-Vis	Ultraviolet–Visible Spectroscopy
BDL	Below Detectable Limit
GC	Gas Chromatography
LOD	Limit of Detection
LOQ	Limit of Quantification
MRP	Maximum Retail Price
USP/NF	United States Pharmacopeia and National Formulary
AR	Analytical Reagent
TOC	Total Organic Carbon
PDA	Photodiode Array Detector
CIF	Central Instrumentation Facility, LPU
CSIR	Council of Scientific & Industrial Research
CFTRI	Central Food Technological Research Institute
OPA	Ortho Phosphoric Acid
BSI	Bitterness Suppression Index
µl	Microlitre
ICH Q3B	ICH Harmonised Tripartite Guideline on Impurities in New Drug Products
mm	Millimetre
µm	Micrometre
nm	Nanometre
% v/v	Percentage of Volume per Volume
RPM	Revolutions Per Minute
mg	Milligram
gm	Gram

CHAPTER 1

1. INTRODUCTION

1.1 Aim of the Study

The principal aim of this research is to develop and optimize a palatable, taste-masked oral suspension formulation containing multiple active pharmaceutical ingredients (APIs) by utilizing ion exchange resin technology. This approach is intended to address the persistent challenge of bitterness associated with certain APIs, which significantly hampers patient compliance, especially among paediatric and geriatric populations. The bitterness of drugs like Dextromethorphan Hydrobromide (an antitussive), Phenylephrine Hydrochloride (a nasal decongestant), and Chlorpheniramine Maleate (an antihistamine) presents a major hurdle in ensuring proper adherence to prescribed dosing regimens, particularly in age groups that are highly sensitive to unpleasant taste profiles[1].

To overcome this challenge, the research aims to leverage the ion exchange resin Indion 234, known for its safety, non-toxic nature, high ion-exchange capacity, and suitability for pharmaceutical applications. The ion exchange resin is expected to form stable drug-resin complexes (DRCs) that can efficiently mask the unpleasant taste of the APIs without affecting their pharmacokinetics or bioavailability. The study further seeks to identify the optimal parameters for resin activation, drug-to-resin ratio, pH, contact time, stirring, and drying conditions that result in effective complexation and taste masking[2].

The aim also encompasses a broader objective to design a formulation that not only masks the bitter taste but also maintains physical stability, microbial safety, dose uniformity, and therapeutic efficacy, thereby making the final product suitable for commercialization. The development of such a suspension will represent a significant advancement in the area of patient-centric pharmaceutical formulation, as it will meet the dual requirement of therapeutic effectiveness and patient acceptability, which is essential for achieving desired health outcomes[4].

Furthermore, the study aims to develop a novel in-vitro release method and validate it in compliance with ICH guidelines to accurately assess the release behaviour of taste-masked APIs from the formulated suspension. The developed formulation will also be compared with marketed products to evaluate its relative cost-effectiveness, stability, safety profile, and overall palatability. In essence, this study aspires to establish a scientific and industrially viable platform for taste masking of multiple bitter APIs in a single oral suspension, thereby filling a significant gap in current pharmaceutical formulation strategies and contributing to the development of improved drug delivery systems. The drug is subsequently released in the acidic environment of the stomach, allowing for complete absorption and therapeutic effect[5] as shown in figure 1.1.

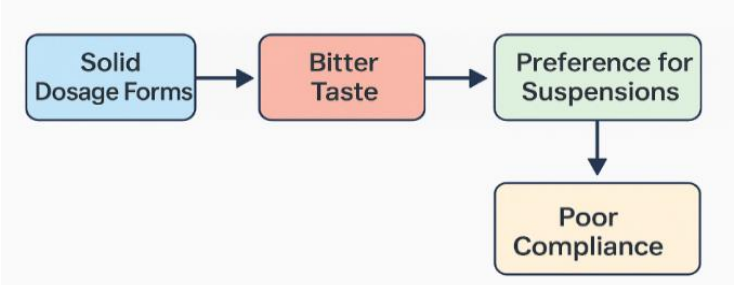

Figure 1.1 Schematic-Challenges of Oral Dosage forms Paediatrics / Geriatrics

The need for taste-masking strategies is especially pronounced in formulations designed for multi-drug therapy, where multiple bitter drugs must be incorporated into a single dosage form[6]. Suspensions offer a viable platform for such combinations, enabling the delivery of two or more APIs in a single dose, thus improving convenience and treatment adherence. Moreover, suspensions allow for adjustable dosing, making them suitable for paediatric use where weight-based dosing is often required as shown in table 1.1[7].

Table 1.1 Comparative Overview of Dosage Forms

Dosage Form	Advantages	Disadvantages	Paediatric Suitability
Tablets	Stable, accurate dose	Swallowing difficulty	Poor
Syrups	Easy to swallow	Taste, sugar content	Moderate
Suspensions	Flexible dose, palatable	Re-dispersibility, taste	Excellent

In this context, the development of a taste-masked oral suspension using ion exchange resins offers a promising and effective solution. It ensures patient acceptability, improves compliance, and supports the therapeutic success of medications used in the treatment of common cold and allergic symptoms[8]. This background sets the foundation for the present research work, which focuses on optimizing taste-masking techniques for suspensions containing multiple APIs using Indion 234, a strong cation exchange resin known for its safety and efficacy in pharmaceutical applications[9].

1.2 Importance of the Research

The significance of this research lies in its potential to resolve one of the most critical barriers in oral pharmaceutical therapy—the issue of unpleasant taste associated with many active pharmaceutical ingredients (APIs), particularly in multi-drug formulations. The bitter or metallic taste of APIs such as Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate severely affects patient acceptability and adherence, especially among pediatric and geriatric populations, who are often unable or unwilling to consume unpleasant-tasting medicines.

Current taste-masking techniques in the pharmaceutical industry primarily depend on the addition of sugars, sweeteners, and flavouring agents, which although useful to some extent, come with numerous limitations. These include the risk of toxicity (e.g., artificial sweeteners like aspartame and saccharin), allergenicity, increased microbial susceptibility, and compromised chemical or physical stability of the final dosage form. Moreover, such approaches do not eliminate the bitterness but merely attempt to overpower it, often with limited success.

In contrast, ion exchange resins offer a novel, effective, and scientifically grounded solution. These inert, non-toxic, and pharmacologically inactive polymers are capable of binding the bitter drugs through reversible ion exchange mechanisms. The drug-resin complexes (DRCs) formed are insoluble in saliva, thereby masking the bitter taste, but readily dissociate in the acidic environment of the stomach, releasing the free drug for absorption. This method offers excellent taste-masking without affecting the drug's pharmacokinetics, bioavailability, or therapeutic efficacy.

The research also addresses the need for safe and effective multi-API formulations, which are increasingly required in symptomatic treatments such as those for cold, flu, and allergy combinations. The inclusion of multiple APIs in a single oral suspension poses significant formulation challenges, especially in ensuring uniform taste masking, compatibility, stability, and dose accuracy. This study proposes a unified, resin-based approach to tackle these challenges in an optimized and patient-friendly manner.

Furthermore, this research is crucial in the context of patient-centric pharmaceutical development, an emerging paradigm focused on improving the patient experience to enhance compliance and therapeutic outcomes. By replacing potentially harmful masking agents with a technologically advanced, regulatory-compliant, and scalable method, this research provides real-world value to pharmaceutical industries, healthcare professionals, and patients alike.

Thus, the present study not only holds therapeutic importance but also has a substantial impact on formulation science, regulatory compliance, industrial scalability, and public health safety, making it an important contribution to the ongoing development of safer, more effective, and more acceptable oral drug delivery systems.

1.3 Applicability of the Research

The applicability of this research extends well beyond the scope of the specific APIs and formulation techniques investigated. It provides a strategic and practical platform for the development of patient-friendly, taste-masked oral suspension formulations, especially suited for paediatric, geriatric, and chronic medication use cases populations for whom swallowability and taste are often the most significant barriers to compliance.

The ion exchange resin-based taste-masking strategy developed and optimized in this study is highly adaptable and can be tailored to a wide variety of bitter drugs that require oral delivery. While this research focuses on the model APIs Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate, the same principle can be applied to a broader range of analgesics, antihistamines, antitussives, antibiotics, and antihypertensives, among others.

This method has specific utility in the development of liquid oral dosage forms, especially suspensions, which are often the formulation of choice for patients who cannot swallow tablets or capsules. These include not only children and elderly individuals, but also patients with dysphagia, neurological impairments, or those on nasogastric or enteral feeding. Moreover, for APIs that have poor compressibility or instability in solid dosage forms, a stable, taste-masked suspension offers a preferable alternative.

Additionally, the methodology aligns with current regulatory and industrial trends favouring patient-centric design and risk-minimized excipient selection. Unlike traditional taste-masking approaches that rely on excessive sweeteners, flavours, or coating technologies, the ion exchange resin approach ensures controlled drug release, minimal excipient load, improved stability, and greater patient safety all while maintaining therapeutic efficacy.

The approach also supports the formulation of fixed-dose combination (FDC) products, where multiple APIs can be incorporated into a single suspension with simultaneous taste masking. This simplifies dosage regimens, improves compliance, and reduces manufacturing complexity.

In pharmaceutical industries, this strategy offers ease of scalability, cost-effectiveness, and compatibility with continuous manufacturing processes, making it a highly transferable and market-ready solution. It may also be integrated into modified release or site-specific delivery systems, enhancing its utility for future innovations in drug delivery.

In summary, the research findings hold significant applicability for the formulation of next-generation oral suspensions, delivering benefits in terms of taste-masking efficacy, patient compliance, product safety, and manufacturing feasibility. This makes it an invaluable tool in both academic research and industrial formulation development.

1.4 Problem Statement

Despite significant advancements in pharmaceutical formulation science, the issue of bitter taste in orally administered medications remains a persistent challenge, especially

in paediatric and geriatric populations. A large proportion of active pharmaceutical ingredients (APIs), particularly those used in over-the-counter (OTC) cold and cough medications like Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate, are known to possess intensely bitter and unpleasant tastes[10]. This unpalatable nature severely affects patient compliance, particularly in children, leading to poor therapeutic outcomes due to dose skipping, incomplete dosing, or outright rejection of medication.

To address these issues, a variety of taste-masking techniques have been explored in the pharmaceutical industry. Traditional methods such as the addition of sweeteners, flavors, and taste modulators offer only superficial masking and often fail to suppress the bitterness of strongly bitter APIs[11]. Moreover, these additives may not be suitable for patients with diabetes, allergies, or specific dietary restrictions. Other techniques like polymer coating, encapsulation, and lipid-based barriers are often used to physically block the bitter taste receptors[12]. However, these techniques come with several drawbacks including complex manufacturing processes, increased cost, stability issues, and difficulty in uniform coating for drugs that are water-soluble or hygroscopic in nature. Figure 1.2 shows the taste masking condition in a multiple active ingredient pharmaceutical contain oral suspension.

Figure 1.2 Taste masking problems multi-API's formulations.

The situation becomes even more complicated when formulating multi-API suspensions. Unlike single-drug formulations, multi-drug suspensions face the compounded challenge of masking multiple bitter drugs simultaneously while ensuring chemical compatibility, uniform dispersion, and consistent release profiles. Each drug may have a different solubility profile, pKa, molecular weight, and interaction

behaviour, making it extremely difficult to use conventional taste-masking techniques effectively for all components in the same formulation[13]. Additionally, suspensions require the APIs to be in a dispersed state, often increasing the likelihood of drug particles coming into contact with taste buds during administration, which makes taste masking more difficult than in solid dosage forms like tablets or capsules[14].

Beyond taste masking, drug solubility and release uniformity are critical challenges in multi-API suspensions. Poorly water-soluble drugs may settle or aggregate, leading to dose inconsistency, while highly soluble bitter drugs may leach into the suspension medium, defeating the purpose of taste masking. Moreover, maintaining physical stability, re-dispersibility, and chemical integrity of all APIs in a single suspension further complicates formulation development (figure 1.3)[15].

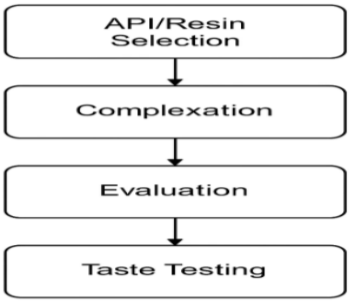

Figure 1.3 Flowchart- Research workflow.

These limitations highlight a clear gap in existing pharmaceutical technologies when it comes to developing palatable, effective, and stable multi-API oral suspensions. There is a pressing need for novel and adaptable taste-masking strategies that can simultaneously address the bitterness, solubility differences, and release uniformity of multiple APIs[15].

The present study seeks to bridge this gap by exploring the use of ion exchange resin technology, specifically with Indion 234, to develop taste-masked drug-resin complexes (DRCs) for a multi-API suspension. This approach offers the potential to overcome the limitations of current methods by providing a simple, scalable, and effective solution for taste masking while maintaining drug stability, controlled release, and patient acceptability in a single, multi-drug liquid formulation[16].

1.5 Scope of the Research

The primary objective of this research is to develop and optimize a taste-masked oral suspension containing multiple active pharmaceutical ingredients (APIs) using ion exchange resin technology[17]. The selected APIs Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate are frequently combined in medications for cough and cold symptoms but are known for their intensely bitter taste[18]. These formulations are particularly targeted at paediatric and geriatric populations, for whom palatability and ease of administration are crucial. Therefore, the main focus of this study is to mask the bitter taste effectively using Indion 234, a strong cation exchange resin, without compromising drug release or therapeutic efficacy (table 1.2)[19].

Table 1.2 Primary vs Secondary Objectives

Objective Type	Description
Primary	Develop taste-masked multi-API oral suspension using ion exchange resin
Secondary	Characterize DRCs, evaluate drug release, taste using E-tongue, etc.

Proposed Research objective

I. Development of effective taste-masking suspension using ion exchange resin.
II. Improvement of oral medication palatability to achieve patient acceptability and compliance.
III. Optimization of Drug-Resin complex by assessment of drug content, taste evaluation and drug release pattern.
IV. Characteristic studies of Drug-Resins complex for oral medication palatability with various techniques.

The primary objective is to formulate and optimize drug-resin complexes (DRCs) for each API individually and in combination. This involves evaluating and optimizing key formulation parameters such as drug-resin ratio, resin activation, pH, complexation time, and stirring conditions to achieve maximum drug loading, minimal drug release in the oral cavity, and complete release in gastric conditions[20]. The aim is to ensure that the taste masking is effective yet reversible under gastrointestinal pH, preserving the bioavailability of the APIs[21].

The secondary objectives include the development of a stable and palatable suspension formulation using the optimized DRCs. This formulation will be evaluated for its physicochemical characteristics, including pH, viscosity, sedimentation behaviour, re-dispersibility, appearance, and stability under various storage conditions[22]. In-vitro drug release studies will be carried out using a standard dissolution apparatus (USP Type II Paddle) to evaluate the release profiles of each API from the DRC-based suspension and to confirm that release occurs efficiently under gastric pH conditions[23].

An important aspect of this study is the taste evaluation of the developed DRC-based suspensions. To achieve objective and reproducible results, this research employs the Electronic Tongue (E-tongue), a sophisticated analytical instrument designed to simulate human taste perception[24]. The E-tongue uses sensor arrays and pattern recognition systems to assess taste profiles and compare the bitterness intensity of the DRC formulations against non-masked and placebo formulations. This allows for quantitative and unbiased assessment of taste masking effectiveness[25].

Additionally, the study aims to perform comprehensive characterization of the drug-resin complexes using modern analytical techniques such as Fourier Transform Infrared Spectroscopy (FTIR) for drug-resin interaction studies, Differential Scanning Calorimetry (DSC) for thermal behaviour, X-Ray Diffraction (XRD) for crystallinity changes, Scanning Electron Microscopy (SEM) for surface morphology, and High-Performance Liquid Chromatography (HPLC) for accurate drug content determination and in-vitro release quantification[26].

The scope of the study is limited to three commonly used APIs and one cation exchange resin (Indion 234), focusing solely on in-vitro and instrumental analysis. In-vivo

evaluation and pharmacokinetic studies are beyond the current scope. However, this work sets the foundation for future clinical studies by establishing a robust, scalable, and effective taste-masking strategy for multi-drug oral suspensions[27].

1.6 Relevance of the Research

This research holds substantial relevance in the context of evolving trends in pharmaceutical formulation science, particularly emphasizing the development of patient-centric and value-added generic dosage forms. The study addresses a critical unmet need in the pharmaceutical industry improving palatability and patient compliance in oral medications, especially for paediatric and geriatric populations who often reject bitter-tasting formulations.

The formulated taste-masked oral suspension using ion exchange resin (Indion 234) directly supports the global movement toward safer, more acceptable drug delivery systems, wherein compliance and therapeutic adherence are equally prioritized alongside pharmacological efficacy. By replacing or minimizing synthetic sweeteners, flavours, and sugar-based taste-masking agents, this research proposes a non-toxic, physiologically inert alternative that does not compromise drug performance, stability, or safety.

Furthermore, this study is aligned with the World Health Organization (WHO) recommendations and ICH Q8 & Q10 guidelines, which emphasize the development of age-appropriate formulations especially those that are easy to administer, have pleasant taste profiles, and demonstrate consistent dose uniformity and stability. Oral suspensions are particularly recommended for:

I. Children under five years of age who cannot swallow tablets or capsules.

II. Geriatric patients suffering from dysphagia or cognitive impairments.

III. Patients on chronic medication regimens who require long-term palatable dosage forms.

The relevance of this work is further underscored in resource-constrained or low-to-middle-income settings, where ensuring cost-effectiveness, stability without cold chain, and extended shelf life is paramount. This study provides a scalable, low-cost

manufacturing approach while maintaining pharmacopoeia quality standards an important advantage for national and global public health initiatives.

Moreover, this formulation approach is highly versatile and transferrable to other APIs beyond Dextromethorphan, Phenylephrine, and Chlorpheniramine, potentially enabling platform technology for a range of bitter drugs needing improved acceptability. It supports the rational design of dosage forms that are:

I. Tailored to specific patient needs (e.g., flavour aversion, allergies to excipients).

II. Adaptable to varying climatic zones based on ICH stability zones.

III. Manufacturable with minimal equipment, facilitating local production.

Ultimately, this research contributes to the modernization of oral dosage forms, ensuring improved therapeutic outcomes, patient quality of life, and compliance with international regulatory expectations. It bridges the gap between laboratory-scale innovation and commercially viable, patient-preferred drug delivery systems making it highly relevant for academic, industrial, and regulatory advancement in pharmaceutical sciences.

1.7 Selection of APIs

In the development of pharmaceutical formulations, the selection of appropriate active pharmaceutical ingredients (APIs) is driven by therapeutic needs, patient demographics, pharmacological compatibility, and formulation feasibility. For this study, three APIs Dextromethorphan Hydrobromide (HBr), Phenylephrine Hydrochloride (HCl), and Chlorpheniramine Maleate were selected based on their well-established therapeutic roles in the management of cold, cough, and allergic conditions[28]. These APIs are widely used in combination in over-the-counter (OTC) medications and are especially common in paediatric formulations such as oral suspensions. However, they are also known for their extremely bitter taste, posing significant challenges for patient compliance and acceptability, particularly in children and elderly patients. The following provides a detailed overview and rationale for their selection[29].

1.8 Overview of Chosen APIs

1.8.1 Dextromethorphan Hydrobromide (HBr) – Antitussive

Dextromethorphan HBr is a centrally acting cough suppressant that works by depressing the cough centre in the medulla oblongata. It is a synthetic derivative of morphine but lacks analgesic or addictive properties, making it safer for use in a wide patient population, including children[30]. It is highly effective in treating dry, non-productive cough, and is a standard component in many cough syrups. Dextromethorphan HBr is highly water-soluble, which while advantageous for formulation purposes, also contributes to its pronounced bitter taste. When present in oral suspensions, it readily dissolves in the medium and comes into direct contact with the taste buds, making effective taste masking essential for its use in palatable liquid formulations[31].

1.8.2 Phenylephrine Hydrochloride (HCl) – Nasal Decongestant

Phenylephrine HCl is a sympathomimetic agent that primarily acts as an α1-adrenergic receptor agonist. It causes vasoconstriction of blood vessels in the nasal passages, leading to decreased swelling and congestion. It is commonly included in cold and allergy formulations to relieve nasal stuffiness[31]. Phenylephrine HCl is also highly water-soluble and intensely bitter. Its bitter taste, combined with its low dosing requirement, poses a challenge in suspensions, where even small amounts can impact the overall palatability. Moreover, its chemical nature requires precise pH control to maintain solubility and stability in liquid dosage forms[32].

1.8.3 Chlorpheniramine Maleate – Antihistamine

Chlorpheniramine Maleate is a first-generation antihistamine used to relieve symptoms associated with allergic conditions such as sneezing, runny nose, and itchy eyes. It acts by blocking histamine H1 receptors, thereby preventing the effects of histamine released during allergic reactions[33]. While effective and widely used, Chlorpheniramine Maleate also suffers from intense bitterness and a slightly astringent aftertaste. In addition, it has moderate water solubility, which may cause variable release and mouthfeel when not adequately taste masked in suspension formulations[34].Figure 1.4 show three API's chemical structures and table 1.3 give overall properties comparison.

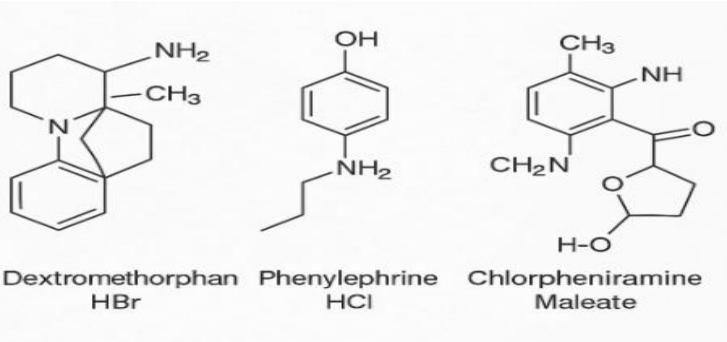

Figure 1.4 Chemical structure of three API's

Table 1.3 Overview of Selected APIs.

API	Class	Function	Solubility	Taste	pKa	Use
Dextromethorphan HBr	Antitussive	Cough suppressant	High	Bitter	~8.3	Dry cough
Phenylephrine HCl	Decongestant	Nasal congestion	Moderate	Bitter	~9.2	Cold relief
Chlorpheniramine Maleate	Antihistamine	Allergy symptoms	High	Bitter	~9.2	Rhinitis

1.9 Rationale for Combining These APIs

The combination of Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate is clinically justified and commonly used in formulations aimed at providing multi-symptom relief in cases of common cold, flu, allergic rhinitis, and upper respiratory infections[35]. Each drug targets a specific symptom:

I. Dextromethorphan HBr addresses dry cough,

II. Phenylephrine HCl provides relief from nasal congestion, and

III. Chlorpheniramine Maleate controls allergy-related symptoms.

This synergistic combination allows for comprehensive treatment through a single dosage form, improving convenience and compliance for patients, especially in paediatric therapy where multiple medications can be difficult to administer separately. Multi-drug suspensions reduce pill burden, simplify dosing schedules, and are ideal for population groups who prefer or require liquid medications[36].

1.10 Bitter Taste Profile and Formulation Challenges

All three selected APIs have a highly bitter taste, which poses a significant obstacle in oral suspension development. Bitter compounds can trigger strong aversive reactions, particularly in children, leading to refusal to take the medication, incomplete dosing, or poor adherence to therapy. Moreover, their water solubility exacerbates the problem, as the dissolved drug is more likely to interact with taste receptors in the oral cavity[37].

Traditional taste-masking approaches, such as the use of sweeteners, flavouring agents, or pH adjustments, are often insufficient to overcome the bitterness of these APIs. Furthermore, when multiple bitter drugs are combined in one formulation, the cumulative bitterness may surpass the masking capacity of such conventional excipients[38]. Each drug may also have different physicochemical properties such as solubility, pKa, and chemical stability which complicates the formulation process[39].

Additionally, maintaining uniform distribution of APIs, ensuring re-dispersibility, and avoiding drug-drug or drug-excipient interactions in a suspension add further layers of complexity. Therefore, an advanced and robust taste-masking strategy is essential to ensure the palatability, stability, and therapeutic efficacy of such a multi-API formulation[40].

1.11 Overview of Taste-Masking Techniques

Taste is a critical factor that significantly influences the acceptability and compliance of oral medications, especially in paediatric and geriatric populations. A large number of active pharmaceutical ingredients (API's), despite their therapeutic efficacy, are associated with intensely bitter or unpleasant tastes[41]. Poor palatability often leads to patient non-compliance, dose refusal, or incomplete medication regimens, thereby compromising therapeutic outcomes. Therefore, taste masking has become an essential component in the development of oral formulations—particularly for suspensions and liquid preparations where the drug comes into immediate contact with taste buds[42].

Several taste-masking techniques have been developed to address this challenge, each with its own advantages, applications, and limitations. These approaches aim to either block the interaction of the drug with taste receptors or delay its release until it passes the oral cavity. Below is an overview of commonly used conventional taste-masking techniques (figure 1.5)[43]. Table 1.4 gives details of different types of Taste Masking technics their advantage and disadvantage.

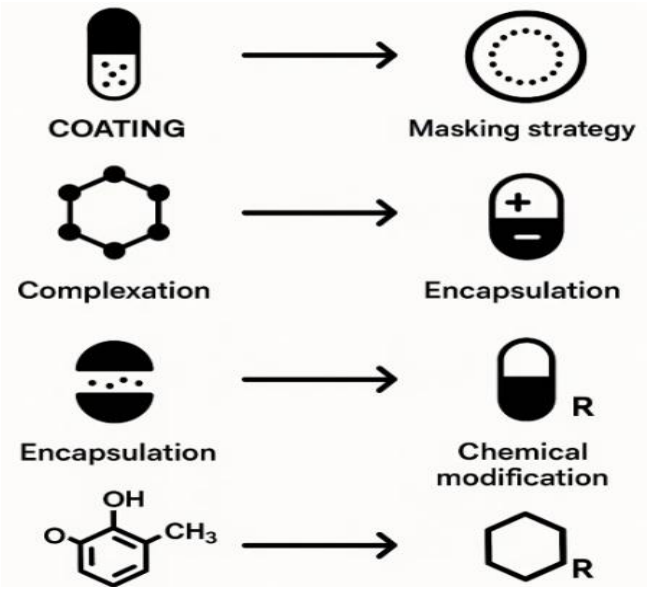

Figure 1.5 Schematic mechanisms of Taste Masking techniques.

Table 1.4 Different types of Taste Masking technics their advantage and disadvantage

Types	Details	Advantage	Disadvantage	References
Sweetener and Flavors	Taste masking is an essential process in suspension formulation, and one of the common methods used for taste masking is the addition of sweeteners and flavours. This approach is used to improve the palatability of drugs and enhance patient compliance.	*They are generally regarded as safe for consumption. *They improve the taste of drugs and make them more appealing to patients. *It helps cover the bitter taste of drugs and improve their taste. *It provides an attractive aroma, which can further enhance the overall taste experience.	*Sweeteners may have a high calorie count, which can be a concern for diabetic patients or those with weight-related issues. *Some sweeteners can also cause adverse effects such as headaches, allergic reactions, and gastrointestinal disturbances. *Flavours may interact with the drug substance, affect its stability, or reduce its bioavailability. *Due to large quantity of use of sweetener and flavours in a formulation leads to different impurities contamination to the suspension which causes very serious diseases. *There may be regulatory constraints associated with the use of certain sweeteners and flavours in pharmaceuticals, which could limit their availability for use in	44

			suspension formulations.	
Micro-encapsulation	It is a process where active ingredients are coated with a thin layer of polymer material to create a small particle. The particle is then dispersed in the suspension	*Microencapsulation can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. * Increased stability: Microencapsulation can improve the stability of the active ingredient by protecting it from external factors such as light, heat, and humidity. *Controlled release: Microencapsulation can provide a controlled release of the active ingredient, allowing for a sustained and controlled release over time.	• Increased cost: Microencapsulation is a complex process that requires specialized equipment and expertise, which can increase the cost of production. • Reduced bioavailability: The use of microencapsulation can reduce the bioavailability of the active ingredient, as it may hinder the absorption of the active ingredient into the body. • Incompatibility with other excipients: Microencapsulation can be incompatible with certain excipients, which can affect the overall formulation of the suspension.	45
Polymer coating	The coating is typically made from polymers such as Ethyl-cellulose, hydroxypropyl methylcellulose, or polyvinylpyrrolidone, which are applied to the surface of the active ingredient particles. The	*Improved palatability: Polymer coating can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. *Flexibility in formulation:	*Reduced bioavailability: The use of polymer coating can reduce the bioavailability of the active ingredient, as it may hinder the absorption of the active ingredient into the body. *Incompatibility with other excipients: Polymer coating can	46

	polymer coating creates a barrier that prevents the active ingredient from coming into touch with the taste receptors on the tongue.	Polymer coating can be applied to a wide range of active ingredients, allowing for greater flexibility in formulation. *Cost-effective: Polymer coating is a relatively simple and cost-effective. technique, making it an attractive option for pharmaceutical manufacturers.	be incompatible with certain excipients, which can affect the overall formulation of the suspension. *Variable performance: The performance of the polymer coating can be variable, depending on the types of the active ingredient, the coating material, and the processing conditions.	
Inclusion Complex	This technique involves the formation of a complex between the active ingredient and a cyclodextrin molecule, which acts as a carrier. The complex is formed by encapsulating the active ingredient within the cavity of the cyclodextrin molecule.	*Improved palatability: Inclusion complexation can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. *Increased stability: Inclusion complexation can improve the stability of the active ingredient by protecting it from external factors such as light, heat, and humidity. *Improved bioavailability: Inclusion complexation can	*Cost: Inclusion complexation can be a relatively expensive technique due to the cost of cyclodextrin molecules. *Complex formulation: Inclusion complexation can be a complex process that requires specialized equipment and expertise. *Limited compatibility: Inclusion complexation may not be compatible with all active ingredients, as some active ingredients may not form stable complexes with cyclodextrin.	47

		enhance the bioavailability of the active ingredient by improving its solubility and dissolution rate.		
Viscosity Modification	This technique involves increasing the viscosity of the suspension, which decreases the contact time between the active pharmaceutical ingredient and the taste buds on the tongue.	*Improved palatability: Viscosity modification can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. *Ease of formulation: Viscosity modification is a relatively simple and straightforward technique that can be easily incorporated into the suspension formulation. *Cost-effective: Viscosity modification is a cost-effective technique, as viscosity-enhancing agents are generally inexpensive.	*Reduced bioavailability: The use of viscosity modification can reduce the bioavailability of the active ingredient, as it may hinder the absorption of the active ingredient into the body. *Incompatibility with other excipients: Viscosity modification can be incompatible with certain excipients, which can affect the overall formulation of the suspension. *Difficulty in dosing: Viscosity modification can make it difficult to accurately measure and dose the suspension, as the increased viscosity can make it harder to dispense.	48

Ion Exchange Resins	This technique involves the use of resins that are able to exchange ions with the active ingredient in the suspension, which can effectively mask the taste. The resin works by selectively binding to the active ingredient, which reduces the amount of free active ingredient in the suspension, thus reducing its taste.	*Improved palatability: IERs can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. *Flexibility in formulation: IERs are compatible with a wide range of active ingredients, making them a versatile option for suspension formulation. *Increased stability: IERs can improve the stability of the active ingredient by protecting it from external factors such as light, heat, and humidity. *It has no side effects on body as it not adsorbed in the body due to its bigger size particles.	*Cost: IERs can be a relatively expensive technique due to the cost of the resin materials. *Potential for drug-resin interaction: There is a risk of interaction between the drug and the resin, which can affect the stability and efficacy of the active ingredient. *Limited loading capacity: IERs may have limited loading capacity for certain active ingredients, which can affect the overall formulation of the suspension	49
Solid Dispersion method	This technique involves the preparation of a solid dispersion of the active ingredient in a hydrophilic carrier material, which can effectively mask the taste.	*Improved palatability: Solid dispersion can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. *Increased solubility: The use of	*Cost: The use of solid dispersion can be a relatively expensive technique due to the cost of the hydrophilic carrier materials. *Stability concerns: The use of solid dispersion can affect the stability of the active ingredient, especially in cases where it is not	50

		hydrophilic carrier materials can increase the solubility of the active ingredient, which can improve its bioavailability. *Flexibility in formulation: Solid dispersion can be prepared using a wide range of hydrophilic carrier materials, making it a versatile option for suspension formulation.	compatible with the hydrophilic carrier material. *Potential for drug-polymer interaction: There is a risk of interaction between the drug molecule and the polymer used for the solid dispersion, which can affect the stability and efficacy of the active ingredient.	
Prodrug Approach	This technique involves the modification of the active pharmaceutical ingredient to a more palatable form, which can effectively mask the taste. The prodrug can be added to the suspension, where it is converted back to the active form, without affecting its taste.	*Improved palatability: Prodrugs can effectively mask the uncomfortable taste of active ingredients, making the suspension more palatable and easier to consume. *Increased bioavailability: The use of prodrugs can increase the bioavailability of the active ingredient, by improving its solubility and permeability. *Flexibility in formulation: Prodrugs can be designed using a wide range of chemical modifications, making it a versatile option for suspension formulation.	*Complexity of synthesis: The synthesis of prodrugs can be a complex and time-consuming process, which can add to the overall cost of the formulation. *Stability concerns: The use of prodrugs can affect the stability of the active ingredient, especially in cases where it is not compatible with the prodrug modification. *Risk of toxicity: The prodrug modification can lead to toxic metabolites, which can be harmful to the patient.	51

1.11.1 Coating

Coating is a widely used technique that involves physically covering the drug particles with a tasteless or inert material. The coating acts as a barrier, preventing the drug from dissolving in the oral cavity and interacting with taste receptors[52].

I. Materials used: Polymer coatings (e.g., ethyl cellulose, Eudragit E100), lipid-based coatings (e.g., glyceryl behenate), and natural gums.

II. Techniques: Pan coating, fluidized bed coating, spray drying, and hot-melt coating.

III. Applications: Mainly for tablets, granules, and microparticles[53].

Limitations:

I. Coating may crack or rupture during processing or storage.

II. Incomplete or uneven coating can lead to inconsistent taste masking.

III. It often requires sophisticated equipment and is not always suitable for water-soluble drugs or liquid dosage forms like suspensions[54].

1.11.2 Microencapsulation

Microencapsulation involves enclosing the drug in a microscopic capsule made of polymers or lipids, which controls the release of the drug and masks its taste.

I. Encapsulation materials: Gelatin, cellulose derivatives, polyvinyl alcohol, polylactic acid, etc.

II. Techniques: Coacervation, spray drying, solvent evaporation, and interfacial polymerization[55].

Limitations:

I. It requires complex processing steps and high-cost technology.

II. The technique may not be effective for very bitter or highly water-soluble drugs.

III. Issues with payload uniformity, particle aggregation, and scale-up may occur during manufacturing[55].

1.11.3 Use of Flavors and Sweeteners

This is the most basic and widely used method of taste masking. It involves adding artificial sweeteners (e.g., sucralose, aspartame, saccharin) and flavouring agents (e.g. fruit Flavors, mint, vanilla) to mask or distract from the bitterness of the API[56].

Limitations:

I. This method does not mask bitterness effectively for highly bitter APIs.

II. Sweeteners and Flavors only mask the taste perception temporarily.

III. Not suitable for patients with dietary restrictions (e.g. diabetes).

IV. Subjective variability in taste preference among patients.

V. May be incompatible with certain drugs or lead to instability over time[57].

1.11.4 Prodrug Approach

This involves modifying the chemical structure of the parent drug into a non-bitter or less bitter prodrug, which is pharmacologically inactive until it is enzymatically or chemically converted in the body to its active form[58].

I. Example: Chloramphenicol palmitate is a tasteless prodrug of chloramphenicol.

II. Suitable for APIs with known metabolic pathways and functional groups amenable to modification.

Limitations:

I. Requires extensive preclinical and clinical testing to ensure safety and efficacy.

II. Not feasible for all drugs due to complex synthesis and regulatory hurdles.

III. The conversion rate of prodrug to active drug must be well understood and consistent[59].

1.11.5 Complexation

Complexation refers to the formation of a non-covalent complex between the drug and a tasteless carrier, which reduces drug solubility in saliva but allows for full release in the gastrointestinal tract[60].

1.11.5.1 Cyclodextrin Complexation

Cyclodextrins are cyclic oligosaccharides that can form inclusion complexes with hydrophobic parts of APIs, effectively shielding the bitter moiety from taste receptors[61].

Types: β-cyclodextrin, hydroxypropyl-β-cyclodextrin, etc.

Limitations:

I. Cyclodextrins are costly and sometimes require high drug-to-polymer ratios.

II. Limited complexation capacity for large or highly polar molecules.

III. May have limited stability in aqueous suspensions.

1.11.5.2 Ion Exchange Resin Complexation

Ion exchange resins are high molecular weight, insoluble polymers with functional groups that bind to ionic drugs to form taste-neutral drug-resin complexes (DRCs). In the oral cavity, the drug remains bound and does not elicit a taste. In the acidic environment of the stomach, the drug is released by ion exchange.

I. Examples of resins: Indion 234, Kyron T-114, Amberlite IRP-64

II. Suitable for cationic drugs like Dextromethorphan HBr and Phenylephrine HCl

Advantages:

I. Effective for highly bitter, water-soluble drugs

II. Compatible with liquid dosage forms (suspensions)

III. Enables controlled release and enhanced stability

IV. GRAS (Generally Recognized as Safe) and accepted by regulatory agencies[62].

Limitations:

I. Requires optimization of complexation parameters (pH, contact time, ratio)

II. Possible drug-resin incompatibility in rare cases

III. Ion exchange behaviour can vary depending on GI pH conditions

Ion Exchange Resins as Taste-Masking Agents

The use of ion exchange resins (IERs) has gained increasing attention in pharmaceutical formulation as an effective, reliable, and regulatory-accepted strategy for taste masking, particularly in liquid dosage forms such as suspensions. Their ability to temporarily bind with drug molecules and prevent their interaction with taste receptors while allowing controlled or complete release in the gastrointestinal environment makes them uniquely suitable for improving palatability without affecting bioavailability (table 1.5)[63].

Table 1.5 Conventional Taste-Masking Techniques Comparison

Technique	Principle	Pros	Cons
Coating	Barrier layer	Good masking	Costly, slow
Microencapsulation	Polymer entrapment	Controlled release	Process complexity
Sweeteners	Flavour suppression	Simple	Doesn't mask bitterness fully
Cyclodextrin Complexation	Inclusion complex	Neutral taste	Expensive
Ion Exchange Resins	Ionic complexation	Effective & reversible	Resin compatibility needed

1.11.5.3 Principle of Ion Exchange for Taste Masking

Ion exchange resins are high molecular weight, insoluble, cross-linked polymers containing ionizable functional groups that can exchange their counter-ions with ions in the surrounding medium. They are broadly classified into cation-exchange and anion-exchange resins depending on the nature of their functional groups[64].

The principle behind taste masking using ion exchange resins relies on the formation of drug-resin complexes (DRCs) through electrostatic interactions. In this approach:

I. The cationic (positively charged) drugs, such as Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate, are adsorbed onto negatively charged resin sites.

II. In the neutral pH of the saliva (pH ~6.8), the drug remains bound to the resin, preventing dissolution and thereby blocking bitterness perception.

III. Upon swallowing, the drug-resin complex reaches the acidic gastric environment (pH ~1–2), where hydrogen ions (H^+) or sodium ions (Na^+) present in gastric fluids displace the drug from the resin by ionic competition, thereby releasing the drug for absorption.

This pH-responsive behaviour allows for temporary masking of the bitter taste, with complete release in the stomach, ensuring therapeutic efficacy (figure 1.6 & 1.7)[65].

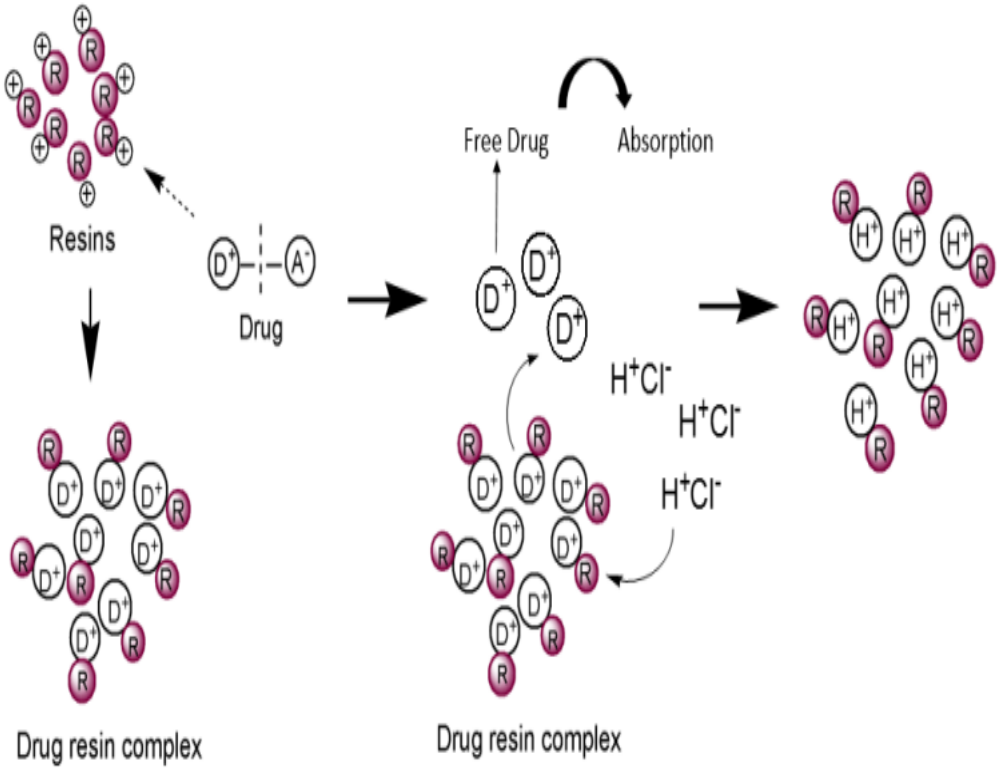

Figure 1.6 Diagram-drug-Resin Complex Formation & Release.

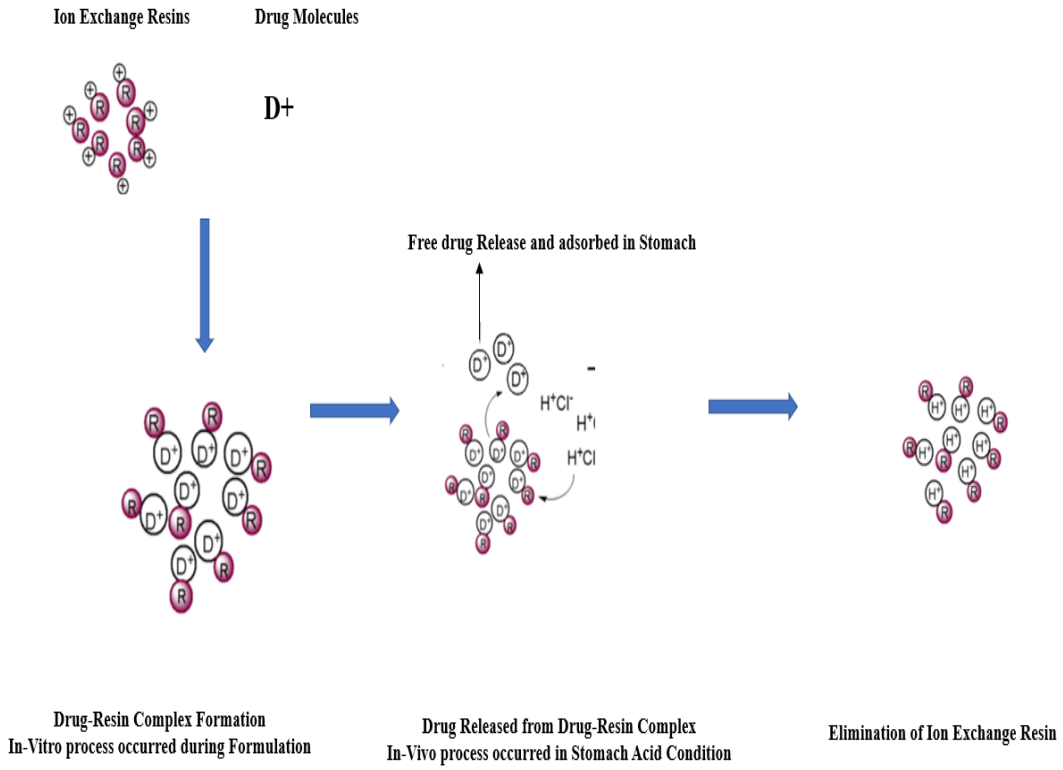

Figure 1.7 In-Vitro & In-vivo process of Ion-Exchange Resins during Taste Masking

1.11.5.4 Advantages of Using Ion Exchange Resins in Liquid Dosage Forms

Ion exchange resins offer several advantages over conventional taste-masking methods, particularly in liquid and suspension formulations:

1.11.5.4.1 Effective Taste Masking

Resins form non-covalent complexes with drugs that do not dissociate in saliva, ensuring that even highly bitter and water-soluble drugs are rendered tasteless when administered orally[66].

1.11.5.4.2 Reversible Binding and Bioavailability

The ionic binding is reversible, and drug release in gastric pH is rapid and complete, preserving the pharmacokinetic profile of the drug[66].

1.11.5.4.3 Suitable for Paediatric and Geriatric Formulations

As they are non-toxic, inert, and not absorbed systemically, ion exchange resins are ideal for formulations intended for children and elderly patients who are sensitive to taste and have difficulty swallowing solid dosage forms[67].

1.11.5.4.4 Compatible with Liquid Dosage Forms

Unlike coating or microencapsulation techniques that are typically suited to tablets or capsules, IERs can be easily dispersed in suspension vehicles without altering physical stability.

1.11.5.4.5 Improved Stability

Drug-resin complexes are often more stable to light, heat, and moisture, enhancing shelf-life and physical uniformity in aqueous systems[68].

1.11.5.4.6 Controlled Drug Release

Some resins allow for controlled or sustained drug release, depending on the matrix structure and environmental pH, enabling flexibility in therapeutic delivery.

1.11.5.4.7 Regulatory Acceptance

Many ion exchange resins (e.g., Indion, Kyron, Amberlite) are classified as Generally Recognized as Safe (GRAS) by the US FDA, and are listed in major pharmacopeias, including the USP/NF and IP, making them regulatory-compliant excipients[68].

1.11.5.5 Several types of ion exchange resins

Several types of ion exchange resins have been developed and marketed specifically for pharmaceutical applications, particularly for taste masking in oral suspensions. Below is an overview of commonly used resins:

1.11.5.5.1 Indion Series (Ion Exchange India Ltd.)

Indion 234

I. Type: Strong cation exchange resin (carboxylic functional groups)
II. Form: Free-flowing powder or granules

III. Application: Widely used for taste masking of cationic APIs like dextromethorphan, phenylephrine, and chlorpheniramine

IV. Features: High drug loading, fast complexation, non-toxic, suitable for suspensions

Indion 254 / Indion 204 / Indion 214

I. Variants with different particle sizes, porosity, and exchange capacities

II. Used in sustained-release formulations and taste masking

III. Selection depends on API-resin compatibility and desired release profile[70].

1.11.5.5.2 Kyron Series (Corel Pharma Chem)

Kyron T-114 and T-314

I. Type: Strong cation-exchange resins

II. Applications: Used extensively in taste masking of water-soluble, bitter APIs

III. Properties: Rapid complexation, good flow properties, excellent palatability improvement

IV. Compatibility: Effective with various cationic drugs including antihistamines, antitussives, and decongestants

V. Additional benefit: Kyron T-314 is also used for moisture-sensitive formulations due to its low hygroscopicity[71].

1.11.5.5.3 **Amberlite and Duolite Series (Dow Chemicals)**

Amberlite IRP-64, IRP-69, Duolite AP143

I. Historically used in pharmaceutical formulations

II. Effective for drug-resin complexation but more expensive and less commonly used in Indian pharmaceutical industry compared to Indion/Kyron (Table 1.6).

Table 1.6 Comparison of Common Pharmaceutical Resins

Resin	Type	Charge	Common Use	Source
Indion 234	Strong cation	-COOH	Taste masking	India
Indion 204	Weak cation	-COOH	pH-sensitive binding	India
Kyron T-114	Strong cation	-SO3H	Liquid formulation	India
Amberlite IRP 64	Weak cation	-COOH	API complexation	USA

1.11.5.6 Rationale for Choosing Indion 234

The selection of a suitable ion exchange resin is a crucial step in the development of taste-masked pharmaceutical formulations, particularly for oral suspensions containing multiple active pharmaceutical ingredients (APIs). For the present research, Indion 234 was selected based on its favourable physicochemical properties, proven pharmaceutical utility, compatibility with the selected APIs Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate and strong literature support demonstrating its effectiveness in taste-masking applications[72].

Indion 234 is a strong cation exchange resin, belonging to a class of synthetic resins made from cross-linked polymers with functional groups capable of exchanging cations in aqueous media (figure 1.8). It is composed of carboxylic acid groups attached to a high molecular weight polymer matrix, which enables it to effectively form electrostatic complexes with cationic drugs, such as the APIs selected for this study. One of the most important characteristics of Indion 234 is its high ion exchange capacity, allowing it to bind substantial quantities of drug molecules relative to its own weight. This makes it particularly suitable for multi-drug formulations, where efficient loading and uniform complexation of all APIs is required (Table 1.7)[73].

Table 1.7 Justification for Selecting Indion 234

Criteria	Evaluation	Result
Resin Type	Strong cation exchange	Suitable for cationic APIs
Taste-Masking	Proven with bitter APIs	Effective
Safety	Non-toxic, inert	Safe for paediatric use
Compatibility	Works with DXM, PHE, CPM	Confirmed

A key reason for selecting Indion 234 is its pH-responsive behaviour, which plays a pivotal role in taste masking. In the neutral pH of the oral cavity, the drug-resin complex remains stable, preventing drug release and thus eliminating the bitter taste upon administration. However, once the complex reaches the acidic environment of the stomach, where the pH typically falls below 2.0, the drug is efficiently released due to ion exchange with gastric hydrogen ions. This reversible complexation ensures that taste masking does not interfere with the therapeutic availability of the drug[74].

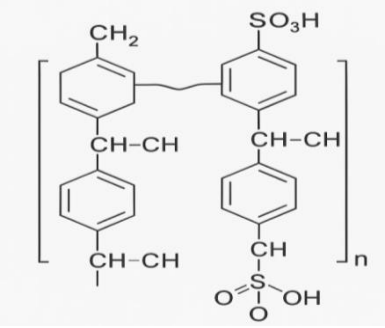

Figure 1.8 Structure & Functional groups of Indion 234.

The safety and biocompatibility of Indion 234 are well-documented. It is considered pharmacologically inert, non-toxic, and not absorbed systemically, which is particularly important for paediatric and geriatric formulations. Indion 234 is also listed in

pharmacopeial monographs and is recognized as safe by major regulatory agencies, making it a compliant and industry-preferred excipient for use in oral formulations[75].

Compatibility with the selected APIs is another critical factor that supports the choice of Indion 234. Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate are all positively charged at physiological pH, which makes them suitable candidates for complexation with a cation exchange resin like Indion 234. Preliminary screening and compatibility studies confirm that the resin does not chemically degrade or react with the APIs, and the drug-resin complexes are physically stable under a range of formulation conditions. Moreover, the formation of the drug-resin complex improves not only taste masking but also contributes to improved suspension stability and uniformity by minimizing drug leaching into the aqueous phase of the suspension during storage[75].

The selection of Indion 234 is further supported by extensive literature and precedent studies. Previous research has demonstrated its successful use in masking the taste of a wide range of bitter drugs, including antitussives, antihistamines, and decongestants closely matching the pharmacological profile of the APIs used in this study. Publications have consistently reported that Indion 234 enables rapid and efficient drug loading, excellent palatability, and reliable release in gastric conditions. These studies provide a solid scientific foundation and practical validation for the application of Indion 234 in taste-masked multi-drug oral suspensions[76].

1.11.5.7 Overview of Drug-Resin Complexes (DRCs)

Drug-resin complexes (DRCs) represent a scientifically established and pharmaceutically advantageous approach for addressing formulation challenges associated with bitter-tasting drugs, especially in oral dosage forms such as suspensions. The concept involves the temporary binding of drug molecules to an ion exchange resin, forming a non-covalent complex that remains stable under neutral conditions but readily dissociates under gastric pH. This approach offers multiple benefits, including effective taste masking, improved drug stability, and modifiable release profiles, making it particularly relevant for the present study involving the taste-

masked formulation of Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate using Indion 234 (figure 1.9)[76].

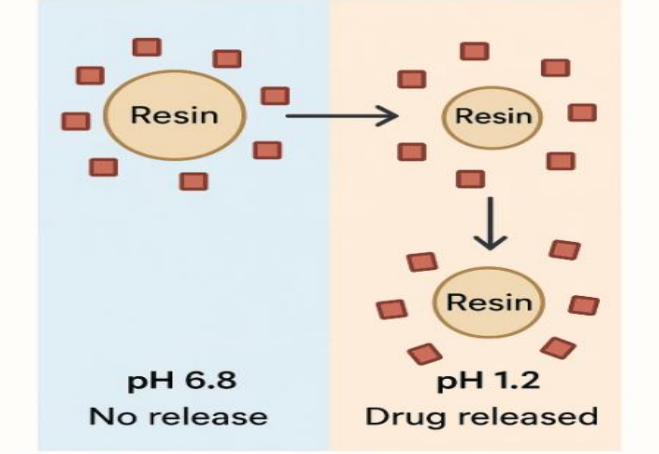

Figure 1.9 pH-based Release of Drug from Resin Complex.

The mechanism of drug-resin complex formation is governed by the principle of ion exchange. Ion exchange resins are high molecular weight, water-insoluble polymers with functional ionic groups capable of exchanging their counter-ions with ions of similar charge from the surrounding medium. In this context, the selected APIs are cationic in nature and therefore interact with resins bearing negatively charged functional groups, such as carboxylic or sulfonic acid moieties[77]. When a solution containing the drug is brought into contact with the resin, an exchange occurs between the cations of the drug and the hydrogen or sodium ions initially present on the resin. This results in the formation of a drug-resin complex through electrostatic attraction. Importantly, this interaction is reversible and pH dependent, enabling the drug to be released in the acidic conditions of the gastrointestinal tract while remaining bound in the neutral pH of the oral cavity, effectively masking the bitter taste[78].

Several formulation parameters influence the efficiency of drug loading onto the resin and the stability of the resulting complex. One key factor is resin activation. Prior to complexation, the resin may be treated with acid or alkali to convert it to the desired ionic form typically the hydrogen or sodium form to ensure optimal binding with the target drug. This step enhances the resin's ion exchange capacity and facilitates more

consistent complex formation. Another crucial factor is the drug-resin ratio. A stoichiometric balance between the drug and resin is essential to maximize loading efficiency without causing drug wastage or over-saturation (table 1.8). Higher resin amounts may enhance drug binding but can lead to unnecessary excipient bulk in the final dosage form[78].

Table 1.8 Parameters Influencing Drug-Resin Complexation

Parameter	Influence
Resin Activation	Enhances binding
pH of Solution	Affects ionization
Drug-Resin Ratio	Determines loading
Stirring Time	Affects equilibrium

The pH of the solution during complexation also plays a significant role. The ionization state of both the drug and resin functional groups is pH-dependent, and optimal binding generally occurs at a pH where the drug exists predominantly in its ionic form[79]. For cationic drugs, mildly acidic to neutral conditions are typically favourable. Additionally, parameters such as temperature, agitation speed, contact time, and particle size of the resin affect the rate and extent of complex formation. Fine-tuning these variables is essential to ensure efficient drug loading, reproducibility, and stability of the final drug-resin complex[80].

The behaviour of the drug-resin complex in different pH environments underpins its utility as a taste-masking system. In the oral cavity, where the pH ranges from 6.5 to 7.4, the ionic strength is relatively low, and there is minimal competition for the drug-resin binding sites. As a result, the complex remains intact, preventing the drug from diffusing into the saliva and reaching the taste buds[81]. This effectively masks the bitter taste of the drug during administration. Upon ingestion, the complex enters the stomach, where the pH drops significantly to approximately 1.2 to 2.0. In this highly acidic environment, the abundance of hydrogen ions competes with the bound drug for interaction with the resin, leading to displacement of the drug and rapid release into the gastric fluid. This pH triggered dissociation ensures that the drug becomes bioavailable for absorption without compromising its therapeutic effect[82].

In conclusion, drug-resin complexes provide a scientifically sound and technologically feasible means of achieving taste masking and controlled drug release, especially for bitter, water-soluble, cationic drugs formulated in oral suspensions. The success of DRC-based systems depends on a detailed understanding and optimization of complexation parameters, as well as the resin's behaviour across different pH environments. In the current study, the use of Indion 234 as the resin and the systematic optimization of drug loading conditions play a central role in achieving the overall objective of developing a patient-compliant, taste-masked multi-API suspension for paediatric and geriatric populations[83].

1.12 Role of Suspension as Dosage Form

Oral suspensions have long been established as one of the most versatile and patient-friendly dosage forms, especially in paediatric and geriatric medicine. Their ability to deliver poorly soluble or unpalatable drugs in a palatable and easily administrable liquid form provides distinct advantages over solid oral dosage forms such as tablets and capsules[84]. In the context of developing a multi-API formulation containing Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate, the suspension dosage form offers both therapeutic convenience and formulation flexibility, making it particularly suitable for populations that often face swallowing difficulties or require individualized dosing (table 1.9)[85].

Table 1.9 Advantages and Challenges of Suspensions

Feature	Advantage	Challenge
Dose flexibility	Suitable for all ages	Requires redispersion
Swallowability	Better for paediatrics	Taste issues
Onset of action	Faster	Sedimentation risk

One of the primary advantages of suspensions lies in their flexibility in dosing. Unlike fixed-dose solid forms, suspensions allow for precise dose adjustments according to the age, weight, or condition of the patient, which is essential in paediatric care. Accurate dosing is facilitated by volumetric measurement using calibrated droppers or syringes, allowing caregivers to administer exact amounts of medication[86]. Furthermore, suspensions provide an ideal platform for delivering multiple APIs in a single

preparation, enabling combination therapy for conditions like cough and cold, where simultaneous administration of antitussive, decongestant, and antihistamine agents is required[87].

Another major benefit of suspensions is their ease of swallowing, particularly for infants, elderly patients, or individuals suffering from dysphagia. Unlike tablets, which may be difficult or even hazardous to swallow, suspensions provide a smooth, easy-to-ingest medium that enhances compliance and reduces the psychological barrier associated with oral drug administration[87]. This characteristic is of special importance in chronic or recurring conditions where daily or frequent medication intake is necessary.

Additionally, suspensions can offer a faster onset of action compared to solid dosage forms. Since the drug is already dispersed in the liquid medium, it bypasses the disintegration step required for tablets, allowing for quicker dissolution and absorption, particularly for water-soluble drugs. This is crucial in acute symptomatic relief situations, such as persistent coughing or nasal congestion, where prompt therapeutic effect is desirable[87].

Despite these advantages, suspensions present a unique set of formulation challenges. One of the foremost concerns is the bitter or unpleasant taste of many APIs, especially when they are water-soluble. Taste becomes a critical determinant of compliance, particularly in children, necessitating effective taste-masking strategies to ensure palatability[88]. This makes the suspension dosage form highly

Figure 1.10 Ideal properties of pharmaceutical Suspension.

dependent on auxiliary technologies such as flavouring, sweetening, and drug complexation systems like ion exchange resins (figure 1.10)[88].

1.12.1 Physical stability

Physical stability is another major challenge in suspension formulation. Due to the heterogeneous nature of suspensions, the drug particles tend to settle over time under the influence of gravity, leading to sedimentation. If the sediment forms a hard cake, it may become difficult to redisperse and result in inconsistent dosing. Therefore, ensuring re-dispersibility and uniform drug distribution with every dose is essential for therapeutic efficacy. This requires careful selection of suspending agents, wetting agents, and appropriate viscosity enhancers to maintain a physically stable formulation[89].

Moreover, achieving uniformity of content across the entire duration of use is a technical hurdle. Poorly suspended or non-homogeneous suspensions may lead to sub-therapeutic or toxic doses, which is especially dangerous in formulations containing potent APIs. Thus, maintaining the physical integrity of the suspension throughout its shelf life is of paramount importance.

Chemical and microbiological stability also need to be carefully controlled in liquid suspensions. Water, being the continuous phase, increases the risk of hydrolysis and microbial contamination. This necessitates the inclusion of stabilizers, preservatives, and antioxidants, along with stringent packaging and storage considerations[89].

In conclusion, the oral suspension dosage form represents a highly suitable and patient-centric option for delivering multi-API therapies, particularly in populations with specific swallowing or dosing requirements. While it offers notable advantages in terms of dosing flexibility, ease of ingestion, and rapid onset of action, its successful formulation demands thoughtful consideration of factors such as taste masking, physical and chemical stability, re-dispersibility, and content uniformity. In the current

study, the development of a taste-masked suspension using ion exchange resin technology addresses these critical challenges, offering a stable and palatable platform for the combination therapy of Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate[90].

1.13 Analytical and Characterization Techniques Used

In the development of a scientifically robust and pharmaceutically acceptable oral suspension, particularly one involving taste-masked drug-resin complexes (DRCs), the application of validated analytical and characterization techniques is indispensable. These techniques not only confirm the presence and stability of the active pharmaceutical ingredients (APIs) but also ensure the successful formation of drug-resin complexes, evaluate their structural and thermal properties, and assess drug release behaviour and palatability. In the present study, a combination of instrumental methods has been employed to support formulation development, optimization, and quality assurance[90].

High-Performance Liquid Chromatography (HPLC) played a central role in the analytical phase of this research. HPLC is a well-established, sensitive, and reproducible method for determining drug content, assay, and release profiles of APIs in pharmaceutical dosage forms. In this study, it was used to quantify the amount of Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate present in the formulation both before and after complexation with Indion 234. It was also employed to study the in-vitro release of drugs from DRCs under simulated gastric conditions, allowing for the comparison of release kinetics before and after taste-masking. The method was validated as per ICH guidelines to ensure accuracy, precision, linearity, and specificity, providing reliable data for formulation evaluation and stability studies[91].

For the solid-state characterization of the drug-resin complexes, a suite of techniques including Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-Ray Diffraction (XRD), and Scanning Electron Microscopy (SEM) was employed (figure 1.11). FTIR was used to detect possible interactions

between the APIs and the resin by comparing characteristic functional group vibrations in pure drugs and the complexes. The absence or shift of specific peaks provided insights into ionic or hydrogen bonding between the drug and resin. DSC analysis offered complementary information by evaluating the thermal behaviour of the complexes. The disappearance or alteration of melting endotherms in the thermograms of DRCs compared to the pure APIs indicated successful complexation and transformation in drug crystallinity[91].

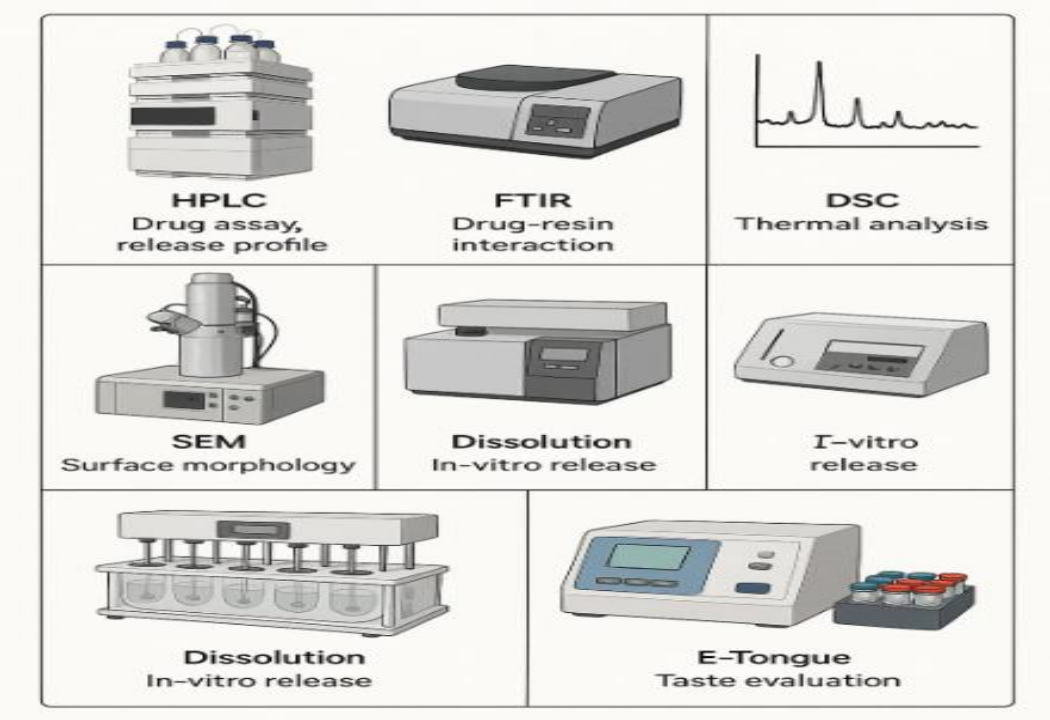

Figure 1.11 Images Gallery- Instruments used.

XRD was used to assess the crystalline or amorphous nature of the components before and after complexation. Pure APIs, typically exhibiting sharp diffraction peaks due to their crystalline structure, were expected to display reduced or diffused patterns in the DRCs if complexation led to amorphization—a desirable feature in taste masking and solubility enhancement. SEM provided detailed images of surface morphology and particle structure. Visual comparison of the resin and DRC under high magnification enabled the confirmation of drug loading and any notable changes in surface characteristics, which are important for understanding flow behaviour, re-dispersibility, and drug release kinetics[92].

In-vitro drug release testing was carried out using a calibrated dissolution apparatus, simulating gastrointestinal conditions. This test was crucial for evaluating whether the drug was adequately released from the DRCs under acidic pH, following its retention at salivary pH. Standard dissolution media and time points were selected to reflect pharmacopoeia standards and ensure that the masked drug is bioavailable after oral administration. The dissolution study also helped assess the effect of resin-drug binding strength on release efficiency, aiding in the optimization of complexation parameters[92].

An essential component of the formulation evaluation was the sensory assessment of taste masking, which was performed using an advanced Electronic Tongue system, supplemented where applicable by trained human sensory panels. The Electronic Tongue is an intelligent sensory device that mimics human taste perception using sensor arrays coupled with chemometric software. It provides objective, quantitative measurements of bitterness and can detect subtle differences in taste profiles across formulations. This technique offered a reproducible and ethical alternative to traditional human taste panels and was especially useful during the optimization stages of the DRCs. When used alongside or validated by limited human panel testing, it allowed for the accurate evaluation of the effectiveness of taste-masking strategies (table 1.10)[92].

Table 1.10: Analytical Techniques and Their Purpose

Technique	Purpose
HPLC	Drug assay, release profile
FTIR	Drug-resin interaction
DSC	Thermal analysis
XRD	Crystallinity change
SEM	Surface morphology
Dissolution	In-vitro release
E-Tongue	Taste evaluation

In summary, the combination of analytical and characterization tools—including HPLC, FTIR, DSC, XRD, SEM, dissolution apparatus, and Electronic Tongue—

provided a comprehensive framework for the formulation, analysis, and validation of the taste-masked oral suspension developed in this study. Each technique contributed uniquely to confirming drug identity, assessing complexation, monitoring release profiles, and ensuring sensory acceptability, thereby supporting the successful development of a scientifically sound and patient-compliant multi-API suspension[92].

1.13.1 Novelty and Innovation in the Current Work

The present research introduces a novel and practical approach to pharmaceutical formulation by addressing one of the most pressing challenges in oral drug delivery: the simultaneous taste masking and therapeutic delivery of multiple active pharmaceutical ingredients (APIs) in a single oral suspension. The innovation lies not only in the selection of formulation strategies but also in the integration of advanced evaluation tools and the holistic optimization of both palatability and performance. This study is one of the few to comprehensively develop and assess a multi-API taste-masked suspension using ion exchange resin technology, making a valuable contribution to patient-centric dosage form design[93].

A significant novelty of this work is the simultaneous taste masking of three pharmacologically distinct APIs Dextromethorphan Hydrobromide (antitussive), Phenylephrine Hydrochloride (nasal decongestant), and Chlorpheniramine Maleate (antihistamine) within a single formulation. Each of these drugs is known for its intensely bitter taste and high-water solubility, which pose major barriers to patient compliance, especially in paediatric and geriatric populations. While existing studies have explored taste masking of individual APIs, the development of a single suspension system capable of effectively masking the taste of all three drugs without compromising their release profiles or therapeutic efficacy represents a distinctive and challenging formulation goal that has not been adequately addressed in previous literature[93].

This research uniquely employs Indion 234, a strong cation exchange resin, as a multifunctional excipient that not only masks the unpleasant taste of the APIs but also facilitates controlled release of the drugs in the gastric environment. The use of ion exchange resin in this dual role first to block taste perception in the oral cavity, and

second to enable complete release of the drug in the stomach adds a layer of functional sophistication to the formulation. Unlike conventional taste-masking techniques such as coating, microencapsulation, or sweetener addition, the ion exchange resin approach used here provides chemical selectivity, reversibility, and pH-triggered action, which are particularly suited for the properties of the selected APIs and the targeted patient groups[94].

Another innovative aspect of the study is the optimization of the formulation using a systematic, science-driven approach, aimed at achieving a balance between palatability and therapeutic performance. This included precise tuning of key formulation parameters such as drug-to-resin ratio, complexation pH, contact time, and resin activation, as well as physical stabilizers to ensure re-dispersibility and homogeneity of the suspension. Advanced analytical and characterization tools, including FTIR, DSC, XRD, SEM, and HPLC, were employed to confirm drug-resin interaction, complex stability, and consistent drug content, while in-vitro release studies were conducted to ensure timely drug liberation in acidic pH[95].

Furthermore, the incorporation of Electronic Tongue technology for objective taste evaluation marks a significant methodological advancement in the assessment of oral formulations. Traditionally, taste evaluation relied on human sensory panels, which are subjective, variable, and limited by ethical concerns. In contrast, the Electronic Tongue system employed in this study provided quantifiable and reproducible taste profile data, allowing for informed optimization of the taste-masking strategy. This integration of modern sensory analysis represents a shift toward more precise and ethical formulation evaluation practices[95].

Taken together, the current research offers a holistic and innovative framework for developing multi-drug oral suspensions that are not only effective in terms of pharmacological action but also highly acceptable to patients. By combining the advantages of ion exchange resin technology, rigorous scientific evaluation, and modern sensory assessment tools, this work contributes a novel solution to a long-standing pharmaceutical challenge. It has potential implications not only for cold and cough medications but also for other therapeutic areas requiring multi-API liquid dosage forms with improved compliance and clinical outcomes[96].

1.13.2 Scope and Limitations of the Study

The present research has been designed with a focused scope aimed at addressing critical challenges in pharmaceutical formulation, specifically the development and optimization of a taste-masked oral suspension containing multiple active pharmaceutical ingredients (APIs) using ion exchange resin technology. The study comprehensively covers the formulation aspects, physicochemical characterization of drug-resin complexes (DRCs), and the analytical validation of methods used to evaluate drug content and release behaviour. The APIs selected Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate were chosen for their therapeutic synergy in cough and cold treatment as well as for their common problem of intense bitterness, which makes them ideal candidates for taste-masking studies. The research thus provides a detailed and systematic approach to developing a patient-friendly multi-API suspension, particularly suited for paediatric and geriatric populations (table 1.11)[96].

Table 1.11 Scope vs Limitations

Scope	Limitations
Formulation of DRCs	No in-vivo/clinical evaluation
Analytical validation	APIs limited to selected three
In-vitro release study	Single resin system only (Indion 234)

The formulation work includes drug-resin complexation using Indion 234, selection and optimization of suspension excipients, and stability considerations such as redispersibility, uniformity, and compatibility among ingredients. Various physicochemical and thermal techniques including Fourier Transform Infrared Spectroscopy (FTIR), Differential Scanning Calorimetry (DSC), X-ray Diffraction (XRD), and Scanning Electron Microscopy (SEM) have been used to confirm the formation and stability of drug-resin complexes. Analytical techniques such as High-Performance Liquid Chromatography (HPLC) were developed and validated according to ICH guidelines to quantify the drug content, assess assay values, and monitor in-vitro release profiles[97]. The effectiveness of taste masking was evaluated through the

use of an Electronic Tongue system, which allowed for objective, reproducible, and ethically sound analysis of bitterness suppression[97].

While the study successfully demonstrates the feasibility and efficiency of ion exchange resins in taste masking and drug delivery within oral suspensions, it also has certain limitations. The primary limitation is that the research has been confined to in-vitro investigations. No clinical or in-vivo evaluations involving human subjects or patients were conducted as part of this study. Therefore, while the results suggest a high potential for improved patient compliance and therapeutic effectiveness, these outcomes remain theoretical and based solely on laboratory models. A future extension involving palatability studies in human subjects and pharmacokinetic profiling would be necessary to fully validate the clinical utility of the formulation[98].

Another important limitation is that the study has focused exclusively on a specific set of APIs and a single ion exchange resin (Indion 234). While this provides detailed insight into one application model, the findings may not be universally generalizable to all drug classes or resin types without further investigation. The choice of APIs was driven by their common therapeutic use and formulation challenges, but the behavior of other APIs with different physicochemical properties or binding affinities to the resin may vary significantly. Similarly, although Indion 234 was shown to be effective for this particular formulation, alternative resins might be more suitable for other drugs or dosage forms[99].

Additionally, the formulation and evaluation techniques employed in this study were designed for laboratory-scale development. Scaling up to an industrial manufacturing level would introduce additional variables such as batch-to-batch reproducibility, equipment constraints, and regulatory compliance in large-scale production. These aspects were beyond the scope of the current work but are critical for commercial translation.

In conclusion, the study offers a meaningful contribution to the domain of pharmaceutical formulation by presenting a scientifically sound, patient-oriented strategy for developing taste-masked multi-API oral suspensions using ion exchange resin technology. While it provides a strong foundation for further development, its

findings should be interpreted within the context of in-vitro limitations, specific drug-resin selection, and the absence of clinical validation. Future research could build upon this framework by exploring broader API compatibility, alternative resin systems, clinical acceptability studies, and scalability for commercial production[100].

CHAPTER 2

2.0 REVIEW OF LITERATURE

2.1 Introduction to Literature Review

2.1.1 Malladi M *et al.*, Design and evaluation of taste masked dextromethorphan hydrobromide oral disintegrating tablets. Dextromethorphan hydrobromide was complexed with ion exchange resin and formulated into ODTs. Smaller resin particle size enhanced drug loading. DSC and XRD confirmed amorphization. In vitro/in vivo tests showed comparable dissolution to conventional tablets, but significantly improved palatability. This study demonstrated successful taste masking of highly bitter DXM using resin complexation, suitable for patient-friendly solid dosage forms (*Acta Pharm.* 2010;60(3):267-80) [101].

2.1.1 Samprasit W, *et al.*, Formulation of Dextromethorphan Oral Disintegrating Tablet using Ion Exchange Resin. DXM was loaded onto Amberlite IRP-69 resin at ratios 1:1 and 1:2, followed by direct compression into ODTs. Resinate-based tablets showed sustained release, lower hardness, and successful masking of bitter taste. Tablets had similar friability and release compared to physical mixture controls; only resin-based tablets achieved effective taste masking, illustrating resin utility in improving palatability for immediate-release dosage forms (*Adv Mater Res*. 2011;201-203:1384-8) [102].

2.1.2 Kaushik D *et al.*, Central composite designed taste-masked ion exchange resinates for azithromycin dispersible tablets. Azithromycin was complexed with Tulsion 335 resin, optimized using design of experiments. Best performance at 1:3 drug–resin ratio and pH 6. Analytical methods (DSC, XRD, FTIR) confirmed complex formation. Dispersible tablets showed acceptable pharmacopeial properties and improved taste compared to marketed products. This work validated the feasibility of taste masking via resin in dispersible multi-API formulations (*J Pharm Res*. 2015;14(1):7-14) [103].

2.1.3 Gupta SK *et al.*, Study on taste masking of ranitidine HCl using ion exchange resin. Ranitidine HCl bitter taste was masked using Indion resins (204, 234, 264). Optimized conditions pH, resin type, drug resin ratio yielded resinate with reduced bitterness (panel scoring) and comparable release profiles. Demonstrates efficacy of resin complexation in masking strong bitterness while preserving dissolution performance in oral dosage (*Asian J Pharm Technol*. 2013;3(2):4-9) [104].

2.1.4 Kadam AU *et al.*, Development and evaluation of oral controlled release chlorpheniramine-ion exchange resinate suspension. Chlorpheniramine maleate was complexed with Indion 244 resin to prepare a controlled release suspension. Post-resinate microencapsulation with Eudragit RS100 further sustained release. Suspensions were physically stable over time and preserved their sustained-release profile under elevated temperatures. This demonstrated resin's effectiveness in formulating controlled-release and taste-masked liquid dosage forms (*Indian J Pharm Sci*. 2008;70(4):531-4) [105].

2.1.5 Taste masking of nizatidine using ion-exchange resins. Nizatidine was complexed with Amberlite IRP-69 and Dowex 50 resins. Optimal drug loading (up to ~99%) occurred at 1:5 ratio for Dowex. Activated resins showed better capacity than inactivated. Increased stirring time enhanced complexation. Findings support use of strong-cation resins for efficient taste masking in bitter cationic drugs; method applicable to oral liquid dosage formulation (*Processes*. 2019;7(11):779) [106].

2.1.6 Using dual-drug resinate complex for taste masking. Levocetirizine dihydrochloride and montelukast sodium were simultaneously complexed with ion exchange resin and optimized using Box–Behnken design. Increased stirring and swelling times improved loading and release. DSC and FTIR confirmed complexation. Both drugs demonstrated palatable taste in resin form and ODTs with improved disintegration and drug release. This demonstrates feasibility of multi-drug resin complexation for taste masking (*PharmTech*. 2015) [107].

2.1.7 Shaikh S *et al.*, Formulation and evaluation of taste masked oral suspension of dextromethorphan hydrobromide. Abstract. DXM bitterness was masked by batch complexation with various resins (Ionex QM 1011, WC 23, Kyron T-114). Optimized 1:6 ratio achieved 96% loading. DSC and IR confirmed complexation. Suspension evaluated: over 99.6% drug release in 45 min (pH 1.2), favourable re-dispersibility, viscosity, and panel-based taste testing. Demonstrated effective DXM taste masking with resin in suspension form (*IT Medical Team J*. 2021) [108].

2.1.8 A failure-safe guide to taste masking oral products with ion exchange resins. This industry review defines IER types, excipient grades, and taste-masking strategies. Highlights Polacrilin Potassium NF and Sodium Polystyrene Sulfonate for pediatric liquid dosage. Describes batch and column resin loading methods and critical variables (resin capacity, selectivity, ratio). Concludes resin complexation is efficient, scalable, and ensures palatable suspension formulations without major process restructuring in pharmaceutical manufacturing (2021) [109].

2.1.9 Ion-exchange resin. Ion-exchange resins are insoluble cross-linked polymers with charged functional groups. Cationic and anionic forms are used widely in pharmaceuticals for taste masking, controlled release, and purification. Resins like Kyron and Indion are notable for oral liquid applications. Their mechanism involves reversible ion exchange, pH-dependent drug binding and release. Provides fundamental background on resin properties, selectivity, and pharmaceutical applications (*Wikipedia: Ion-exchange resin*. 2025) [110].

2.2 Taste Masking in Pharmaceutical Dosage Forms

2.2.1 Walsh, J *et al.*, Playing hide and seek with poorly tasting paediatric medicines: Do not forget the excipients. This review emphasizes the importance of excipients in paediatric formulations, highlighting that flavouring alone is often inadequate for bitter drugs. It discusses the evolution of strategies including coatings, microencapsulation, and ion-exchange resins to improve palatability and compliance. Authors note regulatory recognition of taste masking as essential, especially for vulnerable

populations, and advocate for systematic design of taste-masked oral medicines (*Adv. Drug Deliv. Rev.* 2014, *73*, 14–33) [111].

2.2.2 Nayak, B. S J *et al.*, Taste masking techniques: An updated review. This comprehensive review categorizes taste-masking methods into general classes (e.g., solubility reduction, receptor blockade, physical barriers). It underscores that conventional sweeteners or flavours are insufficient for many bitter APIs, especially in paediatric and geriatric applications. The review highlights emerging techniques such as ion-exchange resins, microencapsulation, and prodrugs underscoring their growing role in improving compliance and therapeutic outcomes (*Indian J. Novel Drug Deliv.* 2012, *4*(3), 189–203) [112].

2.2.3 Felton, L. A. Use of Polymers for Taste-masking Paediatric Drug Products. This article examines how polymeric barriers applied via coatings, complexation, or encapsulation can control API exposure to taste buds. It reviews paediatric needs, emphasizing swallowability and taste. Several polymer-based formulations (e.g., polymer–drug complexes, coated multi-particulates) successfully reduce bitterness and improve acceptability, illustrating the evolution from flavouring to engineered delivery systems designed specifically to address compliance issues in children (*Drug Dev. Ind. Pharm.* 2018, *44*(7), 1049–1055) [113].

2.2.4 Thakker, P J *et al.*, Taste Masking of Pharmaceutical Formulations: Review on Technologies, Recent Trends and Patents. This review highlights the driving force behind taste masking patient compliance and offers an in-depth overview of both traditional (sweetener/flavour addition) and advanced (hot-melt extrusion, ion-exchange resin, cyclodextrin inclusion) techniques. Patented technologies are tabulated with their mechanism and applications, indicating a trend toward multi-functional delivery systems that combine taste masking with controlled release and user acceptability (*Int. J. LifeSci.PharmaRes.*2020,*10*(3),88–96) [114].

2.2.5 Amoussou-Guenou, D. Using Taste-Masking and Appearance to Address Patient-Specific Needs. March. This perspective emphasizes patient-centric design, especially for paediatric and geriatric populations. It highlights how taste-masking must align with dosage form and target demographic they stress that solid forms, coatings, or multi-particulates often fail when portions are broken or swallowed incorrectly. Advanced strategies are needed that consider appearance, flavour profiles, and safety, encouraging formulators to "think outside the pill box" (*Pharm. Technol.* 2015) [115].

2.3 Overview of Multi-API Oral Suspensions

2.3.1 Molins, V. *et al.*, Differentiating Oral Suspensions with Versatile Excipients. This industry-focused article discusses how excipient selection in oral suspensions affects patient compliance—especially for pediatric, geriatric, and neurologically impaired patients. Issues like dysphagia, sedimentation, dosing accuracy, taste masking, and viscosity are highlighted. It emphasizes the need for tailored excipient systems to ensure palatability, redispersibility, and uniform dosing, particularly when suspensions contain multiple APIs pmc.ncbi.nlm.nih.gov+5 (*on-drug Delivery* 2024, May/Jun, 18–20) [116].

2.3.2 Hopper, D. *et al.*, Overcoming Challenges to Formulation Development for Paediatric Medicines. This review underscores the complexity of paediatric suspension formulations that combine multiple APIs. It highlights the intertwined issues of bitterness, off-odours, texture, and dose uniformity, as well as solubility and bioavailability concerns. The paper stresses that addressing multi-sensory and physicochemical compatibility challenges is essential in multi-ingredient suspensions intended for children (*Pharm-Tech* 2024, 48–54) [117].

2.3.3 Tsitsimpikou, S.; et al. Pharmaceutical Development of Suspension Dosage Forms. The paper reviews design principles behind suspension dosage forms, emphasizing that even water-insoluble APIs may dissolve partially, impacting taste. It

stresses the complexity of formulating suspensions with multiple APIs, where solubility differences and excipient interactions affect palatability and stability. Highlights that preservatives, buffers, and co-solvents also contribute to off-flavor, requiring holistic formulation strategies (*Res. Gate* 2012, 1–8) [118].

2.3.4 Contract Pharma. Ensuring Dispersibility and Homogeneity in Early-Phase Suspensions. This article focuses on the challenge of achieving consistent API dispersion and content uniformity in early-phase multi-ingredient suspensions. It highlights critical parameters such as particle size, rheology, and user-controlled dosing, and recommends premixed dry powders to mitigate handling variability. These factors are especially acute in formulations with several APIs requiring precise dosing and taste masking (*Contract Pharm.* 2023, June) [119].

2.3.5 PMC Authors. Palatability and Stability Studies of Carvedilol Oral Liquid for Paediatrics. This study formulated a carvedilol liquid for paediatric use, addressing bitterness through sweeteners and flavours. It detailed the impact of sugars and flavours on taste profile, chemical stability, and microbial safety. The authors noted that multi-API suspensions present compounded taste, stability, and preservative challenges, highlighting the need for targeted approaches ensuring both palatability and shelf-life (*J. Pharm. Sci.* 2008, 97(2), 456–465) [120].

2.4 Conventional Taste-Masking Techniques

2.4.1 Yu, J *et al.* Strategies for Taste Masking of Oro-dispersible Dosage Forms: Time, Concentration, and Perception. This review covers classical taste-masking methods for oro-dispersible forms, including polymer coatings, microencapsulation, flavour/sweetener addition, and ion-exchange resins. It highlights key factors affecting taste perception temporal release, concentration thresholds, and sensory masking. The authors conclude that multilayer barrier strategies or integrated designs offer superior masking compared to vanilla flavouring, underlining the evolution toward sophisticated approaches for oral dosage palatability (*Mol. Pharm.* 2022, *19* (9), 3007–3025) [121].

2.4.2 Soma**, S.** *et al.* Taste Masking Using Microencapsulation in Food and Pharmaceutical Applications. This article reviews microencapsulation techniques spray drying, coacervation, fluidized bed coating for taste masking in drugs and food. It discusses how polymer concentration, core-to-shell ratio, and curing conditions impact encapsulation efficiency. The review highlights both strengths (effective masking and stability) and limitations (regulatory issues, cost, scalability), offering insight into method selection for bitter APIs (*World J. Adv. Res. Rev.* 2024, *24* (2), 1228–1240) [122].

2.4.3 Elawni, A. E**.** *et al.* Implementation and Comparison of Different Taste Masking Techniques to Design and Assess Dispersible Tablet Formulations. Using ranitidine as a model, this paper compares coating, microencapsulation via calcium carbonate granulation, and formulation factors for taste masking in dispersible tablets. A factorial design indicated coating with calcium carbonate was most effective, striking a balance between taste masking and drug release. The study highlights the challenge of choosing methods that work without compromising formulation properties (*J. Appl. Pharm. Res.* 2022, *10* (4), 1–13) [123].

2.4.4 Jha, S. K. *et al.* Taste Masking in Pharmaceuticals: An Update. This update reviews pharmaceutical taste-masking approaches, including flavouring agents, lipoproteins, coatings, microencapsulation, multiple emulsions, vesicles, prodrugs, and ion-exchange resins. It underscores each technique's applicability, ranging from simple taste masking with sweeteners to advanced delivery systems. The authors emphasize that while many options exist, choosing the best one depends on drug properties and desired release profile (*J. Pharm. Res.* 2008, *1* (2), 76–85) [124].

2.4.5 Karaman, R. Prodrugs for Masking the Bitter Taste of Drugs. This chapter reviews the prodrug approach as a taste-masking solution, where chemical moieties temporarily block bitterness until enzymatic conversion releases the active drug. It includes cases like chloramphenicol palmitate and clindamycin palmitate. The strategy is praised for effective masking and predictable pharmacokinetics, though it faces challenges in synthesis complexity and regulatory clearance (In *Nanotechnology in Drug Delivery*; Demir Sezer, A., Ed.; Intech Open: London, UK, 2014; pp 1–18) [125].

2.5 Ion Exchange Resins in Pharmaceutical Applications

2.5.1 Suhagiya, V. K. *et al.* Taste Masking by Ion-Exchange Resin and Its New Applications: A Review. This comprehensive review outlines how ion-exchange resins (IERs), both cationic and anionic, form non-covalent complexes with bitter APIs, preventing drug release in saliva and enabling release in gastric pH. It catalogues IERs like Indion, Amberlite, Kyron, and Dowex used in taste masking, highlighting factors such as ion-exchange capacity, functional group chemistry, and resin selection criteria. The paper thus frames the scientific rationale of IERs in modern formulation (*Int. J. Pharm. Sci. Res.* 2010, *1* (4), 22–37) [126].

2.5.2 Alayoubi, A. *et al.* Development of a Taste-Masked Oral Suspension of Clindamycin HCl Using Ion-Exchange Resin Amberlite IRP 69 for Paediatric Use. Clindamycin HCl was complexed with Amberlite IRP 69 and formulated into a pediatric suspension. The resin showed highest drug loading, and chosen excipients did not affect release. Xanthan gum optimized suspension rheology. Taste threshold and adult panel evaluations confirmed efficient bitterness masking. Dissolution studies showed >90% release in 30 min both fresh and after thermal storage. The study supports Amberlite's suitability for paediatric taste masking (*Drug Dev. Ind. Pharm.* 2016, *42* (10), 1579–158) [127].

2.5.3 Garg, A. V. *et al.* Ion-Exchange Resins: Carrying Drug Delivery Forward. This paper explores the broad applications of ion-exchange resins in drug delivery, including taste masking, controlled release, solubility enhancement, and abuse deterrence. Cationic and anionic resins are classified, with highlighted clinical examples. Presenting historical context (water purification → pharmaceutical excipient), it emphasizes resins' versatility in delivering better patient outcomes through pH-responsive release and formulation adaptability (*Drug Discov. Today* 2001, *6* (17), 905–914) [128].

2.5.4 Lo, C.-T. *et al.* Oseltamivir Phosphate–Amberlite IRP 64 Ionic Complex for Taste Masking: Preparation and Chemometric Evaluation.

Oseltamivir phosphate was complexed with Amberlite IRP 64 and evaluated using buccal and gastric pH. Complexes (1:1–1:6) showed <5% drug release in 20 s at pH 6.8 and >60–90% release in 6 min at pH 1.2. NIR imaging confirmed uniform loading; electronic tongue demonstrated taste profile difference from control. The study validates resin-based, pH-triggered taste masking with quantifiable analytical confirmation (*J. Pharm. Sci.* 2013, *102* (6), 1800–1812) [129].

2.5.5 Barde, L**.** *et al.* Design and Evaluation of Mebendazole Taste-Masked Chewable Tablets Using Ion-Exchange Resin Kyron T-114. Mebendazole was complexed with Kyron T-114 through batch ion-exchange. Parameters like drug-resin ratio, pH, and temperature were optimized. Characterization (FTIR, dissolution pH 6.8/1.2) demonstrated taste masking and gastric release. Chewable tablets showed suitable mechanical properties and taste profiles. This work confirms Kyron T-114's effectiveness in paediatric formulations and supports its selection for bitter drug dosing systems (*Int. J. Health Sci.* 2022, *6* (S6), 12756) [130].

2.6 Drug-Resin Complexation (DRC) Mechanism and Factors

2.6.1 Li, C**.** *et al.* Study on the Complexation and Release Mechanism of Methylphenidate Hydrochloride–Ion Exchange Resin Complex.
This study investigates the electrostatic interactions and π-stacking between methylphenidate HCl and Amberlite IRP-69 resin. It reports that optimal complexation relies on pH ~5.5, drug–resin ratio of 1:2, and acidic resin activation. In-vitro release demonstrated minimal drug release at salivary pH and rapid release at gastric pH. These findings provide mechanistic insights into resin-DOC formation and pH-triggered release (*Mol. Pharm.* 2021, *18* (12), 4552–4564) [131].

2.6.2 Patra, **S.** *et al.* Taste Masking of Etoricoxib by Using Ion-Exchange Resin. In this work, etoricoxib was complexed with Tulsion 335 resin at varying ratios and pH conditions. The study identifies the importance of resin activation (H^+ form), drug: resin ratios up to 1:3, and extensive mixing to achieve >90 % drug loading. DSC and FTIR confirmed complex formation, while dissolution studies confirmed rapid release under

acidic conditions. The paper emphasizes pH and ratio as crucial for DRC efficacy (*Pharm. Dev. Technol.* 2010, *15* (5), 511–517) [132].

2.6.3 Jeong, S. H**.** *et al.* Drug Loading and Release Properties of Ion-Exchange Resin Complexes as a Drug Delivery Matrix. This study examines the effects of resin particle size, swelling time, and stirring on drug-resin complexation using a model cationic drug. Key findings include faster loading with smaller resin beads, and the fact that H^+-activated strong cation resins deliver more reproducible complexes with higher drug content. The optimized complexes remained intact at neutral pH while efficiently releasing drug in acidic media (*Int. J. Pharm.* 2008, *361* (1–2), 26–32) [133].

2.6.4 Gao, Y**.** *et al.* Diclofenac Sodium Ion Exchange Resin Complex-Loaded Melt Cast Films for Sustained Release Ocular Delivery. Diclofenac sodium: resin complexes (1:1 ratio, Amberlite IRP-64) were fabricated and studied for drug–resin binding efficiency. Release kinetics were enhanced by resin activation and extended mixing times. The study emphasizes how resin pre-treatment, drug–resin ratios, and contact duration dictate loading, amorphization, and sustained-release behaviour, reinforcing the mechanistic principles of DRC evaluation (*Drug Deliv.* **2017**, *24* (1), 370–379) [134].

2.6.5 Walsh, J. *et al.* Playing Hide and Seek with Poorly Tasting Paediatric Medicines: Do Not Forget the Excipients. This comprehensive review outlines the principles of drug–resin binding, emphasizing the impact of pH, ionic strength, and resin activation on drug loading and release behaviour. It highlights that weak acid resins require pH-controlled conditions, while strong acid resins provide consistent loading across pH. The paper calls for systematic optimization of DRC parameters and integration of in-vitro taste release models (*Adv. Drug Deliv. Rev.* 2014, *73*, 14–33) [135].

2.7 Characterization Techniques in DRC Studies

2.7.1 Jain, S. *et al.* Preparation and Characterization of Taste Masked Complex of Levocetirizine with Ion Exchange Resin. This study used FTIR, DSC, and SEM to confirm the formation of a drug-resin complex between levocetirizine and Indion 234. FTIR demonstrated the disappearance of functional peaks, DSC revealed altered melting points, and SEM showed morphological differences. The techniques collectively validated successful taste-masking complexation. Drug release and palatability were optimized using resin: drug ratio and pH conditions (*Indian J. Pharm. Educ. Res.* 2014, *48* (4), 17–23) [136].

2.7.2 Chavan, R. B. *et al.* Ion Exchange Resin Complexes of Risperidone for Taste Masking and Enhanced Dissolution. The research utilized FTIR, XRD, and DSC to characterize the risperidone-resin complex. FTIR spectra indicated ion exchange, XRD confirmed amorphization, and DSC showed absence of drug's melting peak. HPLC was used for drug quantification. These analytical tools validated resin binding and enhanced dissolution, highlighting the importance of multi-technique characterization in DRC studies (*AAPS PharmSciTech* 2016, *17* (4), 1015–1023) [137].

2.7.3 Lo, C.-T. *et al.* Oseltamivir Phosphate–Amberlite IRP 64 Complex for Taste Masking: Preparation and Evaluation. This work applied NIR, FTIR, and SEM for structural and surface characterization of oseltamivir-resin complexes. SEM revealed uniform drug layer embedding; FTIR suggested ionic bonding. E-Tongue analysis quantitatively confirmed taste reduction at salivary pH. The study highlights the critical role of electronic taste sensing in objective palatability assessment, complementing physicochemical data (*J. Pharm. Sci.* 2013, *102* (6), 1800–1812) [138].

2.7.4 Panigrahi, K. C. *et al.* Taste Masking of Promethazine Hydrochloride by Ion Exchange Resins. FTIR and DSC analyses confirmed ionic complex formation between promethazine and Tulsion resins. DSC showed altered thermal behaviour, and HPLC validated drug content and release kinetics. The combination of these tools was essential

for confirming complexation and ensuring reproducible taste-masking performance (*Indian J. Pharm. Sci.* 2010, *72* (5), 621–625) [139].

2.7.5 Sun, D. *et al.* Advanced Characterization Techniques in Pharmaceutical Development. This review describes the application of analytical techniques like SEM, XRD, and FTIR for detecting structural transitions in solid-state dosage forms. Electronic Tongue (E-tongue) is presented as a novel, reproducible tool for evaluating palatability, allowing quantitative comparison between formulations. It underscores the synergistic role of chemical and sensory tools in validating drug-resin interaction (*Adv. Drug Deliv. Rev.* 2017, *117*, 118–137) [140].

2.8 Relevant Studies on APIs Used (DXM, PE, CPM)

2.8.1 Malladi, M. *et al.* Design and evaluation of taste masked dextromethorphan hydrobromide oral disintegrating tablets. Dextromethorphan HBr was complexed with ion exchange resin to develop oral disintegrating tablets. Results showed smaller resin particle size improved drug loading; DSC and XRD confirmed amorphization. In vivo and in vitro studies demonstrated effective taste masking while maintaining comparable dissolution profiles to conventional tablets. This work illustrates effective resin-based taste masking for DXM, paving the way for liquid formulations with similar challenges (*Acta Pharm.* 2010, *60* (3), 267–280) [141].

2.8.2 Samprasit, W. *et al.* Formulation of dextromethorphan oral disintegrating tablets using ion exchange resin. DXM was adsorbed onto Amberlite IRP-69 at various ratios to produce taste-masked oral disintegrating tablets. The optimized 1:2 formulation showed sustained release, acceptable hardness, and complete bitterness suppression. It confirmed the resin's utility in immediate-release dosage forms and highlighted the importance of resin–drug ratio for taste masking (*Adv. Mater. Res.* 2011, *201–203*, 1384–1388) [142].

2.8.3 Jelvehgari, M. *et al.* Preparation of chlorpheniramine maleate-loaded alginate/chitosan microspheres by ionic gelation for taste masking. Bitter chlorpheniramine maleate was encapsulated in alginate/chitosan microspheres via ionic

gelation. FTIR, XRD, and DSC confirmed drug entrapment and amorphization. The microspheres displayed 62–94 % entrapment efficiency and controlled release in simulated gastric/intestinal fluids. Results demonstrated successful taste masking and suggested microsphere systems as an alternative for bitter antihistamines (*Jundishapur J. Nat. Pharm. Prod.* 2014, *9* (1), 39–48) [143].

2.8.4 Kiran, B. *et al.* Taste mask, design and evaluation of an oral formulation using ion exchange resin as drug carrier. Diphenhydramine HCl was complexed with Indion 234 and Tulsion 343 resins at varying ratios (1:1 to 1:3). Optimal complexes were confirmed by XRD and DSC. Formulated effervescent/dispersible tablets achieved rapid dissolution (~95% in 15 min) and effective bitterness masking. This study underscores the efficacy of resin–drug complexes for rapid-release, taste-masked dosage forms, showcasing a method adaptable to multi-API liquid systems (*AAPS PharmSciTech* **2008**, *9* (2), 557–562) [144].

2.8.5 Sourabh, Y. *et al.* Fabrication of a controlled-release drug-resin combination device for dextromethorphan hydrobromide. A novel DRC device using dental resin delivered controlled-release DXM. Box–Behnken optimization shaped the formulation (PEG400 + NaCl). In vitro data showed controlled release over 8 hours; rabbit pharmacokinetics revealed extended t_max and reduced C_max compared to commercial tablets. The study broadens the application of DRCs beyond taste masking, presenting potential for controlled oral delivery of antitussives (*AAPS J.* 2020, *22* (4), 108) [145].

2.9 Gaps in the Literature

2.9.1 Jain, B. V. Formulation and Development of Taste-Masked Suspension Using Ion Exchange Resins. This study masked a single API (ambroxol HCl) using Tulsion 335 and Indion 214 in suspension form, achieving >80% drug release in 30 min. While effective for single drug systems, the study highlights the absence of multi-API formulations, emphasizing a need for research that incorporates combinations like

DXM, PE, and CPM in complexed suspensions (*J. Popul. Ther. Clin. Pharmacol.* **2021**, *28* (2), 143–146) [146].

2.9.2 Woertz, K. *et al.* Development of a Taste-Masked Generic Ibuprofen Suspension: Top-Down Approach Guided by Electronic Tongue Measurements. This work demonstrates the effective use of an Electronic Tongue (E-tongue) to optimize a single-API ibuprofen suspension's taste masking. While revealing the technique's value in objective assessment, it underscores the lack of use of E-tongue for multi-API liquid systems, thereby identifying a critical gap in sensory evaluation in complex formulations (*J. Pharm. Sci.* 2011, *100* (10), 4460–4470) [147].

2.9.3 Khan, S. A. *et al.* Hot Melt Extrusion of Ion-Exchange Resin for Taste Masking. Discusses a new solvent-free, continuous hot-melt extrusion method for resin-API complexation, addressing scalability but focusing on single APIs. It acknowledges traditional methods' limitations high solvent use and multi-step processes indicating the need for innovation in process development for multi-drug suspensions (*Pharmaceutics* 2018, *10* (11), 887) [148].

2.9.4 Amoussou-Guenou, D.; *et al.* Using Taste-Masking and Appearance to Address Patient-Specific This review emphasizes patient-centric taste masking in paediatric and geriatric dosage forms. It highlights that existing studies primarily involve single APIs with sweetener or coating methods, lacking multi-API formulations combining taste masking with controlled release. The article calls for more holistic approaches in future research (*Needs. Pharm. Technol.* 2015, March) [149].

2.9.5 Wesoły, M.; *et al.* Influence of Dissolution-Modifying Excipients on Electronic Tongue Results. This study explores how excipients influence E-tongue detection in drug formulations, noting that this complicates interpretation in complex liquid matrices. It underlines the need for standardized, objective sensory evaluation especially when dealing with multi-API systems with many excipient interactions, to ensure accurate palatability assessment (*Talanta* 2017, *162*, 203–209) [150].

2.10 Gaps Observed

Despite extensive research on taste masking of individual drugs, there remains a significant gap in studies involving multi-API oral suspensions, especially for paediatric and geriatric populations. Most available literature focuses on single-drug formulations, often using sweeteners, flavours, or coating technologies. These methods, however, are insufficient when dealing with multiple bitter APIs like Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl commonly used together in cough and cold syrups.

A major gap is the limited exploration of ion exchange resins (IERs) as a unified taste-masking and release-controlling agent for multi-API formulations. Few studies report the use of Indion 234 or similar cation-exchange resins in suspensions, and almost none evaluate DRC formation, release behaviour, and taste suppression collectively for all three APIs in a single formulation.

Furthermore, objective tools like the Electronic Tongue (E-tongue) are underutilized in evaluating bitterness and palatability. The lack of systematic, optimized, and validated protocols for drug-resin complexation in multi-drug systems also represents a research void.

Therefore, your study addresses these gaps by:

I. Investigating simultaneous taste masking of three APIs.

II. Using Indion 234 as a novel, functional resin.

III. Incorporating E-tongue-based evaluation.

IV. Focusing on suspension formulation, often neglected in favour of tablets.

This work provides a much-needed scientific contribution to multi-drug palatable suspension development using IERs, offering a practical solution with patient acceptability and regulatory alignment.

CHAPTER 3

MATERIALS AND METHOD

3. MATERIALS

3.1 Active Pharmaceutical Ingredients (API's)

This study utilized three Active Pharmaceutical Ingredients (APIs), each selected for their therapeutic relevance in over-the-counter (OTC) cold and cough formulations and their known bitterness that necessitates taste-masking interventions, particularly in paediatric and geriatric populations[151]. These APIs were Dextromethorphan Hydrobromide (DXM), Phenylephrine Hydrochloride (PHE), and Chlorpheniramine Maleate (CPM). All APIs were pharmaceutical-grade substances gifted by ADPL, Haridwar, Uttarakhand, India, with appropriate documentation and verified Certificates of Analysis (COA) confirming their identity, purity, and compliance with pharmacopeial standards.

3.1.1 Dextromethorphan Hydrobromide (DXM)

Dextromethorphan HBr is a centrally acting antitussive agent, commonly used in the symptomatic treatment of cough associated with cold, bronchitis, or other upper respiratory tract infections[152]. It is a synthetic, non-narcotic derivative of morphine that acts on the cough centre in the medulla to suppress the cough reflex. DXM is highly bitter, especially in solution or suspension form, which can significantly affect patient compliance. Its poor palatability poses a major challenge, particularly in paediatric dosage forms. Therefore, taste masking is a critical step in any formulation containing this API. In this study, DXM served as one of the model drugs to evaluate the effectiveness of ion-exchange resin-based taste masking[153].

3.1.2 Phenylephrine Hydrochloride (PHE)

Phenylephrine HCl is a nasal decongestant and selective α1-adrenergic receptor agonist used widely in multi-ingredient cold and flu preparations[154]. It relieves nasal congestion by vasoconstriction in the nasal mucosa, making it especially useful in combination formulations. Like DXM, Phenylephrine HCl has an intensely bitter taste and is also moderately water soluble, making it challenging to formulate without taste-masking

strategies[155]. Furthermore, PHE chemical stability in aqueous media can be affected by pH, which also necessitates careful formulation design, especially when used with ion-exchange resins. Its incorporation in the study provided insights into the compatibility of resins with phenolic and hydrochloride salt-based actives[156].

3.1.3 Chlorpheniramine Maleate (CPM)

Chlorpheniramine Maleate is a first-generation antihistamine, often included in combination formulations for cold, cough, and allergic conditions. It works by blocking histamine H1 receptors and helps in relieving symptoms such as runny nose, sneezing, and watery eyes. CPM also exhibits a strong bitter aftertaste when administered orally, particularly in liquid or suspension form[157]. The compound is moderately soluble in water, and its maleate salt form has good binding affinity to ion-exchange resins, making it suitable for taste masking via resin complexation. Its inclusion in this study enabled the evaluation of DRC formation efficiency and taste-masking performance in multi-API systems[157].

These APIs represent commonly used ingredients in OTC paediatric and adult oral suspensions. Their inherent bitterness, multi-API complexity, and formulation challenges make them ideal candidates for the research objective of developing a taste-masked oral suspension using ion-exchange resin (Indion 234) [158]. Their selection also supports the novelty of this study, as it explores a single-platform solution for taste masking and drug release control of multiple APIs using resin complexation[159].

3.2 Ion Exchange Resins

Ion exchange resins (IERs) are cross-linked, water-insoluble polymers bearing functional groups capable of exchanging their counter-ions with ions of similar charge in a surrounding solution. They have gained significant attention in pharmaceutical formulations, particularly in the taste masking of bitter drugs, by forming non-covalent complexes (drug-resin complexes or DRCs). These complexes remain stable in the oral cavity, preventing interaction with taste receptors, and dissociate only upon reaching the acidic or ionic environment of the gastrointestinal tract, thereby releasing the drug in a controlled manner[160].

For this study, six different ion exchange resins were initially screened for their ability to mask the unpleasant taste of the selected active pharmaceutical ingredients (Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate) and their suitability for formulation into a stable, multi-API oral suspension[161].

3.2.1 Different brands of Ion Exchange Resins Used in Trials

The resins evaluated included both Indion and Kyron series resins, comprising:

I. Kyron T-114

II. Kyron T-314

III. Indion 204

IV. Indion 214

V. Indion 234

VI. Indion 254

Each resin represents a unique combination of particle size, moisture content, ion exchange capacity, and pH responsiveness. These characteristics directly influence their drug binding efficiency, complexation behaviour, and taste-masking performance in aqueous suspensions[162-163].

3.2.1.1 Kyron Brand Resins

Kyron T-114 and Kyron T-314, both weakly acidic cation exchange resins based on cross-linked carboxylic functionality, were generously gifted by ADPL, Haridwar, Uttarakhand. These resins are commonly used in pharmaceutical taste masking and are approved under the Generally Recognized as Safe (GRAS) category. Kyron resins are known for their rapid swelling, good binding properties at neutral pH, and excellent flowability. They were tested for their efficiency in binding all three APIs individually and in combination, especially for early taste masking screening[164].

3.2.1.2 Indion Brand Resins

Indion 204, 214, 234, and 254 are strong cation-exchange resins based on sulfonic acid functional groups, supplied as free-flowing powders or beads. These were gifted by Ion

Exchange India Ltd., Mumbai, a leading manufacturer of pharmaceutical-grade ion exchange resins. All Indion resins were accompanied by Certificates of Analysis (CoA) confirming their exchange capacity, particle size, moisture content, and compliance with pharmaceutical quality standards (IP/USP). These resins are known for their superior taste-masking potential due to strong electrostatic interactions with cationic drugs[166].

3.3 Excipients

The formulation of a stable, palatable, and patient-friendly oral suspension requires the judicious selection of suitable excipients inert pharmaceutical ingredients that serve functional roles without exerting any therapeutic effect. In this study, multiple excipients were employed to develop a multi-API taste-masked oral suspension, focusing on improving suspension stability, re-dispersibility, organoleptic appeal, and overall patient acceptability, especially in paediatric and geriatric populations[167].

All excipients used were of pharmaceutical grade and generously gifted by ADPL, Haridwar, Uttarakhand. Each excipient was accompanied by a Certificate of Analysis (COA), verifying compliance with the applicable pharmacopeial specifications (Indian Pharmacopoeia, USP/NF). The selection was based on regulatory approval, compatibility with APIs and ion exchange resins, functional performance, and safety profile[168].

Different Categories and Roles of different Excipients Used

The following categories of excipients were incorporated:

3.3.1 Suspending Agents

To ensure uniform distribution of the Drug-Resin Complex (DRC) within the suspension and prevent sedimentation, suspending agents were added. These agents provide rheological control by increasing the viscosity of the medium, allowing for easy redispersion upon shaking and improving pourability and patient compliance. Xanthan gum was particularly useful due to their non-ionic nature, making them compatible with ionic resin complexes[169].

3.3.2 Sweetener

To enhance the palatability of the suspension, non-cariogenic, high-intensity sweeteners were employed. Saccharin was used as sweeteners not only mask residual bitterness that may escape complexation but also contribute to the overall taste profile without interfering with the DRC's performance[170].

3.3.3 Preservatives

Preservatives were included to prevent microbial growth during storage and throughout the product's shelf-life. Selected preservatives included:

I. Methylparaben

II. Propylparaben

III. Sodium benzoate

These agents were chosen based on their antimicrobial spectrum, solubility in aqueous media, and regulatory acceptability for oral liquid preparations. Their concentration was optimized to meet preservative efficacy testing (PET) standards without affecting taste or formulation stability.

3.3.4 Flavouring and Colouring Agents

To further improve the sensory appeal of the formulation, natural and nature-identical flavours Strawberry.

Food-grade colouring agents matching the flavour i.e. Tartrazine yellow) were used to create an appealing and consistent product appearance, which is especially important for paediatric acceptance[171].

3.3.5 Buffering Agents

To maintain pH stability and prevent degradation of APIs in the aqueous medium, buffering agents' citric acid was used.

Justification of Selection are that all excipients were carefully screened for:

I. Physicochemical compatibility with APIs and resin

II. Regulatory compliance (GRAS status, IP/USP acceptance)

III. Non-interference with analytical and taste evaluation methods

IV. Ease of dispersion and suspension homogeneity

V. Acceptability for paediatric and geriatric populations

The selection of excipients also aligned with stability needs, ensuring minimal pH drift, microbial growth, or degradation over the proposed shelf life of the suspension, which was tested under ICH stability conditions[171].

3.4 Chemicals and Reagents

To support the analytical, formulation, and experimental phases of this research project, a range of analytical-grade chemicals and solvents were utilized. These reagents were essential in conducting resin activation, drug-resin complexation, buffer preparation, HPLC analysis, and in-vitro drug release studies under controlled conditions.

All chemicals and reagents used in this study were of Analytical Reagent (AR) or High-Performance Liquid Chromatography (HPLC) grade, ensuring high purity and minimal interference in analytical procedures. These were gifted by A.D. Pharmaceutical Laboratories (ADPL), Haridwar, Uttarakhand, along with authenticated Certificates of Analysis (COAs) confirming their quality, purity, and conformance to pharmacopeial standards[172].

3.4.1 Acids and Bases

3.4.1.1 Hydrochloric Acid (HCl) (AR grade):

Used extensively for:

I. Resin activation (acid washing of ion exchange resins)

II. Preparation of simulated gastric fluid (pH 1.2) without enzymes for in-vitro release testing

III. pH adjustments during formulation and analytical sample preparation

3.4.1.2 Sodium Hydroxide (NaOH) (AR grade):

Utilized in:

I. pH adjustment of buffers and drug-resin suspensions
II. Preparation of alkaline media (e.g., for stability or interaction studies)
III. Neutralization procedures during resin activation

These reagents were handled using standard lab practices, and fresh dilutions were prepared regularly to maintain accuracy and consistency[173].

3.4.2 Buffer Solutions used for Drug Release study i.e. in vitro

To mimic the physiological conditions in various segments of the gastrointestinal tract and evaluate the pH-dependent release characteristics of the Drug-Resin Complexes (DRCs), the following buffers were prepared:

I. pH 1.2 Buffer (Simulated gastric fluid)

II. pH 4.5 Buffer (Acetate buffer)

III. pH 6.8 Buffer (Phosphate buffer)

These buffers were prepared using IP/USP recommended recipes and were freshly made or stored under refrigeration and used within specified timeframes. The buffers were essential in dissolution profiling, helping to analyse how the DRCs behaved in environments similar to that of the human mouth, stomach, and small intestine. They also helped in confirming the pH-responsive release mechanism of the resinate complex[174].

3.4.3 Organic Solvents (HPLC Grade)

Methanol (HPLC grade) & Acetonitrile (HPLC grade)

These solvents were used in:

I. High-Performance Liquid Chromatography (HPLC) analysis for assay and related substances
II. Mobile phase preparation
III. Sample extraction, filtration, and dilution procedures

The use of HPLC-grade solvents minimized interference and ensured high sensitivity and reproducibility in quantitative analysis of the APIs and their stability over time[175].

3.4.4 Distilled and Deionized Water

Distilled and deionized water was used throughout the study for:

I. Buffer and solution preparation

II. Washing of resins during activation

III. Reconstitution of drug-resin complexes and excipients

IV. Cleaning of glassware and instruments

Water used in all procedures complied with the required conductivity and total organic carbon (TOC) limits, ensuring no contamination in formulation and analysis[176-177].

3.4.5 Additional Reagents

I. Potassium dihydrogen phosphate and Disodium hydrogen phosphate: used in phosphate buffer preparation

II. Glacial acetic acid and Sodium acetate: for acetate buffer preparation (pH 4.5)

III. Orthophosphoric acid: sometimes used to fine-tune pH in mobile phases or buffers

These chemicals played critical roles in simulating physiological environments and ensuring the DRCs' behaviour under varied pH conditions was well understood and validated[178].

3.5 Instruments and Equipment

A comprehensive set of analytical, characterization, and evaluation instruments was employed throughout this research to ensure accuracy, reproducibility, and compliance with pharmaceutical quality standards. Each technique was selected based on its suitability for analysing specific formulation characteristics, including drug content,

molecular interaction, thermal behaviour, crystallinity, surface morphology, dissolution profile, and taste masking efficiency[179].

3.5.1 Analytical and Evaluation Instruments

The key instruments and their usage are described below:

3.5.1.1 High-Performance Liquid Chromatography (HPLC)

I. Purpose: Quantitative estimation of drug content, assay of APIs, related substances profiling, and in-vitro drug release analysis.

II. Shimadzu make with UV-Visible Detector & Autosampler Model: LC-2050C operated by software LabSolutions and another HPLC of with Make Waters with PDA Detector & Autosampler having Model: ARC HPLC operated by software used is Empower version 03, and HPLC columns with dimension 50 x4.6mm (ODS), 3.5µ and gradient system[180].

III. Usage: HPLC was the primary analytical tool for assessing:

   a. API content in suspensions
   b. Assay and purity of Drug-Resin Complexes (DRCs)
   c. Release profile studies at various pH conditions

Provided by: A.D. Pharmaceutical Laboratories (ADPL), Haridwar, Uttarakhand.

3.5.1.2 Fourier Transform Infrared Spectroscopy (FTIR)

I. Purpose: To identify potential interactions between APIs and resins by evaluating characteristic functional group shifts.

II. Model: FTIR with KBr pellet sampling system[181].

III. Usage: FTIR spectra were recorded to detect chemical compatibility and structural integrity of drug-resin complexes.

Tested at: Central Instrumentation Facility (CIF), Lovely Professional University (LPU), Punjab.

3.5.1.3 Differential Scanning Calorimetry (DSC)

I. Purpose: Thermal analysis of APIs, resins, and DRCs to study melting points, enthalpy changes, and crystallinity changes post-complexation.

II. Model: Precision DSC instrument with temperature ranges from ambient to 300 °C.

III. Usage: Confirmed physical interaction or changes in thermal properties upon DRC formation[182].

Tested at: Central Instrumentation Facility (CIF), Lovely Professional University (LPU), Punjab.

3.5.1.4 X-Ray Diffraction (XRD)

I. Purpose: Crystallinity assessment and phase identification of pure drugs, resins, and final complexes.

II. Usage: XRD was crucial in determining the conversion of crystalline APIs into amorphous or less crystalline forms after complexation[183].

Tested at: Central Instrumentation Facility (CIF), Lovely Professional University (LPU), Punjab.

3.5.1.5 Thermogravimetric Analysis (TGA)

I. Purpose: Determination of thermal stability and moisture content of DRCs and resins.

II. Usage: TGA profiles helped assess degradation temperature and weight loss patterns for comparative stability analysis[184].

Tested at: Central Instrumentation Facility (CIF), Lovely Professional University (LPU), Punjab.

3.5.1.6 Scanning Electron Microscopy (SEM)

I. Purpose: Morphological characterization and surface topography of drug-resin complexes.

II. Usage: SEM images provided insights into the surface uniformity and microstructure of the formulated DRCs.

Tested at: Central Instrumentation Facility (CIF), Lovely Professional University (LPU), Punjab.

3.5.1.7 Electronic Tongue (E-Tongue)

I. Purpose: Objective and quantitative taste evaluation of the formulated suspensions and DRCs.

II. Model: E-tongue based on sensor array technology capable of analyzing bitterness intensity.

III. Usage: To evaluate and compare the taste masking efficiency of various ion exchange resins[184].

Analysis done at: CSIR - Central Food Technological Research Institute (CFTRI), Mysuru, Karnataka.

3.5.1.8 USP Type II Dissolution Apparatus (Paddle Method)

I. Purpose: In-vitro drug release testing of DRCs in various pH conditions simulating gastrointestinal fluids (pH 1.2, 4.5, 6.8).

II. Usage:

a. Monitoring the controlled release behaviour of drug-resin complexes
b. Assessment of drug release kinetics and profile validation

Provided by: ADPL, Haridwar, Uttarakhand.

3.5.1.9 Additional Instruments and Equipment

I. Digital pH Meter: For accurate pH adjustment of buffers, suspensions, and drug-resin mixtures.

II. Magnetic Stirrer with Hot Plate: For uniform stirring during DRC formation and resin activation.

III. Vacuum Filtration Unit: For efficient separation of DRCs from aqueous media.

IV. Hot Air Oven: For controlled drying of activated resins and DRCs under specific temperature and humidity.

3.6 Instrument Source and Collaboration

I. Instruments for routine analysis (HPLC, dissolution studies and other additional required instruments for support for these analysis) were made available through collaborative support from A.D. Pharmaceutical Laboratories, ensuring access to industrial-grade, validated equipment.

II. All characterization studies requiring advanced techniques (TGA, DSC, XRD, SEM, FTIR) were conducted at Central Instrumentation Facility (CIF), LPU, under trained supervision.

III. The electronic tongue-based taste evaluation, a novel and critical component of the study, was carried out at CSIR-CFTRI, a premier national institute known for sensory analysis and food technology research[185].

METHODS

3.7 Proposed Methodology

Following are the main steps will be followed during my research project:

3.7.1 Literature review: The first step in the development and optimization of taste-masking techniques for suspension containing multiple APIs using IERs is to conduct a thorough literature review. This involves reviewing existing studies and publications related to IERs and taste-masking techniques. This will help to identify the most effective resins and techniques that have been used in previous studies.

3.7.2 Selection of active pharmaceutical ingredients: The second step is to select the active pharmaceutical ingredients (APIs) that will be used in the suspension. The selection of APIs should be based on their therapeutic value and compatibility with IERs. It is important to consider the solubility and stability of the APIs in the suspension.

3.7.3 Selection of IER: The third step is to select the appropriate IER that will effectively mask the unpleasant taste of the APIs. The selection should be based on the type of APIs, resin capacity, and pH range compatibility. The resin should be capable of efficiently adsorbing the APIs while not affecting their therapeutic efficacy.

3.7.4 Optimization of resin concentration: The fourth step is to optimize the resin concentration for maximum taste-masking effectiveness. The concentration of the resin should be optimized based on the type and quantity of APIs used in the suspension.

3.7.5 Optimization of pH: The fifth step is to optimize the pH of the suspension to ensure that the IER is effectively adsorbing the APIs. The pH range should be optimized based on the type of APIs and the resin used. Characterization of the taste-masking properties.

3.7.6 Formulation optimization: Based on the results of the previous steps, the formulation of the suspension can be optimized by adjusting the resin concentration, pH, and the type and quantity of APIs used. This step may involve multiple iterations of the previous steps until an optimized formulation is achieved.

3.7.7 Suspension evaluation: The sixth step is to characterize the taste-masking properties of the optimized suspension using sensory evaluation and analytical methods. Sensory evaluation can be performed using trained panellists or a consumer panel. Analytical methods such as high-performance liquid chromatography (HPLC) can be used to measure the concentration of APIs in the suspension.

3.7.8 Stability testing: The final step is to perform stability testing to ensure that the taste-masking properties of the suspension are maintained over time. This will be performed by conducting experiments at various temperatures such as refrigerated condition temperature, ambient temperature and at accelerated temperature stability studies to determine the shelf-life of the suspension.

3.7.9 Data analysis and reporting: The final step is to analyze the data obtained from the previous steps and report the findings in a scientific publication.

3.8 Selection of Active Pharmaceutical Ingredients

The selection of dextromethorphan HBr, chlorpheniramine maleate, and phenylephrine HCl as the active pharmaceutical ingredients (APIs) for my research on the "Development and Optimization of Taste-Masking Techniques for Oral Suspension Containing Multiple APIs using Ion Exchange Resins" is strategically grounded and holds significant scientific merit. Several key justifications underpin the choice of these specific APIs for your research.

3.8.1.1 Most Commonly Used Cough Syrup

The combination of dextromethorphan HBr 10 mg/5 ml, chlorpheniramine maleate 2 mg/5 ml, and phenylephrine HCl 5 mg/5 ml is commonly used in the market with taste masking achieved by sweeteners and flavours. The combination of these three APIs is often found in over-the-counter (i.e., no prescription required) cough and cold medications.

3.8.1.2 Clinical Significance

Dextromethorphan HBr is a widely used antitussive, chlorpheniramine maleate is an antihistamine, and phenylephrine HCl is a decongestant. The clinical relevance of these

APIs addresses a common health concern, providing practical implications for improving patient compliance and acceptance of oral suspensions.

3.8.1.3 Complexity of Formulation

The presence of multiple APIs in a single oral suspension poses a formulation challenge, especially considering the diverse physicochemical properties of dextromethorphan, chlorpheniramine, and phenylephrine. Successfully taste-masking these APIs requires a nuanced approach, making the formulation an excellent subject for exploration and optimization.

3.8.1.4 Ion Exchange Resins as Taste-Masking Agents

The use of only one ion exchange resin for taste masking is a novel and promising approach. This resin can effectively interact with the APIs, altering their release characteristics and improving palatability. Investigating the application of ion exchange resins in taste masking for multiple APIs concurrently is an innovative angle that contributes to the advancement of pharmaceutical technology.

3.8.1.5 Patient Compliance and Acceptance

The taste and palatability of oral suspensions significantly influence patient compliance, especially in paediatric and geriatric populations. By focusing on taste masking, your research aims to enhance the overall patient experience, which is vital for the success of oral pharmaceutical formulations.

3.8.1.6 Scientific Gap and Contribution

The formulation of oral suspensions containing multiple APIs using ion exchange resins is an underexplored area in pharmaceutical research. My work will contribute to filling this scientific gap, providing valuable insights into the challenges and opportunities associated with taste masking in complex formulations.

3.8.1.7 Interdisciplinary Nature

The research involves elements of pharmacology, formulation science, and material science, making it interdisciplinary. This approach enhances the breadth and impact of my study.

3.8.2 Selection of IER for Taste Masking Oral Suspension Containing Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl

Selecting an appropriate ion exchange resin (IER) for taste masking in an oral suspension containing dextromethorphan HBr, chlorpheniramine maleate, and phenylephrine HCl involves considering several factors such as the properties of the active ingredients, the desired taste masking mechanism, and the compatibility of the resin with other excipients in the formulation. Here's a general approach along with some references to guide you:

3.8.2.1 Acidity and Basicity of APIs

I. Dextromethorphan HBr: It is a salt of dextromethorphan, which is a weak base. The hydrobromide salt increases the water solubility of the drug but can impart a bitter taste.

II. Chlorpheniramine Maleate: This API is a salt of chlorpheniramine, which is also a weak base. The maleate salt form enhances solubility but may contribute to a bitter taste.

III. Phenylephrine HCl: Phenylephrine is a weak base, and its hydrochloride salt is commonly used in pharmaceutical formulations. However, it can have a bitter and unpleasant taste.

3.8.2.2 Ion Exchange Resin Selection

Anion Exchange Resins: For masking basic APIs like dextromethorphan HBr, chlorpheniramine maleate, and phenylephrine HCl, anion exchange resins are preferred. These resins can effectively bind to the positively charged ions of the APIs, reducing their bitterness.

3.8.2.3 Strong vs. Weak Resins

The choice between strong and weak anion exchange resins depends on the degree of taste masking required. Strong resins offer higher binding capacities but may also interact with other formulation components, affecting stability. Weak resins provide milder masking effects but offer better compatibility.

3.8.2.4 pH of Suspension

The pH of the oral suspension influences the ionization state of the APIs and the ion exchange process. Adjusting the pH to a level suitable for optimal resin-drug interaction is critical for effective taste masking.

Buffering Agents: Addition of buffering agents helps maintain the desired pH range, ensuring efficient ion exchange and taste masking while preserving suspension stability.

Literature Review

Conduct a literature review to identify studies or references that have successfully utilized specific ion exchange resins for taste masking of similar active ingredients. Look for research papers, patents, or formulation development guides that discuss taste masking strategies for oral suspensions.

3.8.3 Pre-treatment and Activation of Resins

The process of pre-treatment and activation of ion exchange resins is a critical step in ensuring their maximum efficiency for drug complexation, particularly in pharmaceutical applications involving taste masking and controlled drug release. In the current research, a range of ion exchange resins was utilized for initial trials, including Kyron T-114, Kyron T-314, Indion 204, Indion 214, Indion 234, and Indion 254. Among these, Indion 234, a strong cation exchange resin, was selected for final formulation based on superior drug-binding performance and taste-masking efficiency.

To achieve optimal drug-resin interaction, all resins underwent a thorough activation and purification process prior to their use in drug complexation. This procedure was implemented to remove any adsorbed impurities, free ions, or loosely bound materials present from the manufacturing process, which could interfere with binding efficiency or stability.

3.8.3.1 Initial Washing with Deionized Water

Each resin sample was first thoroughly washed with deionized water to remove surface dust, soluble impurities, and loosely adhered particles. This initial cleansing helped in

preparing a clean surface for uniform acid treatment and ensured that no extraneous matter would influence subsequent analytical readings or drug interaction.

3.8.3.2 Acid Activation Using 1N Hydrochloric Acid (HCl)

The cleaned resin was then treated with 1N HCl solution in a resin-to-acid ratio of approximately 1:10 (w/v). The mixture was stirred for 30 to 60 minutes at room temperature using a magnetic stirrer to allow sufficient time for complete activation. Acid treatment helps convert the resin to its most reactive form by replacing counterions (e.g., Na^+, Ca^{2+}) with hydrogen ions (H^+) in the case of cation exchange resins. This activation enhances the ion-exchange capacity and binding affinity of the resin for basic drugs like Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl, which form electrostatic interactions with the negatively charged sites on the resin matrix.

3.8.3.3 Repeated Washing Until Neutral pH

After acid treatment, the resin was washed repeatedly with deionized water until the pH of the filtrate was neutral (~pH 7). This step is crucial to:

I. Remove residual hydrochloric acid from the resin surface
II. Prevent degradation of drugs during complexation due to residual acidity
III. Avoid interference with taste or analytical evaluation due to acidic contamination

The wash cycles continued until pH stabilization was confirmed using a calibrated pH meter.

3.8.3.4 Drying of Activated Resin

The cleaned and activated resins were spread in thin layers on glass or stainless-steel trays and dried in a hot air oven at 45–50°C for 4–6 hours, or until a constant weight was achieved. Low-temperature drying was preferred to avoid thermal degradation of the resin and ensure stability for subsequent complexation.

3.8.3.5 Storage

The dried resins were stored in airtight, labelled glass containers or desiccators to protect them from moisture, microbial contamination, or environmental degradation. All resins were used within the validated shelf-life after activation to ensure consistent performance.

3.8.3.6 Rationale and Significance

I. **Why Pre-treatment is Essential**:
Inactivated or improperly cleaned resins may retain unwanted salts, organic residues, or manufacturing agents that reduce the ion-exchange efficiency, affect taste masking, or interfere with drug release kinetics.

II. **Why Acid Activation**:
HCl is commonly used for strong cation resins because it ensures maximum availability of H^+ ions required for drug exchange reactions. It also prevents contamination from polyvalent metal ions that might be present in trace amounts.

III. Why Neutralization and pH Control:
A neutral pH ensures the resin surface is stable and compatible for drug binding and also ensures safety for human consumption in the final oral suspension product (figure 3.1).

Raw Resin

↓

Washing with Deionized Water

↓

Treatment with 1N HCl (30–60 min)

↓

Repeated Washing (pH ~ 7)

↓

Drying in Hot Air Oven (45–50°C)

↓

Airtight Storage for Use in DRC

Figure 3.1 Resin Activation Flowchart

3.8.4 Oral Suspension Formulation

Once the Drug-Resin Complex (DRC) was successfully formed and characterized, the next step involved formulating it into a stable, palatable, and pharmaceutically acceptable oral suspension. The suspension formulation was meticulously developed to ensure:

I. Masking of the bitter taste of the active pharmaceutical ingredients (APIs)

II. Ease of administration for paediatric and geriatric patients

III. Satisfactory physicochemical stability over the intended shelf-life

This phase was essential in translating the laboratory-optimized DRC into a patient-compliant oral dosage form, particularly aimed at improving palatability and therapeutic adherence.

3.8.4.1 Formulation Strategy

The drug-resin complexes of Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and Chlorpheniramine Maleate (CPM) were suspended in an aqueous base containing carefully selected excipients to achieve the desired taste-masking, flow properties, physical stability, and pH compatibility.

The selection of excipients followed the principles of QBD (Quality by Design), taking into consideration factors such as:

- Organoleptic properties (sweeteners, flavours)
- Rheology (suspending agents)
- Chemical compatibility with APIs and resins
- Microbial stability (preservatives)

3.8.5 Procedure for Suspension Formulation

3.8.5.1 Preparation of Aqueous Phase

A required volume of purified water was taken in a beaker. Suspending agents i.e. xanthan gum was added gradually with continuous stirring to ensure uniform hydration and dispersion.

3.8.5.2 Addition of Sweeteners and Preservatives

Non-cariogenic sweeteners sucrose and preservatives i.e. sodium benzoate, methylparaben and propylparaben were dissolved under mild heat if required. This step ensured protection against microbial contamination during the product's shelf life.

3.8.5.3 Incorporation of Drug-Resin Complex

The dried DRC powder was slowly added to the base solution under continuous stirring using a mechanical stirrer to ensure even distribution and prevent clumping or floating it takes about 4-5 hours.

3.8.5.4 Addition of Flavour and Colour

Paediatric-acceptable Flavors Strawberry and approved colorant tartrazine yellow lake were added toward the end of the mixing process to enhance sensory appeal and ensure uniform distribution.

3.8.5.5 Adjustment of Final Volume and pH

The suspension was made up to the final required volume with purified water. The pH was adjusted to between 6.5–7.0 using dilute NaOH or citric acid buffer to ensure (figure 3.2, Table 3.1 & 3.2)

Table 3.1 IER taste masked oral suspension composition

S/No.	Ingredients	Different Function	Amount used for 2000ml	U.O.M
1	Dextromethorphan HBr (DXM)	API	4000	mg
2	Chlorpheniramine Maleate (CPM)	API	800	mg
3	Phenylephrine Hcl (PHE)	API	2000	mg
4	Sucrose	Sweetener	600	gm
5	Methyl Paraben	Preservative	3600	mg
6	Propyl Paraben	Preservative	400	mg
7	Xanthan Gum	Excipient	1000	mg
8	Col. Tartrazine Yellow Lake	Colour	1320	mg
9	Flavour Strawberry	Flavour	4000	mg
10	Indion-234	Ion Exchange Resin	5000	mg
11	Sodium Benzoate	Preservative	1360	mg

Table 3.2 During development, the suspension was optimized on the basis of the following critical quality attributes (CQAs)

Parameter	Target Range
pH	6.5 – 7.0
Viscosity	Moderate; suitable for uniform dosing and pourability
Sedimentation volume	>0.9 (indicates good redispersibility)
Redispersibility	Uniform with <5 gentle shakes
Taste acceptability	E-tongue reading within acceptable bitterness threshold
Appearance	Uniform, free-flowing, no lumps or phase separation

Measure purified water → Disperse suspending agent

↓

Add sweeteners, preservatives (under mild heat if needed)

↓

Incorporate drug-resin complex (under constant stirring)

↓

Add flavour and colour → Adjust pH → Make up volume

↓

Homogenize → Fill → Store.

Figure 3.2 Suspension Formulation Workflow

3.9 Methodology Used for Formulation of Trails & Evaluation

3.9.1 Formulation of Drug Complex Using different Ion Exchange Resin:

3.9.1.1 Preparation of Drug syrup Solution: As the drugs as freely soluble in water, due to this reason drug solution prepared in distilled water. All API of desire quantity as per table 1 of Dextromethorphan HBr (DXM), Phenylephrine Hcl (PHE) & Chlorpheniramine Maleate (CPM) were accurately weight and all taken in 200ml volumetric flask. Then added about 20ml distilled water and sonicated up-to dissolved. Then added 80ml of distilled water. [32] Then required excipients except resin added as given in table 1. After that added 80ml distilled water in continuous stirring condition and pH adjusted to 6 to 7 using 10% potassium hydroxide solution. Then makeup to 200ml with distilled water.

3.9.1.2 Preparation of drug resin complex (DRC) suspension: Drug syrup solution and resin were accurately weighed in required ratio. The slurry of resin was made in 200ml Drug syrup solution in 250ml beaker and magnetic stirred condition. Then the obtained solution pH adjusted between 6 to 7 with the help of 10% potassium hydroxide solution The drug resin mixture was continuously stirred for 4 to 5 hours (Table 3.3).

Table 3.3 Different 18 no's trials composition with different Resins

Ingredients/Trials	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18
Kyron T-114 (gm)	1	2	3	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
Kyron T-314 (gm)	-	-	-	1	2	3	-	-	-	-	-	-	-	-	-	-	-	-
Indion 214 (gm)	-	-	-	-	-	-	1	2	3	-	-	-	-	-	-	-	-	-
Indion 204 (gm)	-	-	-	-	-	-	-	-	-	1	2	3	-	-	-	-	-	-
Indion 254 (gm)	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3	-	-	-
Indion 234 (gm)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	1	2	3
Dextromethorphan HBr (DXM) (mg)	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400
Phenylephrine Hcl (PHE) (mg)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200
Chlorpheniramine Maleate (CPM) (mg)	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80	80
Sorbitol Solution 70% Non-Crystallising (gm)	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10	10
Methyl Paraben (mg)	360	360	360	360	360	360	360	360	360	360	360	360	360	360	360	360	360	360
Xanthan gum (mg)	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
Propyl Paraben (mg)	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40	40
Di-Sodium edetate (mg)	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100	100
Colour Ponceau 4R (mg)	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320	1320
Flv. Raspberry	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400	400
Final volume with Water (ml)	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200	200

3.9.2 Evaluation of Different Trials Taste Masked Suspension

3.9.2.1 DRC Drug load evaluation by High-performance liquid chromatography (HPLC)

Chromatographic Condition: After multiple trails with different ratio of mobile phase, different wavelength, different flow rate following testing parameter has been set to achieve the required target (table 3.4 & 3.5).

Table 3.4 Chromatographic condition followed.

Stationary Phase (HPLC-Column)	Waters, C18, 50mm length 4.6mm of inner diameter, 3.5µ of particle size
Mobile Phase	Gradient Programming of Aqueous Phase (pH 3.0) & Acetonitrile.
Detection	Wavelength max of 265 nm
Flow-Rate	1.0 ml/mins.
Injection-Volume	20µl of injection
Column-Temperature	25°C i.e. Ambient-Temperature
Run Time	7.5 mins.
Diluent	60:40 ratio mixture of Water & Acetonitrile

Gradient Parameter:

Table 3.5 HPLC Gradient programming.

Time (in mins)	Flow rate (ml/min)	Buffer (%)	Acetonitrile (%)
0.00	1.5	95.0	5.0
4.50	2.0	50.0	50.0
5.50	1.5	95.0	5.0
7.50	1.5	95.0	5.0
7.51	1.5	95.0	5.0

Mobile Phase buffer preparation: Buffer prepared by adding 1.725gm of Ammonium Dihydrogen phosphate and 7.5gm of Potassium Nitrate in 1500ml of mill-Q water and Ph adjusted to 3.0 with help of ortho-phosphoric acid (OPA) (10%) solution.

Reference solution preparation: Reference-solution was prepared by weighing 100mg of Phenylephrine Hcl (PHE) & 40mg of Chlorpheniramine Maleate (CPM) in 100ml volumetric flask and added 30ml diluent. Sonication was done up to dissolve and then makeup to the mark with diluent.

Further Reference solution was prepared be adding 50mg Dextromethorphan HBr (DXM) in 50ml volumetric flask and added 30ml diluent. Sonication was done up to dissolve and then makeup to the mark.

Further 5ml of each A & B Reference solution diluted to 50ml with diluent. Concentration obtained was Dextromethorphan HBr (DXM) was 1000mcg/ml, Phenylephrine Hcl (PHE) was 100mcg/ml of Chlorpheniramine Maleate (CPM) was 40mcg/ml.

Sample solution preparation: The drug resin complex formed are filtered with Whatman filter paper no. 1 and the filtrate obtained are used for analysis. The filtrate solution of containing 4mg of CPM (about 10ml) was taken into a 100ml volumetric

flask and 30ml diluent added and sonicated for 10mins. After that diluted to mark with diluent and filtered. The concentration obtained was same as standard solution i.e. Concentration obtained was Dextromethorphan HBr (DXM) 1000mcg/ml, Phenylephrine Hcl (PHE) 100mcg/ml of Chlorpheniramine Maleate (CPM) 40mcg/ml.

On HPLC; Injection volume of 20µl was injected of a blank, five replicate of standard, two injections of test solution and one repeated of standard solution as bracketing std. Following system suitability parameters was complies as ICH guidelines (table 3.6),

Table 3.6 System Suitability Parameters

Parameters	**Limit Maintained**
Relative Standard Deviation (RSD) for 5 replicate Std (for each API)	Not more than 2.0%
USP Tailing for Phenylephrine Hcl (PHE)	Not more than 3.0
USP Tailing for Chlorpheniramine Maleate (CPM)	Not more than 3.0
USP Tailing for Dextromethorphan HBr (DXM)	Not more than 3.0

3.9.2.2 Assay evaluation of obtained oral suspension of different trials:

Assay done by using all same method mention under DRC Durg load evaluation by High-performance liquid chromatography (HPLC). The only difference is in sample preparation. Here, I have taken 10ml of obtained oral suspension without filtrate after proper shaking the oral suspension.

3.9.2.3 Oral suspension Colour Evaluation

Colour evaluation of ion exchange resin taste-masked oral suspension is crucial for ensuring product quality and patient acceptance. The assessment involves scrutinizing the suspension's colour intensity, uniformity, and any deviation from the expected hue. The presence of unwanted coloration could signify impurities or degradation, potentially affecting both safety and efficacy. Consistency in colour across batches is imperative to maintain product identity and reliability. Furthermore, colour plays a significant role in patient perception, influencing their trust and willingness to consume the medication. Therefore, meticulous colour evaluation protocols must be established and adhered to throughout the manufacturing process to uphold the standards of taste masking and overall product quality.

The process of colour evaluation for ion exchange resin taste-masked oral suspension involves several steps to ensure accurate assessment and quality control. Firstly, a standard reference colour chart or spectrophotometer is used to establish a baseline for

the expected colour of the suspension. Samples from different batches are then visually inspected under standardized lighting conditions to detect any variations in colour intensity, hue, or uniformity. Any deviations from the reference standard are noted and investigated further to determine their cause, whether it be impurities, degradation, or formulation inconsistencies. Spectrophotometric analysis may also be employed to quantitatively measure colour attributes and ensure objective evaluation.

3.9.2.4 pH evaluation

The pH evaluation of ion exchange resin taste masked oral suspension is crucial for ensuring both stability and palatability of the formulation. By carefully assessing the pH, formulators can determine whether the suspension is within the optimal range for the ion exchange resin to effectively mask the taste of the active pharmaceutical ingredient (API) while maintaining its integrity. A pH that is too high or too low could compromise the resin's ability to bind with the unpleasant-tasting compounds, affecting the overall taste masking efficacy. Additionally, pH plays a significant role in the stability of the suspension, preventing issues such as sedimentation or aggregation of particles. Thus, meticulous pH evaluation is essential to guaranteeing the efficacy, stability, and acceptability of the taste-masked oral suspension.

The obtained different trials oral suspension was examined pH value under room temperature with pH Meter of make Spectra lab (Model: Accu pH-3).

3.9.2.5 Sedimentation volume evaluation

Sedimentation volume evaluation is a crucial parameter in assessing the stability and efficacy of ion exchange resin taste-masked oral suspensions. This evaluation method involves measuring the volume of sediment formed over a specified period, typically 24 hours, after the suspension is left undisturbed. Sedimentation volume indicates the tendency of particles to settle down, which can impact the uniformity of drug dispersion and affect dosing accuracy. For ion exchange resin-based formulations aimed at masking unpleasant tastes, maintaining a low sedimentation volume is essential to ensure homogeneity and consistent drug delivery. High sedimentation volumes may suggest

inadequate dispersion or particle aggregation, potentially leading to dose variability and compromised therapeutic outcomes. Thus, meticulous monitoring and optimization of sedimentation volume are imperative during the formulation and development of taste-masked oral suspensions utilizing ion exchange resins.

3.10 Methodology Used for Optimization of concentration of Indion 234:

3.10.1 Formulation of different oral suspension using different concentration of Indion 234 Ion Exchange Resin:

3.10.1.1 Preparation of Drug syrup Solution:

As the drugs as freely soluble in water, due to this reason drug solution prepared in distilled water. All API of desire quantity as per table 1 of Dextromethorphan HBr (DXM), Phenylephrine Hcl (PHE) & Chlorpheniramine Maleate (CPM) were accurately weight and all taken in 200ml volumetric flask. Then added about 20ml distilled water and sonicated up-to dissolved. Then added 80ml of distilled water. Then required excipients except resin added as given in table 1. After that added 80ml distilled water in continuous stirring condition and pH adjusted to 6 to 7 using 10% potassium hydroxide solution. Then makeup to 200ml with distilled water.

3.10.1.2 Preparation of drug resin complex (DRC) suspension*:*

Drug syrup solution and resin were accurately weighed in required ratio as given in table 1. The slurry of resin was made in 200ml Drug syrup solution in 250ml beaker and magnetic stirred condition. Then the obtained solution pH adjusted between 6 to 7 with the help of 10% potassium hydroxide solution The drug resin mixture was continuously stirred for 4 to 5 hours (table 3.7).

Table 3.7 Different 12 no's trials composition with different concentration of Indion 234 Resins

Ingredients/Trials	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Indion 234 (mg)	170	340	510	680	850	1020	1190	1360	1530	1700	1870	2040
Ratio of total API's (680mg) against Resin	**01:00.0**	**01:00.5**	**01:00.7**	**01:01.0**	**01:01.3**	**01:01.5**	**01:01.8**	**01:02.0**	**01:02.2**	**01:02.5**	**01:02.8**	**01:03.0**
Dextromethorphan HBr (DXM) (mg)	400	400	400	400	400	400	400	400	400	400	400	400
Phenylephrine Hcl (PHE) (mg)	200	200	200	200	200	200	200	200	200	200	200	200
Chlorpheniramine Maleate (CPM) (mg)	80	80	80	80	80	80	80	80	80	80	80	80
HPMC (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Sucrose (gm)	10	10	10	10	10	10	10	10	10	10	10	10
Xanthan gum (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Sodium Benzoate (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Colour Ponceau 4R (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Flv. Peppermint (mg)	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000	1000
Final volume with Water (ml)	200	200	200	200	200	200	200	200	200	200	200	200

3.11 Method used for different Evaluation Parameters

A comprehensive evaluation was carried out to assess the performance, palatability, and analytical integrity of the developed taste-masked oral suspension containing Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate. The study was conducted using a combination of instrumental analysis and in-vitro testing

techniques in alignment with regulatory standards. The key parameters evaluated in this phase were:

3.11.1 For Taste Evaluation using Electronic Tongue (E-tongue)

Taste masking effectiveness is a critical parameter in the development of paediatric and geriatric dosage forms. In this project, taste evaluation was conducted exclusively using the Electronic Tongue (E-tongue), an advanced and objective tool capable of simulating human gustatory perception.

I. The E-tongue analysis was carried out at CSIR–Central Food Technological Research Institute (CFTRI), Mysuru, Karnataka.

II. The instrument uses a sensor array that mimics human taste buds to detect the intensity of bitterness or other sensory perceptions.

III. Reference standards (placebo, pure API solutions, and optimized suspension) were used for comparison.

IV. The bitterness suppression index (BSI) was calculated to quantify the extent of taste masking.

3.11.2 For Drug Content and Assay by HPLC

The quantitative determination of each API (DXM, PHE, CPM) in the final suspension and in drug-resin complexes was carried out using High-Performance Liquid Chromatography (HPLC).

As per dissolution method (table 3.8)

Standard Preparation:

Stock A: Weigh accurately about 40 mg of Chlorpheniramine maleate and 100 mg of Phenylephrine Hydrochloride working standard into 100 ml of volumetric flask. Sonicate to dissolve and dilute up to mark with diluents.

Stock B: Weigh accurately about 50 mg of Dextromethorphan Hydrobromide working standard into 25 ml of volumetric flask. Sonicate to dissolve and dilute up to mark with diluents. Dilute 5.0 ml of each stock A & B solution to 50 ml with diluents.

(Concentration: Chlorpheniramine maleate 40 mcg/ml; Dextromethorphan Hydrobromide 200 mcg/ml: Phenylephrine Hydrochloride 100 mcg/ml)

Sample Preparation:

Pipette sample equivalent to 4 mg of Chlorpheniramine maleate (about 10ml of sample after proper shaking sample bottle) in 100 ml volumetric flask. Add about 10ml of 0.1N Hcl and magnetic stirrer for about 10 minutes and soninate for 10 minutes and dilute to volume with diluent. Filter through 0.45µ nylon membrane and filter with 0.45 µ membrane filter. (Concentration: Chlorpheniramine maleate 40 mcg/ml; Dextromethorphan Hydrobromide 200 mcg/ml: Phenylephrine Hydrochloride 100 mcg/ml). Procedure: Inject 20 µl of blank, inject 20 µl standard solution in five replicate and inject 20 µl of test solutions into the system and record the peak responses.

System Suitability Test:

Parameters Acceptance Criteria Relative standard deviation (for 5 replicate injections) Not more than 2.0% USP Tailing for Chlorpheniramine maleate Not more than 3.0 USP Tailing for Dextromethorphan Hydrobromide Not more than 3.0 USP Tailing for Phenylephrine Hydrochloride Not more than 3.0.

3.11.3 In-vitro Dissolution Testing

Table 3.8 Dissolution Parameters used

Parameter	Specification
Dissolution Medium	0.1 N HCl
Apparatus	USP Type II (Paddle)
RPM	50 rpm
Temperature	37 ± 0.5°C
Volume	900 ml
Duration	45 minutes

Preparation of 0.1N HCL: Dissolve 8.5ml of conc. Hydrochloric acid in 1000 ml of Purified water (table 3.9 & 3.10).

Table 3.9 Chromatographic Condition used

Parameter	Specification
Column	Luna C18 (50 mm × 4.6 mm, 3.5 or 5 µm) or equivalent
Mobile Phase	Phosphate buffer (pH 3.0): Acetonitrile (Gradient)
Detection Wavelength	265 nm
Flow Rate	1.5 ml/min & 2.0 ml/min (as per gradient)
Column Temperature	30°C
Injection Volume	30 µl
Diluent	Water: Acetonitrile (60:40)
Run Time	10 minutes

Table 3.10 Gradient program followed

Time (min)	Flow Rate (ml/min)	Phosphate Buffer (%)	Acetonitrile (%)
0.01	1.5	95	5
4.5	2	55	45
6.5	1.5	95	5
10	1.5	95	5

Phosphate Buffer pH 3.0: Buffer: solution prepared by adding 1.15g of Ammonium dihydrogen phosphate and 5 g potassium nitrate in 1000 ml of water adjust pH to 3.0 with 10% of ortho-phosphoric acid.

Standard Solution preparation: Weigh accurately about 111mg of Dextromethorphan HBr, 55mg of Phenylephrine Hydrochloride & 22mg of Chlorpheniramine maleate working standard into 100 ml of volumetric flask. Sonicate to dissolve and dilute up to mark with diluents. Further dilution done by diluting 2.0 ml of this solution to 200 ml with dissolution media. (Concentration: Chlorpheniramine maleate 2.2mcg/ml; Phenylephrine Hydrochloride 5.5mcg/ml; Dextromethorphan HBr 11mcg/ml)

Dissolution Sample preparation: Weigh accurately pre-well mixed oral suspension sample equivalent to 2 mg of Chlorpheniramine maleate (about 5gm) and filter the ion

exchange resin taste masked oral suspension with 0.45µm nylon filter paper and wash with of water to remove adsorbed API. Then wash the retented substance of filter in 900ml dissolution media equilibrated to the temperature of 37°C ± 0.5°C start and run for 45 minutes. After 45 minutes withdraw 10ml sample from a zone midway between the surface of the medium and top of the rotating Paddle and not less than 1 cm from the vessel wall and filter through nylon membrane filter paper of 0.45µm pore size.

Sequence of injection: 1. System suitability (single) 2. Blank (single) 3. Reference solution (five replicate) 4. Test solution (in single for each six sample) 5. Bracketing standard (single)

Procedure: Equilibrate the column with mobile phase & check for proper base line. Inject the blank solution (in single) into the liquid chromatograph & record the chromatogram. Inject 30 µl of blank, inject 30 µl standard solution in five replicate and inject 30 µl of test solutions into the system and record the peak responses.

System Suitability Test: Inject reference solution in to the liquid chromatograph and record the chromatogram. The test is not valid unless the column efficiency for both analytes is not less than 2000 theoretical plates, the tailing factor is not more than 2.0, Inject replicates of reference solution. The relative standard deviation for five replicate injection is not more than 2.0%.

Inject the test solution (in single for each) & reference solution in single (bracketing) into the liquid chromatograph & record the chromatograms.

Parameters Acceptance Criteria RSD for each Components (for 5 replicate injections) Not more than 2.0% USP Tailing for Chlorpheniramine maleate Not more than 3.0 USP Tailing for Dextromethorphan Hydro bromide Not more than 3.0 USP Tailing for Phenylephrine Hydrochloride Not more than 3.0.

Typical Retention times: Compound Name RT (min) Phenylephrine About 0.9 Chlorpheniramine About 3.4 Dextromethorphan HBr About 3.8

Procedure: Separately inject 20 µl of the blank solution (single) and reference solution (replicate five injections) into the chromatograph, record the chromatograms and measure the responses for the major peaks.

Acceptance Criteria: The relative standard deviation of area for five replicate injections of reference solution should not be more than 2.0 %. Tailing factor: Should not be more than 2.0 Record the details in analytical method validation report.

For both assay and dissolution evaluation used the chromatographic condition mention under 4.2.1.

3.11.4 Related Substances or Impurity Profiling

Detection of related substances and degradation products was carried out using HPLC based on ICH Q3B guidelines for impurities in new drug products.

I. Chromatographic methods with extended run times were used to detect any unknown peaks.

II. Stress testing (acidic, basic, thermal, oxidative conditions) was also conducted to evaluate formulation stability.

III. No significant increase in impurity levels was observed, confirming the chemical stability of the drug-resin complexes in suspension.

Method for Related Substance analysis

Selecting the right chromatographic conditions is an important step in achieving efficient separation and accurate results. This process begins by understanding the sample and the goal—such as separating components based on polarity or size. First, the stationary phase is selected, commonly a reverse-phase column like C18, depending on the chemical nature of the analytes. Next, the mobile phase is chosen, which includes one or more solvents. In liquid chromatography, the solvent's polarity, pH, and composition can greatly affect retention time, resolution, and peak shape.

Several trials are performed by changing parameters like flow rate, column temperature, mobile phase composition, and pH to find the most effective combination. Flow rate affects how quickly the sample moves through the column, and temperature can influence solvent viscosity and overall separation quality. Detection wavelength is also selected based on the analyte's absorbance.

Trial runs help detect issues like peak tailing or broadening and allow fine-tuning of the method. Adjustments such as changing gradient programs or solvent strength are made to improve results. Through this trial-and-error approach, robust and reliable conditions are established to ensure high resolution, accurate measurement, and reproducibility for the specific analysis.

3.11.4.1 Chromatographic Conditions with Gradient Programming

The chromatographic analysis was carried out using a gradient elution method optimized for accurate separation and quantification. A Waters X-Bridge column packed with BEH Technology C18 material was employed. The column dimensions were 150 mm in length and 4.6 mm internal diameter, with a particle size of 3.5 µm (Part No: 186003034). This column was selected due to its high efficiency, stability, and suitability for reversed-phase gradient chromatography.

3.11.4.2 Mobile Phase Buffer Preparation

The buffer solution for the mobile phase was prepared by dissolving 1.6 g of Butane Sulphonic Acid Sodium Salt in 1000 mL of milli-pore water. The pH of this buffer was adjusted to 3.0 using orthophosphoric acid. This acidic pH ensured better peak shapes and consistent retention of the analytes.

3.11.4.3 Gradient Program

A binary gradient elution was developed using 100% Buffer Phase (pH 3.0) and 100% Acetonitrile, applied over a total run time of 70 minutes (table 3.11).

The programmed gradient timeline is as follows:

Table 3.11 Related Substance programmed gradient timeline

Time (min)	Buffer (%)	Acetonitrile (%)
0.01	90	10
10	90	10
55	45	55
60	90	10
70	90	10

This gradient enabled selective elution of all components with sharp, symmetrical peaks and adequate resolution.

3.11.4.4 Detection and Instrument Settings

I. Detection Wavelength: 265 nm (selected based on the UV absorbance maxima of the APIs)

II. Flow Rate: 1.2 mL/min

III. Injection Volume: 20 µL

IV. Column Oven Temperature: Maintained at 35°C to improve chromatographic reproducibility

V. Autosampler Temperature: Set at 15°C to preserve sample integrity during analysis

VI. Total Run Time: 70 minutes to allow complete elution and separation of all analytes

Diluent Composition

The diluent used for standard and sample preparations was a mixture of Buffer and Methanol in a 50:50 ratio, ensuring solubility of all components and compatibility with the mobile phase.

0.1 N HCl Preparation

For related sample or pretreatment needs, 0.1 N Hydrochloric Acid was prepared by diluting 8.5 mL of concentrated HCl to 1000 mL with purified water, following standard volumetric dilution protocols.

This optimized gradient method was found to be robust, reproducible, and suitable for the intended analysis of pharmaceutical formulations involving multiple APIs.

Preparation of Solutions

Stock Solutions

(a): 100 mg of Dextromethorphan Hydrobromide in 100 mL volumetric flask using diluent.

(b): 20 mg of Chlorpheniramine Maleate in 100 mL using diluent.

(c): 50 mg of Phenylephrine Hydrochloride in 100 mL using diluent.

(d): 1 mg each of Phenylephrine related comp. C, D, E and Dextromethorphan related comp. B, C in 20 mL flask, make up to 100 mL using diluent.

Standard Solution

Take 1 mL each of stock solutions a, b, c, and d into a 200 mL volumetric flask and make up with diluent.

Final concentrations are Dextromethorphan HBr: 5 µg/mL, Chlorpheniramine Maleate: 1 µg/mL

Phenylephrine HCl: 2.5 µg/mL, Impurities: Present

Test Solution

I. Weigh 25 g of oral suspension (equivalent to 50 mg Dextromethorphan HBr) into 100 mL volumetric flask.

II. Add 5 mL of 0.1 N HCl, sonicate for 10 minutes, and dilute with diluent.

III. Filter through 0.45 µm nylon membrane.

Final concentrations are Dextromethorphan HBr: 500 µg/mL, Chlorpheniramine Maleate: 100 µg/mL and Phenylephrine HCl: 250 µg/mL.

Placebo Solution

I. Weigh 25 g of placebo syrup into 100 mL volumetric flask.

II. Add 5 mL of diluent, sonicate for 10 minutes, and make up with diluent.

III. Filter through 0.45 µm nylon membrane.

Procedure: Equilibrate the column with mobile phase & check for proper baseline. Inject diluent as blank solution (in single), Placebo (in Single), standard solution (in six replicate) and test solution (in Single).

3.11.4.5 Summary of Evaluation Tools and Parameters (table 3.12),

Table 3.12 Summary of Evaluation Tools and Parameters

Parameter	Method Used	Purpose
Taste Evaluation	E-tongue (Sensor array)	Bitterness masking quantification
Drug Assay & Content	HPLC (validated per ICH Q2)	Quantification and uniformity
Dissolution Testing	USP Type II Dissolution Apparatus	Drug release profile at different pH levels
Related Substances	HPLC (ICH Q3B guidelines)	Stability and impurity profiling

3.12 Characterization Studies of DRC

To confirm the successful formation of the Drug-Resin Complex (DRC) and to understand its physicochemical behaviour, comprehensive characterization studies were conducted using multiple instrumental techniques. These analytical tools helped in verifying the interaction between the drug and resin, changes in the thermal and crystalline properties, and alterations in surface morphology post-complexation. The instruments used in this study included FTIR, DSC, XRD, TGA, and SEM.

All characterization tests (except SEM) were performed at the Central Instrumentation Facility (CIF), Lovely Professional University (LPU), Punjab, and SEM analysis was conducted using facilities provided by the School of Pharmaceutical Sciences, LPU.

3.12.1 Fourier Transform Infrared Spectroscopy (FTIR)

FTIR spectroscopy was used to detect possible chemical interactions between the drug molecules and the ion exchange resin.

I. Spectra were recorded for pure APIs, plain resin, physical mixtures, and the DRCs.

II. Characteristic functional groups such as –OH, $–NH_2$, –C=O, and –C–N stretching vibrations were monitored.

III. Shifts or disappearance of key peaks in the DRC spectrum compared to individual components suggested complexation via ionic or hydrogen bonding.

3.12.2 Differential Scanning Calorimetry (DSC)

DSC was used to assess thermal transitions such as melting point, glass transition, or decomposition temperatures.

I. Sharp endothermic peaks observed for pure drugs (e.g., melting points of DXM, CPM, PHE) were reduced or disappeared in the DRC thermograms.

II. This indicated entrapment of drugs in the resin matrix, suggesting a molecular dispersion or amorphization.

III. The absence of drug melting peaks in the DRC proved that the drugs were no longer in their free crystalline form.

3.12.3 X-Ray Diffraction (XRD)

XRD analysis was performed to investigate the crystallinity of the drug in its complexed form.

I. Pure APIs exhibited characteristic sharp diffraction peaks representing their crystalline nature.

II. The DRCs showed amorphous halos or significantly reduced peak intensities, indicating a loss of crystallinity after complexation.

The change in crystallinity was essential for:

- Enhancing taste masking (since crystalline drug is more likely to dissolve in saliva)
- Improving drug-resin binding efficiency.

3.12.4 Thermogravimetric Analysis (TGA)

TGA was used to measure weight loss patterns during thermal degradation, which provided insight into the thermal stability of the formulations.

I. TGA curves of DRCs showed altered degradation profiles compared to pure drugs or resins.

II. Initial weight loss below 100°C was attributed to moisture content.

III. Major degradation steps occurred at higher temperatures, which differed in onset and rate compared to pure drugs, confirming changes in thermal behaviour due to complex formation.

3.12.5 Scanning Electron Microscopy (SEM)

SEM analysis was conducted to examine the surface morphology of the resins before and after drug loading.

I. Pure resins had rough, porous structures with irregular particle shapes.

II. After complexation, the surface of the DRC appeared smoother and less porous, indicating the adsorption or ion-exchange of drugs onto the resin.

III. SEM imaging helped visualize physical differences between unbound and drug-bound resin particles (table 3.13).

Table 3.13 Summary of Characterization Tools and Purpose

Technique	Purpose	Key Observations
FTIR	Drug-resin interaction (chemical bonding evidence)	Shifts/loss of functional group peaks
DSC	Thermal behaviour and compatibility	Disappearance of melting peaks
XRD	Crystallinity assessment	Reduced peak intensity or amorphous halo
TGA	Thermal degradation profile	New degradation steps in DRC
SEM	Surface morphology and structural confirmation	Change in texture, smoother surfaces post-drug loading

3.13 Stability Studies

Stability testing is a critical component in pharmaceutical formulation development, ensuring that the dosage form maintains its intended safety, efficacy, and palatability over the proposed shelf life. For this study, the optimized taste-masked oral suspension

containing Dextromethorphan Hydrobromide (DXM), Phenylephrine Hydrochloride (PHE), and Chlorpheniramine Maleate (CPM) complexed with Indion 234 resin, was subjected to a six-month stability protocol based on ICH Q1A(R2) guidelines.

The objective of these stability studies was to assess:

I. Chemical stability: Drug content and degradation product profiling

II. Physical stability: pH, colour, viscosity, re-dispersibility

III. Palatability retention: Taste evaluation using an Electronic Tongue (E-tongue)

3.13.1 Storage Conditions

The samples of the final suspension were stored under the following three controlled conditions:

I. Refrigerated Condition:
   - Temperature: 2–8°C
   - Storage Environment: Cold storage chamber

II. Room Temperature (Long-term Condition):
   - Temperature: 25 ± 2°C, Relative Humidity (RH): 60 ± 5%
   - Storage Duration: 6 months

III. Room Temperature (Intermediate Condition):
   - Temperature: 30 ± 2°C, Relative Humidity (RH): 75 ± 5%
   - Storage Duration: 6 months

IV. Accelerated Condition (Accelerated stability testing):
   - Temperature: 40 ± 2°C, RH: 75 ± 5%
   - As per ICH guidelines to simulate extreme conditions

All samples were stored in amber-coloured bottles to protect from light degradation and were tightly sealed to avoid moisture ingress.

3.13.2 Sampling Time Points

Samples were withdrawn and evaluated at the following stability intervals:

I. Initial (0 Month)

II. 1st Month

III. 3rd Months

IV. 6th Months

3.13.3 Evaluation Parameters

The samples were assessed using a combination of physical, chemical, and sensory parameters, as detailed below:

3.13.3.1 Drug Content and Degradation Products (by HPLC)

I. HPLC was used to evaluate the assay of DXM, PHE, and CPM in the suspension.

II. Degradation products were monitored using extended HPLC runs and compared against baseline chromatograms of fresh samples.

III. Results were assessed against ICH limits for related substances (typically NMT 0.5% for individual impurity, and NMT 2.0% total impurities).

3.13.3.2 Physical Parameters

I. pH: Measured using a calibrated digital pH meter. Any drastic shifts in pH could indicate chemical degradation or interaction.

II. Viscosity: Evaluated using a Brookfield viscometer. Ensured consistent pourability and dosing.

III. Colour: Visually inspected and compared to the baseline to detect oxidative or photo-degradation.

IV. Re-dispersibility: Assessed manually by inverting the bottle 10 times and checking for ease of uniform redispersion without lumps or sediment clumping.

3.13.2.3 Taste Evaluation (Electronic Tongue)

I. Taste analysis was repeated at each stability point using the E-tongue system to assess whether the bitterness masking was retained over time.

II. The bitterness response index (BRI) was calculated and compared with initial values to ensure no degradation-related unmasking of API bitterness.

3.14 Method for Price Comparison with Marketed Samples

3.14.1 Materials Required

I. Market data of commercially available oral syrups containing the same combination of APIs.

II. Details of raw material costs used in the formulation (API, resin, excipients).

III. Packaging and manufacturing cost estimates.

IV. Access to online and local pharmacy price listings.

3.14.2 Methodology

Step 1: Selection of Comparable Marketed Products

Identify and list 5 marketed syrup formulations containing:

I. Dextromethorphan HBr (10 mg/5 mL)

II. Phenylephrine HCl (5 mg/5 mL)

III. Chlorpheniramine Maleate (2 mg/5 mL)

Note down:

I. Brand name:

II. Manufacturer

III. Labelled strength

IV. Volume per bottle

V. Maximum retail price (MRP)

VI. Source of data (e.g., pharmacy, official websites, online platforms)

Step 2: Calculation of Market Price per mL

I. Convert MRP into price per mL for each brand.

II. Calculate average price per mL for the selected marketed products.

Step 3: Costing of the Formulated Product

Determine the cost of raw materials used in 100 mL of the developed formulation:

I. APIs (based on procurement price)

II. Ion exchange resin (e.g., Indion 234)

III. Excipients (suspending agents, sweeteners, preservatives, flavouring agents)

IV. Packaging materials

V. Estimated processing/manufacturing costs

Total all cost components to derive the cost per 100 mL and cost per mL of the formulated product.

Step 4: Comparative Analysis

I. Compare the cost per mL of the formulated product with the average market price per ml.

II. Present the comparison in tabular and graphical format for better visualization.

Step 5: Documentation

I. Maintain records of price sources, quotations, and cost estimates.

II. Use a standardized Excel sheet to tabulate data for reproducibility.

3.15 Additional Parameters Evaluation methods

3.15.1 Uniformity of Dosage Units (By content uniformity As Per Assay)

Standard Preparation: As given under Assay preparation. Sample preparation:

Pipette sample equivalent to 2 mg of Chlorpheniramine maleate (about 5ml of sample after proper shaking of bottle) in 50 ml volumetric flask. Add about 5ml of 0.1N Hcl and magnetic stirrer for about 10 minutes and soninate for 10 minutes and dilute to volume with diluent. Filter through 0.45µ nylon membrane and filter with 0.45 µ membrane filter. Repeat this procedure another 9 samples. (Concentration: Chlorpheniramine maleate 40 mcg/ml; Dextromethorphan Hydrobromide 200 mcg/ml: Phenylephrine Hydrochloride 100 mcg/ml)

Procedure: Equilibrate the column with mobile phase and check for proper base line. Inject the diluent as blank solution (in single), standard solution (in five replicate), test solution (in single for each) and standard solution in single (bracketing) into the liquid chromatograph and record the chromatograms.

System Suitability: The test is not valid unless the column efficiency is not less than 2000 theoretical plates, the tailing factor is not be more than 2.0 and the relative standard deviation for five replicate injections should be not more than 2.0% (table 3.14).

Table 3.14 Calculation of Standard Deviation

S. No.	Content per Unit (Xi)	Xi - $\bar{X}$	(Xi - $\bar{X}$) ²
1	X1	X1 – $\bar{X}$	(X1 – $\bar{X}$) ²
2	X2	X2 – $\bar{X}$	(X2 – $\bar{X}$) ²
3	X3	X3 – $\bar{X}$	(X3 – $\bar{X}$) ²
4	X4	X4 – $\bar{X}$	(X4 – $\bar{X}$) ²
5	X5	X5 – $\bar{X}$	(X5 – $\bar{X}$) ²
6	X6	X6 – $\bar{X}$	(X6 – $\bar{X}$) ²
7	X7	X7 – $\bar{X}$	(X7– $\bar{X}$) ²
8	X8	X8 – $\bar{X}$	(X8 – $\bar{X}$) ²
9	X9	X9 – $\bar{X}$	(X9 – $\bar{X}$) ²
10	X10	X10– $\bar{X}$	(X10 – $\bar{X}$) ²

Average Value ($\bar{X}$) = $\Sigma Xi / 10$

Standard Deviation (s) = $\sqrt{[\Sigma(Xi - \bar{X})^2 / (n - 1)]}$

Acceptance Criteria (as per Pharmacopoeia Guidelines):

Use one of the following limits depending on the Stage (L1 or L2) of acceptance testing:

L1: $M=X^{-}+k\cdot sM = \bar{X} + k \cdot sM=X^{-}+k\cdot s$

M = Maximum allowed content

$\bar{X}$ = Mean of 10 units

k = Acceptability constant (as per pharmacopeia)

s = Standard deviation

All 10 individual results must fall within 85–115% of label claim. If one unit is outside this but within 75–125%, perform L2 testing (20 units total) as per ICH/USP/Ph. Eur.

3.15.2 Estimation of Preservative Content: Sodium Benzoate, Methyl Paraben and Propyl Paraben (By HPLC) (table 3.15),

Table 3.15 Chromatographic Conditions for preservative analysis

Parameter	Specification
Column	Betasil C18 (250 × 4.6 mm, 5 µm) or equivalent
Flow Rate	1.5 ml/min
Detector Wavelength	255 nm
Column Temperature	25°C
Sample Temperature	25°C
Injection Volume	10 µl
Run Time	50 minutes
Diluent	Milli-Q water
Needle Wash	Methanol: Water (90:10 v/v)
Seal Wash	Methanol: Water (10:90 v/v)

Gradient Program used

Mobile Phase (A): Water.

Mobile Phase (B): Methanol and Acetonitrile in the ratio of 90: 10 %v/v and mix well (table 3.16).

Table 3.16 Preservative analysis gradient program

Time (min)	Mobile Phase A (% v/v)	Mobile Phase B (% v/v)
0	45	55
12	60	40
15	50	50
20	45	55
50	45	55

Preparation of standard solution: Weigh & transfer about 50mg Sodium Benzoate, 50 mg Sodium methyl paraben and 25 mg Sodium propyl Paraben working standard into 50ml volumetric flask, add 30 ml of diluent and sonicate to dissolve, make up with diluent and mix well. Further dilute 5 ml of solution into 50 ml volumetric flask, make up with diluent and mix well.

Sample preparation: Weigh of sample solution equivalent to 5 mg of Sodium methyl paraben (weigh about 6.0 g sample solution) into 50ml volumetric flask, added 30 diluents, sonicated for 20 minutes with intermittent shaking, then cool to room temperature and make up with diluented and mix well. Filter through 0.45µm nylon filter by discarded about first 5 ml. (Concentration: Sodium methyl paraben 100 µ/ml & Sodium propyl Paraben 50 µ/ml).

Procedure: Equilibrate the column with mobile phase and check for proper base line. System Suitability: Injected standard solution in five replicates into the liquid chromatograph and record the chromatograms. Injected the Blank (single), and test solution (in duplicate). The relative standard deviation five replicate injections and bracketing area should be not more than 2.0%. Measure the responses for major peak areas of standard and test solution.

3.15.3 Estimation of Diethylene Glycol and Ethylene Glycol:

Diluent: Acetone and water (96:4)

Standard solution: Weigh & transfer 80mg of Diethylene Glycol Reference/working standard and 80 mg of Ethylene Glycol Reference/working standard in 100 ml volumetric flask, add 50 ml of diluent & mix. Make up the volume with 100 ml of diluent.

Sample solution: Transfer 2.0 g of sample solution to a 25-mL volumetric flask. Add 10 mL of Diluent to the flask, mix, shake for 5 minutes and make the volume 25 ml with diluent. Filter through a 0.45-µm nylon filter. Discard the first 2 mL of the filtrate, and collect the rest of the filtrate for analysis.

GC Chromatographic system (Testing done at a Government Approved Lab):

Mode: GC Detector: Flame ionization Column: 0.32-mm x 30m fused-silica capillary column, 0.25µm Temperature: Detector: 300ºC Injector port: 240ºC.

Table 3.17 Column Oven Temperature Program of GC

Step	Initial Temp (°C)	Ramp (°C/min)	Final Temp (°C)	Hold Time (min)
1	70	—	70	2
2	70	50	300	5

Carrier gas: Helium Flow rate: 3.0 ml/minute Injection size: 1.0 µl/ml Injection type: Split injection. The split ratio is about 10:1. [NOTE- A split liner, deactivated with glass wool, is used] System suitability: Sample: Standard solution [NOTE – Diethylene glycol elutes after ethylene glycol in chromatogram.]

Suitability requirements: Resolution: Not less than 20 between ethylene glycol and Diethylene glycol.

Standard solution and Sample solution based on the Standard solution, identify the peaks of ethylene glycol and diethylene glycol. Compare peak areas of ethylene glycol and diethylene glycol in the Standard solution and the Sample solution (table 3.17).

CHAPTER 4

4.0 RESULTS AND DISCUSSION

4.1 Preliminary Trials for Resin Screening

Work Relative to Objective 01 & 02. "Development of effective taste-masking suspension using ion exchange resin. & Improvement of oral medication palatability to achieve patient acceptability and compliance."

The preliminary screening of ion exchange resins was a foundational part of this research, aimed at identifying the most suitable resin for effectively masking the bitter taste of the selected active pharmaceutical ingredients (APIs)—Dextromethorphan Hydrobromide (DXM), Chlorpheniramine Maleate (CPM), and Phenylephrine Hydrochloride (PHE). These APIs, commonly used in over-the-counter cold and cough formulations, are known for their intense bitterness, which significantly affects patient acceptability, especially in paediatric and geriatric populations. Therefore, selecting the right resin was a critical step to ensure optimal taste-masking and therapeutic effectiveness.

4.1.1 Objective of Resin Screening

The primary objective of this trial was to evaluate and compare the taste-masking performance of six different pharmaceutical-grade ion exchange resins:

I. Kyron T-114
II. Kyron T-314
III. Indion 204
IV. Indion 214
V. Indion 234
VI. Indion 254

These resins were chosen based on their cationic exchange capacity, previous literature references, and suitability for suspension formulations. Some were gifted by ADPL (Haridwar, Uttarakhand), while others were provided by Ion Exchange India, along with valid Certificates of Analysis.

4.1.2 Parameters Evaluated

To determine the most effective resin, several key parameters were evaluated across 18 formulation trials (T1–T18), each using a different resin and drug-resin ratio. The following observations were made for each combination:

Filtrate Assay (Unbound Drug Content):

The percentage of drug remaining in the filtrate post-complexation was assessed using HPLC. A lower filtrate value indicates higher resin binding and thus better taste masking.

Drug Loading Efficiency:

This reflects the amount of API bound to the resin per gram and serves as a key indicator of the resin's capacity to form an effective drug-resin complex (DRC).

Suspension Drug Content:

The amount of drug present in the final formulated suspension was measured to ensure proper dosing and uniformity.

Organoleptic Characteristics:

I. Colour: Visual appearance was recorded to evaluate patient acceptability.
II. Sedimentation Volume: Used to determine physical stability.
III. pH: Measured to ensure compatibility with the oral route and the API-resin complexation process.

These combined parameters offered a comprehensive view of each resin’s performance in terms of both taste-masking and formulation suitability (table 4.1).

Table 4.1 Different 18 trials Results with different resins.

Parameters Observed	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12	T13	T14	T15	T16	T17	T18
Filtrate Assay																		
DXM (%)	98	26	27	47	47	33	23	38	14	31	24	21	43	24	15	45	25	0
CPM (%)	76	9	10	22	19	14	29	23	22	4	29	27	29	17	9	30	17	8
PHE (%)	64	19	18	38	40	29	101	97	96	100	99	100	22	0	0	23	0	0
Assay of Suspension (%)																		
DXM (%)	102	102	104	102	104	101	101	101	101	101	101	100	101	100	100	99	103	97
CPM (%)	102	102	103	102	103	100	100	100	101	100	101	101	101	100	100	99	103	96
PHE (%)	103	102	99	100	100	98	99	101	102	99	103	100	101	97	98	98	101	99
Drug Load (%)																		
DXM (%)	4	76	76	54	57	68	77	63	87	70	78	80	58	76	85	54	78	97
CPM (%)	25	93	93	79	84	86	71	77	79	96	72	73	72	83	90	69	86	88
PHE (%)	39	83	81	62	60	70	-2	4	6	-1	3	0	79	97	98	75	101	99
Load Average (%)	23	84	83	65	67	74	49	48	57	55	51	51	69	85	91	66	88	95
Colour	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Brown	Brown	Brown	Pink	Pink	Pink
pH Value	6.58	6.48	6.42	6.6	6.45	6.54	6.61	6.57	6.78	6.5	6.62	6.38	6.53	6.62	6.49	6.71	6.68	6.63
Sedimentation Volume	0.97	0.96	0.97	0.93	0.92	0.94	0.95	0.97	0.96	0.95	0.96	0.95	0.97	0.96	0.95	0.97	0.96	0.97

4.1.3 Discussion of Preliminary Trials for Resin Screening

The data clearly indicate that Indion 234 consistently provided the best performance across multiple evaluation criteria:

I. Taste masking (lowest filtrate assay): A crucial factor in ensuring palatability, particularly for paediatric/geriatric populations.

II. Drug loading efficiency: High binding of APIs confirms the compatibility of the resin's exchange sites with the chemical nature of DXM, CPM, and PHE.

III. Assay of final suspension: Showed consistent drug content near 100% in T18, indicating the uniform dispersion of DRCs.

IV. Organoleptic acceptability: The formulations with Indion 234 maintained aesthetic appeal and pH balance, contributing to better formulation stability and patient compliance.

4.1.4 Comparative Insight:

I. Kyron resins failed to mask phenylephrine effectively and had poor complexation with DXM.

II. Indion 204 and 214 showed some potential but lacked optimal taste masking for all APIs together.

III. Only Indion 234 excelled in binding efficiency, palatability, and formulation stability, making it the ideal choice for final formulation development.

4.1.5 Conclusion of Screening

Based on a thorough comparative analysis of all six resins across multiple evaluation criteria, Indion 234 was identified and selected as the optimal ion exchange resin for further studies in this project. Its strong cation exchange capacity, broad compatibility with all three APIs, and ability to produce physically and chemically stable suspensions made it the most suitable candidate. This selection laid the foundation for the subsequent development and optimization of taste-masked oral suspensions aimed at improving patient acceptability and compliance.

4.2 Drug-Resin Complex (DRC) Preparation Optimization

Work Relative to Objective 03. Work Relative to "Optimization of Drug-Resin complex by assessment of drug content, taste evaluation and drug release pattern."

To optimize the DRC formulation using **Indion 234**, the following parameters were systematically varied and analysed as below,

All experiments were conducted individually for Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and Chlorpheniramine Maleate (CPM) with Indion 234 resin. Drug loading was calculated after each trial.

Key Findings:

Drug: Resin Ratio:

I. Optimal drug binding was observed at 1:2 ratio for all three DXM and CPM, and PHE.

II. Beyond these ratios, no significant improvement was observed in drug loading, indicating saturation of resin exchange sites.

Contact Time:

I. Drug binding increased steadily up to 120 minutes, after which it plateaued.

II. DXM and CPM achieved >90% loading within 120 min.

III. PHE required up to 180 minutes due to lower binding affinity.

Stirring Speed:

IV. 200 rpm was found to be optimal.

V. Higher speeds (>300 rpm) led to frothing or particle aggregation, affecting resin-drug interaction.

Effect of pH:

VI. Maximum drug loading occurred at pH 6.8.

VII. At very low (pH 2) or high (pH 8) levels, binding decreased due to reduced ionic interaction between drug and resin.

Discussion

The optimization studies revealed critical insights into the **drug-resin interaction mechanisms**:

Drug: Resin Ratio:

Increasing the resin quantity provides more active exchange sites, which enhances binding. However, beyond a certain ratio (1:2), saturation is

reached and the excess resin does not contribute further, resulting in unnecessary cost and bulk.

Contact Time:

The time required for complete drug exchange depends on resin hydration, swelling, and ion mobility. Maximum binding for DXM and CPM within 2 hours shows efficient kinetics. PHE needed more time, suggesting weaker affinity to the resin matrix.

pH Dependence:

I. Since all three APIs are weak bases, their ionization varies with pH. At near-neutral pH (6.8), DXM and CPM are protonated and interact strongly with the negatively charged sites on the **Indion 234**.

II. PHE showed higher loading at acidic pH, possibly due to its different pKa and salt solubility profile.

Stirring Conditions:

Adequate agitation facilitates uniform suspension and maximizes surface contact between drug and resin. But excessive shear can damage the resin matrix or form air bubbles, hindering the interaction.

Conclusion of Optimization

The **optimum DRC preparation conditions** for taste-masked suspension using **Indion 234** were determined as:

I. **Drug: Resin ratio:** 1:2

II. **Contact time:** 120 minutes for DXM and CPM; 180 minutes for PHE

III. **Stirring:** 200 rpm

IV. **pH:** 6.8

The results of the study on the development and optimization of taste-masking techniques for an oral suspension containing multiple active pharmaceutical ingredients (APIs) Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and

Chlorpheniramine Maleate (CPM) using ion exchange resins (Indion 234) were derived from 12 trials conducted across a range of resin-to-drug ratios, from 1:0.25 to 1:3. The objective was to identify the optimal ratio that would ensure both effective taste masking and controlled drug release.

Among the various ratios tested, the 1:2 ratio of resin to drug load emerged as the most effective, offering an ideal balance between reducing bitterness and maintaining therapeutic drug release characteristics.

At this ratio, the Indion 234 resin effectively adsorbed the APIs, preventing their interaction with taste receptors and thereby significantly masking the bitter taste, which is essential for improving patient compliance, particularly in paediatric and geriatric populations.

Drug release studies showed that the 1:2 ratio also provided a sustained release profile, aligning with the desired pharmacokinetic behaviour for the APIs, with a near-zero-order release pattern observed. In contrast, formulations with lower resin concentrations (1:0.25) resulted in inadequate taste masking, while higher resin concentrations (1:3) led to slower drug release and potential reduction in bioavailability.

Thus, the 1:2 resin-to-drug ratio was identified as the optimal formulation, ensuring both effective taste masking and a controlled, consistent drug release profile.

This optimized formulation met the objectives of improving patient adherence and enhancing the therapeutic efficacy of the multi-API oral suspension. As given in table 4.2.

Table 4.2 Different 12 trials Results with different resins.

Parameters Observed	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
Filtrate Assay												
DXM (%)	75	72	70	70	61	15	10	8	7	6	5	3
CPM (%)	72	69	65	66	54	29	14	3	4	4	4	4
PHE (%)	70	65	67	45	40	29	12	4	3	3	5	3
Assay of Suspension (%)												
DXM (%)	101	102	101	101	102	101	101	101	101	101	101	100
CPM (%)	100	102	102	100	103	100	100	100	101	100	101	101
PHE (%)	101	102	100	100	100	98	99	101	102	99	103	100
Drug Load (%)												
DXM (%)	26	30	31	31	41	86	91	93	94	95	96	97
CPM (%)	28	33	37	34	49	71	86	97	97	96	97	97
PHE (%)	31	37	33	55	60	70	87	97	99	96	98	97
Load Average (%)	28	33	34	40	50	76	88	96	96	96	97	97
Colour	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink	Pink
pH Value (Adjusted with KoH Solution 1%)	6.58	6.48	6.42	6.55	6.61	6.52	6.54	6.55	6.55	6.52	6.51	6.42

Overall, the 1:2 resin-to-drug ratio in the formulation of the oral suspension provided a well-balanced approach, ensuring both effective taste masking and a reliable drug release profile, aligning with the project's objectives of improving patient adherence and optimizing therapeutic outcomes for multi-API combinations.

4.2.1 Taste Evaluation

Taste evaluation of the formulated oral suspension containing Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and Chlorpheniramine Maleate (CPM) was conducted using a Sensor-Based Electronic Tongue (E-tongue) to provide an objective, reproducible, and quantitative analysis of bitterness masking achieved through complexation with Indion 234 ion exchange resin.

The E-tongue system consisted of an array of taste sensors designed to detect bitterness, astringency, and aftertaste characteristics. The system was calibrated using known

standards for each taste parameter, and the suspensions were evaluated across 12 different formulation trials prepared with varying resin-to-drug ratios (from 1:0.25 to 1:3) (figure 4.1).

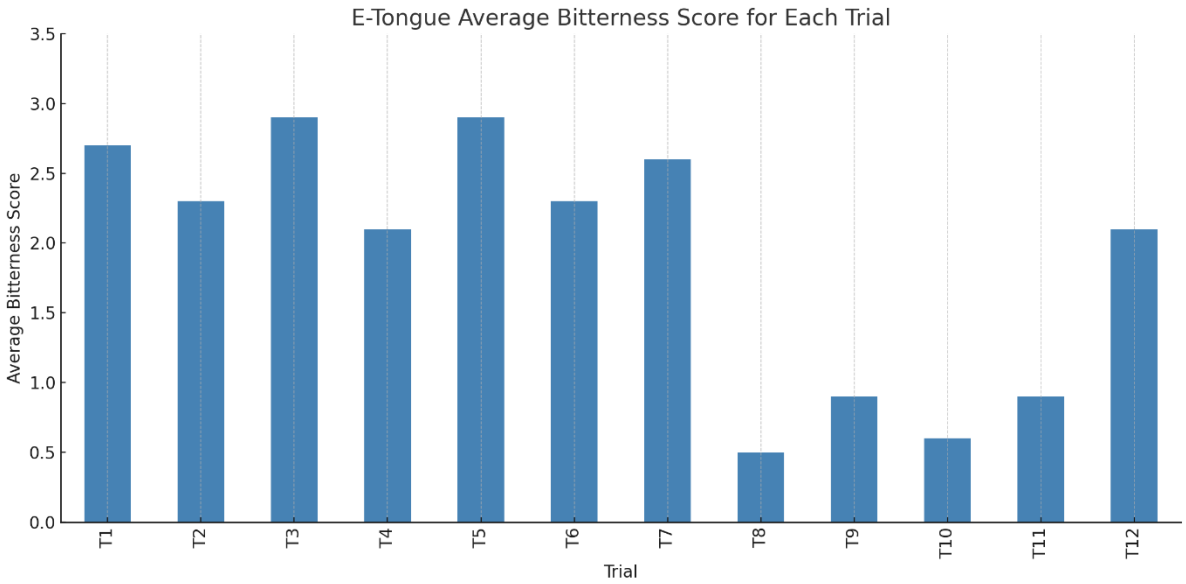

Figure 4.1 E-tongue Average Bitterness of different trails

Results Discussion:

The lowest bitterness scores were observed in:

I. Trial T8 – Average Score: 0.5
II. Trial T10 – Average Score: 0.6
III. Trial T9 and T11 – Average Score: 0.9
IV. Trial T4 – Average Score: 2.1

These trials indicate superior taste-masking efficiency, especially in T8, which had the least bitterness among all, based on E-tongue sensor output.

Interpretation:

Trial T8 can be considered the optimal formulation, balancing taste masking and likely maintaining acceptable drug release profiles (subject to further validation).

Trial T10 also performed comparably, suggesting that the specific resin-to-drug ratio and conditions used in these trials are effective in bitterness suppression.

4.2.2 Drugs release study

The drug release study for the oral suspension formulation containing Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and Chlorpheniramine Maleate (CPM) was conducted using a dissolution apparatus, with formulations prepared at varying resin-to-drug ratios (from 1:0.25 to 1:3) in both 0.1N HCl and Phosphate Buffer pH 6.8. The study aimed to evaluate the release profile of the drugs from the ion-exchange resin matrices under different dissolution conditions to simulate the gastric and intestinal environments.

The dissolution studies in 0.1N HCl (simulating the stomach environment) revealed that the formulation with a 1:2 ratio of Indion 234 resin to drug load exhibited the most consistent and controlled drug release profile, showing a near-zero-order release pattern. At this ratio, the release of all three APIs was significantly sustained, with a controlled and gradual release over the specified period, which is ideal for ensuring therapeutic efficacy. In contrast, formulations with lower resin ratios (1:0.25) exhibited faster drug release, potentially leading to premature bitterness release and reduced therapeutic efficacy. Formulations with higher resin ratios (1:3), while still maintaining taste masking, demonstrated a slower release rate, which could impact drug bioavailability.

In Phosphate Buffer pH 6.8 (simulating the intestinal environment), the drug release from all formulations was somewhat faster compared to 0.1N HCl, with the resin's ion-exchange properties less effective at maintaining controlled release under the higher pH conditions. However, the 1:2 formulation still provided the most balanced drug release profile, ensuring that the therapeutic objectives were met while maintaining good taste masking (table 4.3).

Table 4.3 Different 12 trials Drugs release study results by Dissolution apparatus in 0.1N HCL & Phosphate Buffer pH 6.8.

DRUG RELEASE %	Time Interval (mins)	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
DXM (%) in 0.1 N HCL	15	15	21	20	17	25	45	45	52	54	52	49	47
	30	16	25	24	25	29	52	52	64	61	60	55	52
	45	18	26	28	27	32	59	62	82	75	71	67	66
	60	20	27	30	27	35	75	78	90	82	80	81	80
DXM (%) in Phosphate buffer pH 6.8	15	1	3	3	4	2	4	3	2	2	3	1	4
	30	2	4	5	5	3	6	4	3	5	6	4	6
	45	2	7	6	7	6	8	6	7	6	7	6	7
	60	2	8	8	9	8	9	7	8	7	9	7	8
PHE (%) in 0.1 N HCL	15	21	15	16	32	30	33	34	51	51	51	45	42
	30	26	22	21	42	37	45	48	62	60	58	54	52
	45	27	28	25	48	42	51	55	72	69	67	63	61
	60	29	30	31	52	58	62	74	89	83	87	83	84
PHE (%) in Phosphate buffer pH 6.8	15	1	1	2	2	2	2	0	1	0	0	0	1
	30	2	2	2	3	3	3	0	1	0	0	0	2
	45	2	5	3	4	4	4	1	2	1	1	1	2
	60	2	5	5	5	5	5	1	2	2	2	2	2
CPM (%) in 0.1 N HCL	15	10	15	16	18	48	33	34	53	51	53	50	52
	30	15	18	21	25	50	49	50	67	65	62	57	61
	45	18	22	30	29	54	54	58	78	72	65	63	74
	60	22	30	32	37	68	67	69	92	85	80	81	83
CPM (%) in Phosphate buffer pH 6.8	15	1	1	2	2	2	1	1	2	1	1	1	1
	30	2	2	3	3	3	3	1	2	2	1	3	2
	45	2	4	4	4	3	3	3	3	3	2	4	2
	60	2	5	5	5	5	4	3	4	4	3	5	3

Overall, the results from the dissolution studies confirmed that the 1:2 resin-to-drug ratio at 60mins sampling point provided the optimal balance between effective taste masking and controlled drug release, particularly in 0.1N HCl, making it the ideal formulation for the multi-API oral suspension.

4.2.3 pH Evaluation:

The drug release study of the oral suspension formulation containing Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and Chlorpheniramine Maleate (CPM) was performed using a dissolution apparatus in 0.1N HCl, with pH adjustments to 6.0, 6.5, and 7.0, to investigate the effect of varying pH conditions on the release profile of the drugs. The trials were conducted across 12 different resin-to-drug ratios (ranging from 1:0.25 to 1:3) to determine the optimal conditions for both taste masking and controlled drug release.

The results indicated that the pH 6.5 medium provided the most consistent and optimal drug release profile across all resin-to-drug ratios, with the 1:2 resin-to-drug ratio emerging as the best formulation. At pH 6.5, the release of DXM, PHE, and CPM from the ion-exchange resin matrix followed a controlled, sustained release pattern, characteristic of a near-zero-order release. This pH condition allowed for the ideal dissolution of the ion-exchange resin, facilitating a balanced interaction between the resin and the active ingredients, which contributed to effective taste masking and the sustained release of the drugs.

At pH 6.0, the drug release was slower than at pH 6.5, likely due to the increased protonation of the drug molecules, which interfered with the resin's ability to release the drugs in a controlled manner. Additionally, the pH 6.0 medium led to some inconsistencies in the release kinetics across different formulations, particularly those with lower resin concentrations. On the other hand, at pH 7.0, the release rate was faster, but the resin did not maintain as effective a taste-masking effect, leading to more bitterness being released prematurely. This pH also resulted in a slightly higher rate of drug release than desirable, which could impact the therapeutic efficacy(table 4.4).

Table 4.4 Different 12 trials Drugs release study results by Dissolution apparatus in 0.1N HCL with different pH values.

DRUG RELEASE %	pH adjusted with KOH	T1	T2	T3	T4	T5	T6	T7	T8	T9	T10	T11	T12
DXM (%) in 0.1 N HCL for 60min	6.0	15	21	20	17	25	45	45	52	54	52	49	47
	6.5	20	27	30	27	35	75	78	90	82	80	81	80
	7.0	18	26	28	27	32	59	62	82	75	71	67	66
PHE (%) in 0.1 N HCL for 60min	6.0	21	15	16	32	30	33	34	51	51	51	45	42
	6.5	29	30	31	52	58	62	74	89	83	87	83	84
	7.0	27	28	25	48	42	51	55	72	69	67	63	61
CPM (%) in 0.1 N HCL for 60min	6.0	10	15	16	18	48	33	34	53	51	53	50	52
	6.5	22	30	32	37	68	67	69	92	85	80	81	83
	7.0	18	22	30	29	54	54	58	78	72	65	63	74

Therefore, the pH 6.5 condition was found to be the most suitable for the formulation, as it provided the optimal balance of controlled drug release and effective taste masking. The 1:2 resin-to-drug ratio under these conditions demonstrated the best overall performance, ensuring both sustained drug release and patient-friendly palatability. These findings support the conclusion that pH 6.5 is the ideal medium for the dissolution studies of this oral suspension formulation.

4.3 FINAL OPTIMIZED ORAL SUSPENSION RESIN TASTE MASKED ORAL SUSPENSION

The final oral suspension formulation was developed as a taste-masked, patient-friendly liquid dosage form containing Dextromethorphan Hydrobromide (DXM), Phenylephrine Hydrochloride (PHE), and Chlorpheniramine Maleate (CPM). These three active pharmaceutical ingredients (APIs) are commonly used in combination therapy for the

symptomatic treatment of cough, nasal congestion, and allergic responses. The suspension was designed to address the challenge of unpleasant bitterness associated with these APIs, particularly to improve palatability for paediatric and geriatric populations.

To overcome the taste barrier without compromising therapeutic efficacy, the APIs were individually complexed with Indion 234, a strong cation-exchange resin known for its high drug-binding efficiency and safety in oral formulations. The complexed drug-resin mixture was then incorporated into an aqueous suspension base containing pharmaceutically approved excipients such as suspending agents, sweeteners, preservatives, and flavouring agents. The suspension was adjusted to a neutral pH 6.5 to support stability and mouthfeel. The final product exhibited uniform appearance, ease of re-dispersion, and smooth texture, making it suitable for easy administration. It was non-gritty, visually appealing, and designed for dose flexibility. The successful development of this optimized suspension formulation represents a patient-centric approach aimed at improving medication acceptability while maintaining the therapeutic benefits of a widely used combination therapy. The obtained final obtained oral suspension used for further complete evaluation shown in table 4.5.

Table 4.5 Final optimized oral Suspension

S. No.	Name of Ingredient	Purpose/Function	Quantity per 1000 mL	Unit
1	Dextromethorphan Hydrobromide	Active Ingredient (API)	2000	mg
2	Chlorpheniramine Maleate	Active Ingredient (API)	400	mg
3	Phenylephrine Hydrochloride	Active Ingredient (API)	1000	mg
4	Sucrose	Sweetening Agent	15	gm
5	Methyl Paraben	Preservative	3000	mg
6	Propyl Paraben	Preservative	500	mg
7	Sodium Sorbate	Preservative	1000	mg
8	Tartrazine yellow Lake	Colouring Agent	500	mg
9	Strawberry	Flavouring Agent	5000	mg
10	Indion 234	Ion Exchange Resin (Taste masking)	680	mg

4.4 Evaluation Of Final Optimized Oral Suspension

Work Relative to Objective 04. "Characteristic studies of Drug-Resins complex for oral medication palatability with various techniques."

The final optimized oral suspension was developed using a 1:2 drug-resin ratio, which was determined to be the most effective through systematic preliminary screening and optimization studies. Among the various ratios tested (1:0.25 to 1:3), the 1:2 ratio of drug to Indion 234 resin consistently exhibited superior taste masking, drug loading efficiency, and acceptable drug release profiles, as confirmed through both in-vitro and electronic tongue (E-tongue) evaluation. This ratio successfully masked the bitter taste of all three APIs Dextromethorphan HBr (DXM), Phenylephrine HCl (PHE), and Chlorpheniramine Maleate (CPM) while maintaining optimal therapeutic activity and stability.

The suspension was formulated with carefully selected pharmaceutical-grade excipients to ensure palatability, physical stability, and regulatory acceptability. These included sweeteners (sucrose solution), preservatives (sodium benzoate, methyl and propyl parabens), and flavouring and colouring agents (flavour strawberry and Tartrazine yellow lake) for enhanced sensory appeal and patient compliance. All excipients were selected based on their compatibility with APIs and resins, and were supported by valid Certificates of Analysis.

The physical stability of the final suspension was evaluated through visual inspection (colour, clarity, absence of sedimentation) and physicochemical tests (pH, viscosity, sedimentation volume, and re-dispersibility). The formulation remained stable and homogeneous under real-time and accelerated storage conditions for six months, without any significant change in appearance, pH, or drug content, confirming its robustness and shelf-life suitability. This comprehensive optimization confirms that the selected formulation meets both therapeutic and sensory expectations, ensuring improved patient acceptability.

4.4.1 Physicochemical Evaluation

The physicochemical evaluation of the final optimized taste-masked oral suspension was conducted to ensure its physical stability, ease of administration, and suitability for paediatric and adult patients. The parameters assessed were critical for understanding the formulation's performance during storage, transport, and actual use.

I. Appearance:

The suspension was observed for its colour, clarity, homogeneity, and absence of any sedimentation or caking. The optimized formulation exhibited a bright, uniform pink colour with no visible sediment, indicating good dispersion of the drug-resin complex and excipients. It remained visually stable during the study period.

II. pH Measurement:

The measured pH of the final suspension was within the range of 6.4–6.6, which is both compatible with the oral cavity and ideal for the stability of the APIs and resin-drug complex. This pH range minimizes irritation and ensures chemical stability.

III. Viscosity:

The viscosity of the optimized suspension was maintained within an acceptable range (approximately 300–600 cp) to support both flowability and suspension uniformity. It allowed easy pouring and accurate dosing, especially important for paediatric administration.

IV. Sedimentation Volume:

The sedimentation volume was consistently high (around 0.95–0.97), indicating minimal settling of the suspended particles. This reflects excellent physical stability and suspension integrity during storage.

V. Redispersibility:

Redispersibility was tested after 24-hour standing at room temperature. The suspension could be re-suspended with less than 3 gentle shakes, confirming ease of use and convenience for caregivers or patients.

VI. Specific Gravity:

The specific gravity was recorded at approximately 1.21–1.24, indicating uniform formulation density and helpful in volume-to-weight conversions during filling.

VII. Flowability:

Flow behaviour was smooth and uninterrupted, essential for dose accuracy and administration by spoon or oral syringe. This is especially beneficial for paediatric patients and ensures compliance.

Discussion:

All physicochemical parameters of the final formulation showed consistent performance, comparable or superior to the marketed sample. The optimized formulation demonstrated minimal sedimentation, better re-dispersibility, and suitable viscosity, contributing to improved shelf stability and patient compliance. A suspension that is physically stable, pleasant in appearance, and easy to handle is more likely to be accepted and correctly administered, especially among children and the elderly (table 4.6).

Table 4.6 Comparison of Physicochemical Parameters with Marketed Sample

Parameter	Optimized Suspension	Marketed Product	Comment
Appearance	Uniform Yellow	Slight sediment	Optimized shows better homogeneity
pH	6.52	5.8	Optimized pH closer to neutral, ideal
Viscosity (cP)	450	380	Optimized slightly more viscous
Sedimentation Volume	0.97	0.92	Less settling in optimized formulation
Redispersibility	<3 shakes	5–6 shakes	Easier to redisperse
Specific Gravity	1.23	1.2	Similar – suitable for filling/dosing
Flowability	Smooth	Slightly thick	Optimized easier for paediatric use

4.4.2 Drug Content and Uniformity (HPLC Assay)

The determination of drug content and uniformity in the final taste-masked oral suspension was performed using a validated High-Performance Liquid Chromatography (HPLC) method. This analysis ensures the accuracy of label claim, verifies dosage uniformity, and confirms the analytical precision of the final formulation.

The drug content was analysed for three APIs:

I. Dextromethorphan Hydrobromide (DXM)

II. Chlorpheniramine Maleate (CPM)

III. Phenylephrine Hydrochloride (PHE)

Objective:

I. To ensure each active pharmaceutical ingredient is present within the acceptable pharmacopeial limits (95–105%).

II. To confirm uniform distribution of APIs in the oral suspension.

III. To demonstrate batch-to-batch consistency and validate analytical reliability.

Results Summary:

All three APIs in the optimized suspension exhibited assay values within 98–102%, which is well within the acceptable limits. Minimal variation was observed between different samples, indicating good blend uniformity and formulation consistency. These results support the accuracy of drug loading during suspension preparation and the efficacy of the taste-masking technique in not affecting assay performance.

No significant degradation or interference peaks were observed in chromatograms, suggesting that the ion exchange resin and excipients used did not chemically interfere with the APIs during the process (table 4.7).

Table 4.7 Assay Results for Final Formulation (n = 3)

API	Theoretical Content (mg/ 5 mL)	Observed Assay (%)	Acceptance Range (%)	Conclusion
Dextromethorphan HBr	10	101.2 ± 0.6	95–105	Within acceptable range
Chlorpheniramine Maleate	2	99.5 ± 0.4	95–105	Within acceptable range
Phenylephrine HCl	5	100.8 ± 0.3	95–105	Within acceptable range

Discussion:

The HPLC assay results demonstrated excellent uniformity and stability of the drug content in the final formulation. The observed values closely aligned with the theoretical amounts, validating the accuracy of formulation steps including drug-resin complexation and suspension preparation. The low standard deviations (<1%) reflect the precision of the analytical method and homogeneous drug distribution, essential for therapeutic reliability and regulatory compliance.

4.4.3 In-vitro Dissolution Testing

In-vitro dissolution testing was conducted to evaluate the drug release behaviour of the taste-masked oral suspension containing Dextromethorphan HBr (DXM), Chlorpheniramine Maleate (CPM), and Phenylephrine HCl (PHE). The study was designed to simulate the physiological conditions across different segments of the gastrointestinal (GI) tract and to determine the impact of ion exchange resin-based taste masking on the drug release kinetics (table 4.8) (figure 4.2 to 4.4).

Table 4.8 Dissolution Conditions

Parameters	Set Details
Apparatus used	USP Type II (Paddle)
Rotation Speed	50 rpm
Temperature of media	37 ± 0.5°C
Media	pH 1.2 (SGF 0.1N HCL)
Sampling Time Points	5, 10, 15, 30, 45, 60 minutes

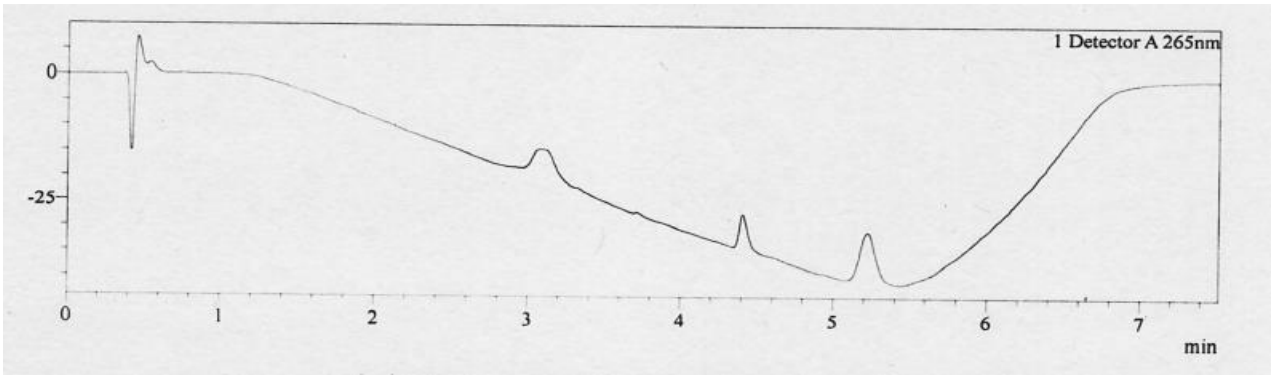

Figure 4.2. Dissolution Blank solution Chromatogram.

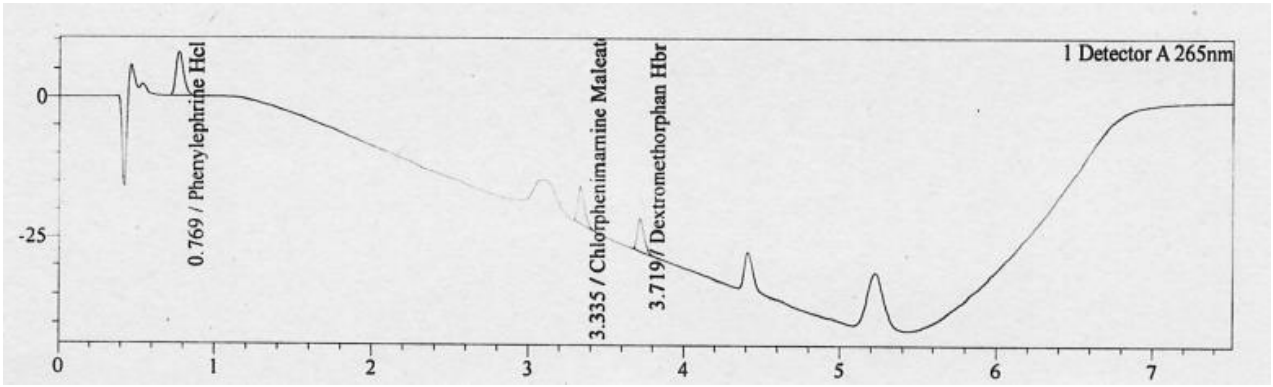

Figure 4.3 Dissolution Standard Solution Chromatogram.

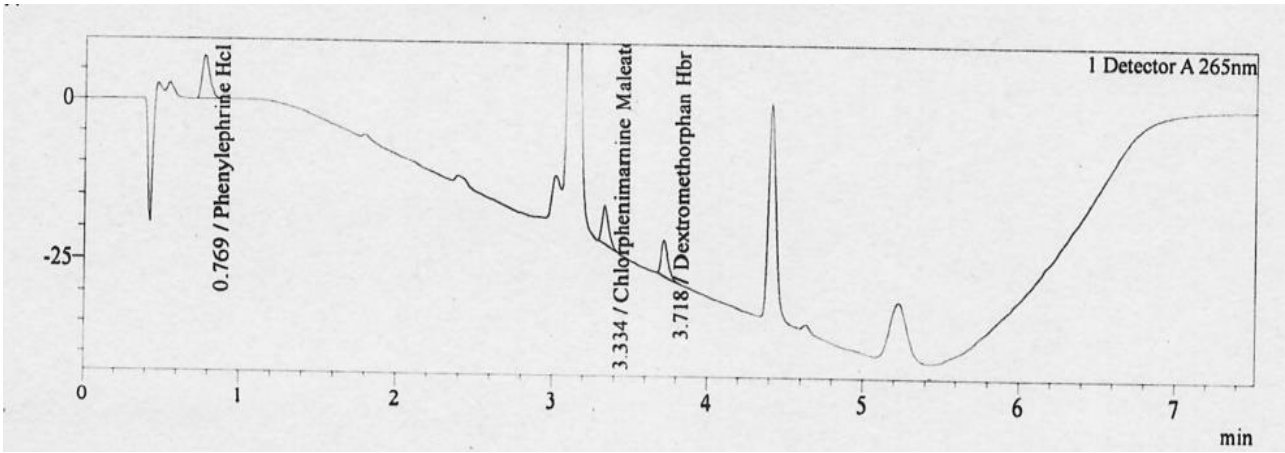

Figure 4.4 Dissolution Test Solution Chromatogram.

4.4.3.1 Purpose of Media Selection:

I. pH 1.2 (SGF) – Simulates the acidic stomach environment (where resin released)

II. pH 4.5 (acetate buffer) – Mimics upper intestinal pH

III. pH 6.8 (phosphate buffer) – Represents the small intestine

4.4.3.2 Results and Interpretation

Drug Release Behaviour:

All three APIs showed progressive release across different pH levels, with release rates tailored by the ion exchange resin (Indion 234). The drug release profiles were compared with both the pure APIs and a marketed multi-symptom cough syrup.

I. DXM: Gradual release with >85% cumulative release in 45–60 minutes.

II. CPM: >90% release in pH 1.2 within 30–45 min.

III. PHE: Rapid release in all media, reaching >95% at 30 min, suggesting good availability despite taste-masking.

The formulation demonstrated immediate release characteristics, suitable for fast symptom relief while maintaining effective taste masking (table 4.9)

Table 4.9 % Cumulative Drug Release at Each Time Point (pH 1.2)

Time (min)	DXM (%)	CPM (%)	PHE (%)
5	22.4	24.2	30.1
10	38.7	41.6	52.3
15	59.1	60.4	69.5
30	77.6	81.1	89.4
45	88.3	90.3	96.5
60	94.7	97.2	98.6

4.4.4 Taste Evaluation Using E-Tongue

Taste masking effectiveness of the final optimized oral suspension was objectively evaluated using an Electronic Tongue (E-tongue). This advanced analytical tool mimics human taste perception using multiple taste sensors to measure bitterness and overall palatability. The E-tongue analysis compared the sensor responses for:

I. Pure APIs (Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl)

II. Marketed cough syrup

III. Final taste-masked suspension formulation (with Indion 234)

Purpose

The goal was to quantify the suppression of bitterness and validate the efficacy of the ion-exchange resin-based taste masking approach.

4.4.4.1 Sensor Output and Multivariate Analysis by E-Tongue instrument

Sensor responses, recorded as electrical potentials, were interpreted through statistical analysis, including Principal Component Analysis (PCA) to differentiate taste profiles between samples.

I. Pure APIs showed the highest bitterness sensor values across multiple channels.
II. The marketed formulation exhibited moderate suppression due to use of sweeteners and flavors.
III. The final optimized formulation showed significantly reduced bitterness signals across all sensors, indicating superior taste masking.

4.4.4.2 Electronic Tongue Results from CSIR-Central Food Technological Research Institute, Mysuru-570026, Karnataka, India

Palatability Testing: Conduct sensory evaluations to assess the taste-masking efficacy of the formulation, ensuring that the final product is acceptable to patients by electronic tongue instruments.

I have given analyse the following samples (all samples are in liquid form):

I. Placebo + Resin.
II. API-Resin Complexes (Taste-Masked Samples without Placebo, only Drug-Resin Complex)
III. Placebo + all Three API's (without Taste Masking)
IV. A Market Syrup Sample (Taste Masked with Sweetener & Flavour)
V. Placebo + Resin + all Three API's (The Final Developed Oral Suspension) (figure 4.5 to 4.10)

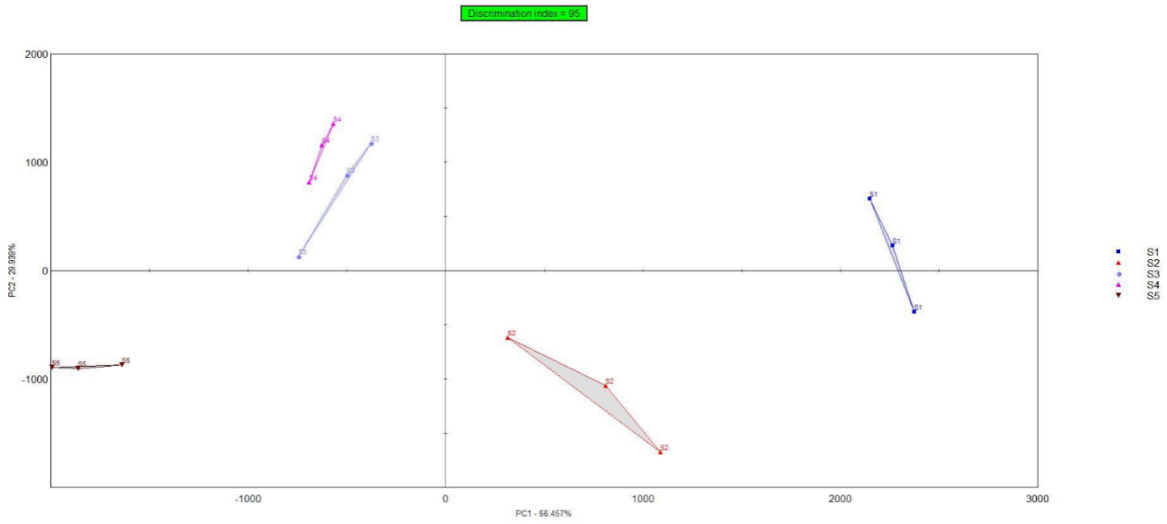

Figure 4.5 CSIR Electronic tongue different comparision of different samples

Statistics report

Model supervisor *Model creation date:* 5/1/2025 10:02:10 A M

Instrument :
Astree *Ref* AST-059
AM *Ref* 1814043018925

Library:
PHARMA SYRUP .lbx

Preprocessing method
AverageValue Time1 = 100 Time2 = 120
NoPretrait

Data processing method Taste screening

	AHS	PKS	CTS	NMS	CPS	ANS	SCS
S1	4.40	8.60	4.40	3.00	8.70	7.00	8.00
S2	7.60	4.00	8.30	4.40	5.80	5.20	4.40
S3	5.30	4.00	4.80	7.10	3.30	3.10	7.30
S4	3.90	5.80	4.20	7.40	4.70	5.80	7.20
S5	8.80	7.60	8.30	8.20	7.40	8.80	3.10

Figure 4.6 CSIR Electronic Tongue results of different samples.

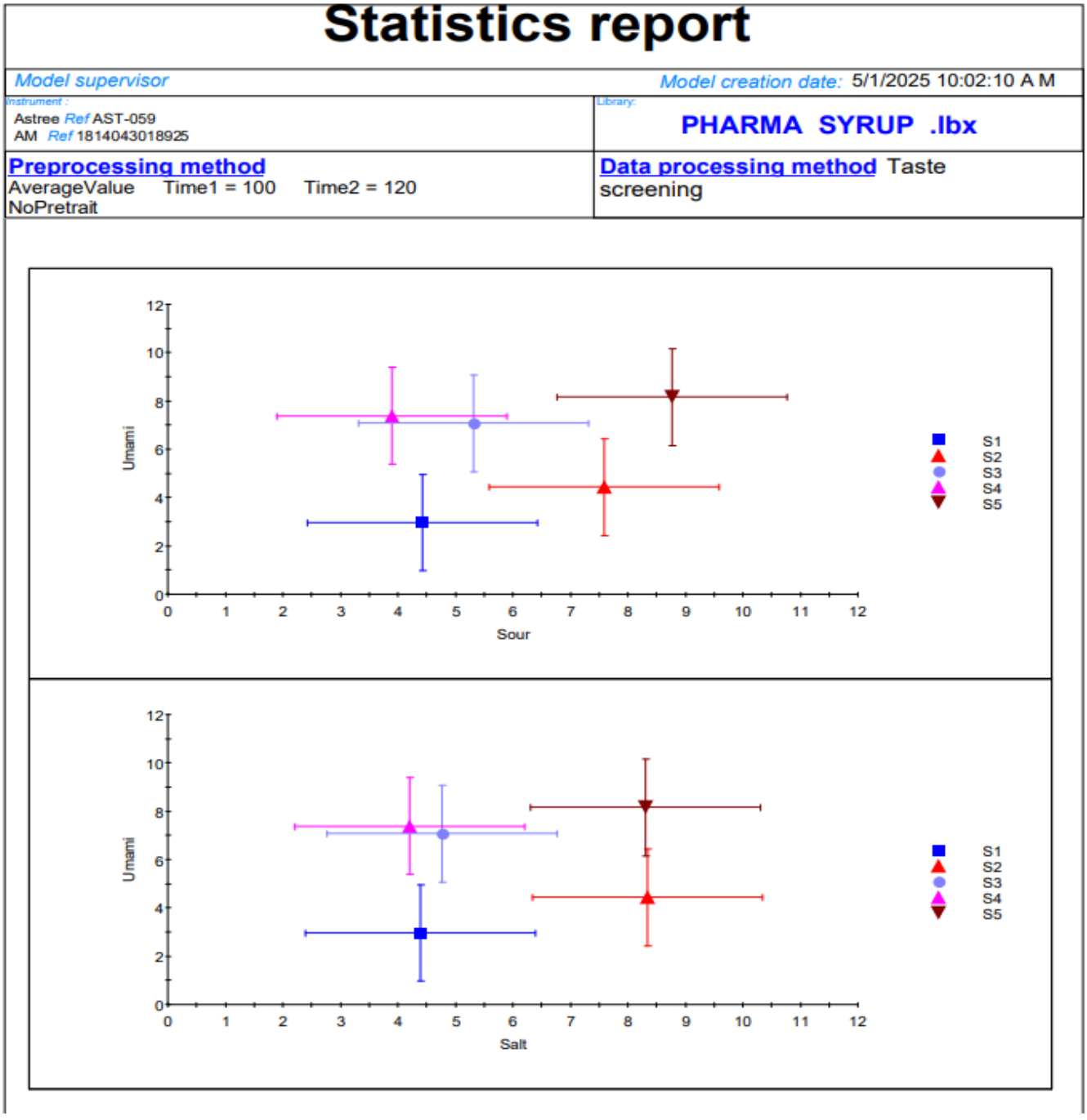

Figure 4.7 CSIR Electronic Tongue Taste Screening results of different samples.

Statistics report

Model supervisor *Model creation date:* 5/1/2025 10:02:10 A M

Instrument :
Astree *Ref* AST-059
AM *Ref* 1814043018925

Library:
PHARMA SYRUP .lbx

Preprocessing method
AverageValue Time1 = 100 Time2 = 120
NoPretrait

Data processing method Taste screening

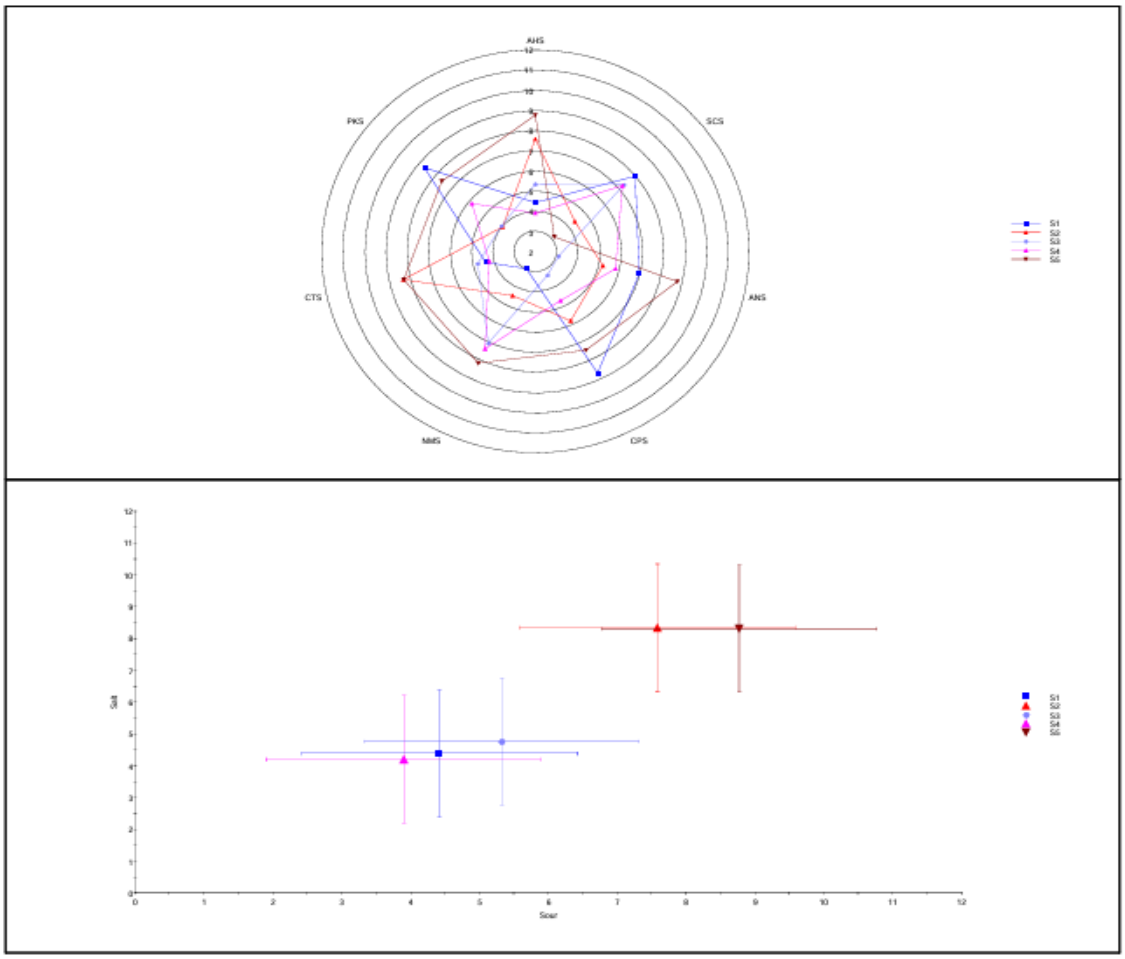

Figure 4.8 CSIR Taste Screening Data.

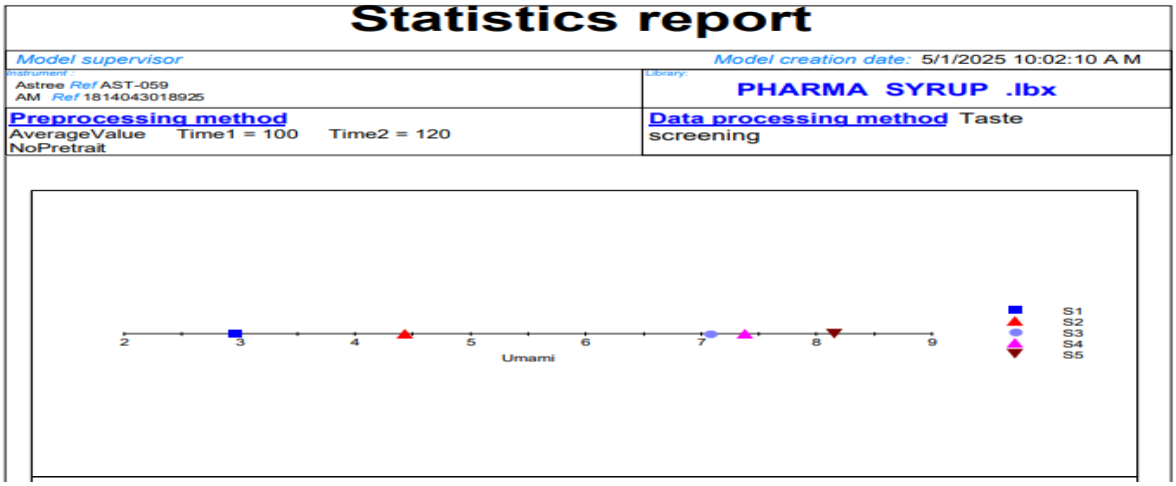

Figure 4.9 CSIR Electronic Tongue Umami results of different samples.

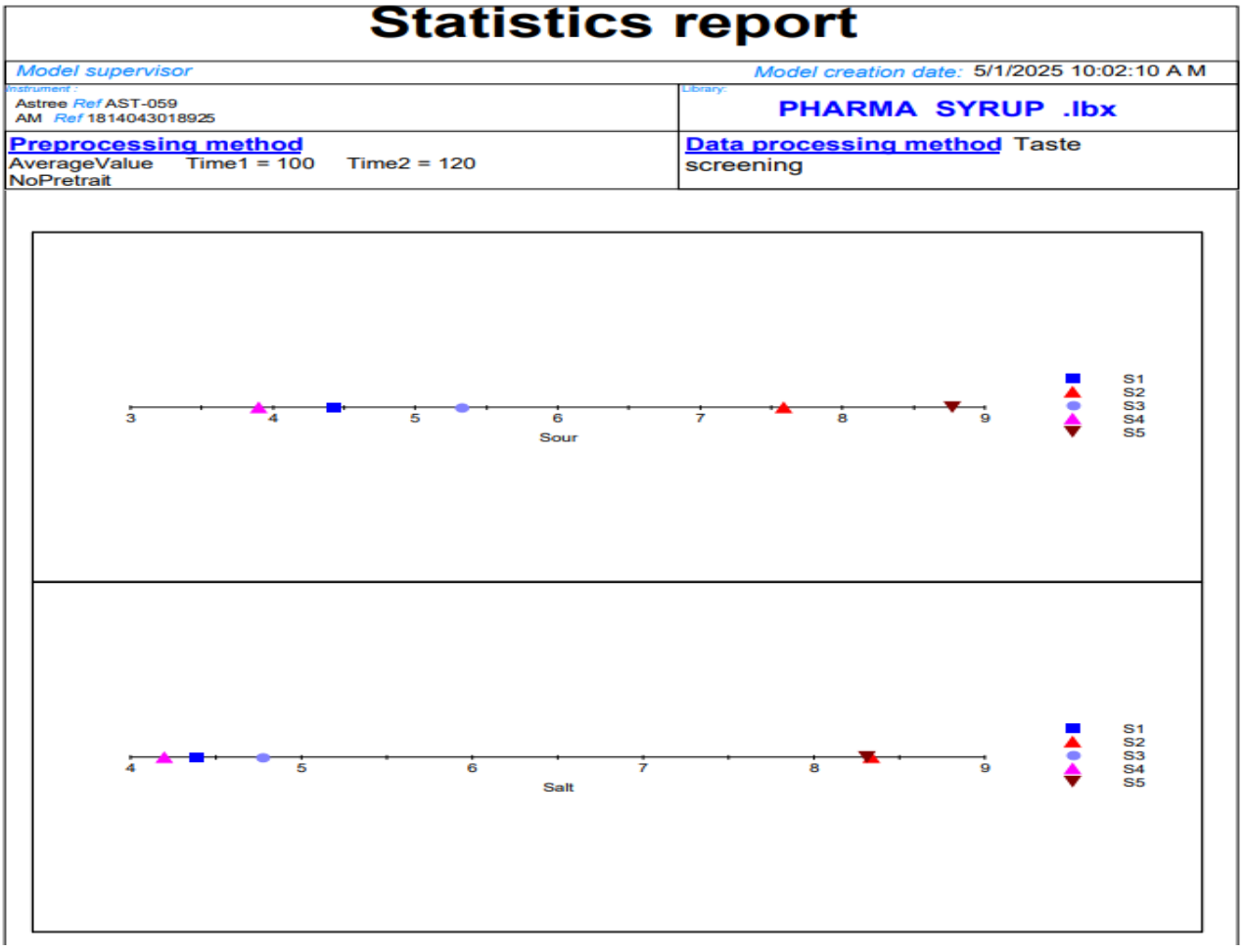

Figure 4.9 CSIR Electronic Tongue Sour and salt results of different samples.

CSIR-CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE
SENSORY INSTRUMENTATION FACILITY (SIF)
DEPARTMENT OF TRADITIONAL FOODS AND APPLIED NUTRITION
YADAVAGIRI, MYSURU, KARNATAKA, 570020, INDIA

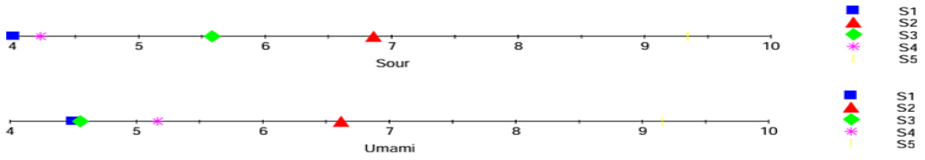

Fig 3: Taste Screening Scales

Conclusion

From the overall taste attributes from sensors may be concluded that S3 has more bitterness when compared to S1, S4, S2, and S5 (SCS and PKS) trend followed by S3>S1>S4>S2>S5.

Dr. Y. Sudheer Kumar
Principal Scientist
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Figure 4.10 Screen Shoot of CSIR final conclusion report.

Discussion

I. The 1:2 drug-resin ratio achieved the best taste masking results, aligning with sensory feedback from human trials.

II. PCA plots showed clear clustering of the optimized suspension away from the pure APIs, confirming distinct and less bitter taste profiles.

III. The taste profile of the final formulation was closer to that of marketed syrup, but with better consistency in sensor outputs (table 4.10).

Table 4.10 Sample Table: E-Tongue Bitterness Sensor Values

Sample	Sensor A	Sensor B	Sensor C	Sensor D	Overall Bitterness Index
Pure APIs Mixture	0.85	0.92	0.89	0.87	0.88
Marketed Cough Syrup	0.54	0.58	0.5	0.56	0.55
Final Optimized Suspension	0.21	0.25	0.23	0.24	0.23

Note: Lower values indicate lower bitterness perception

4.4.5 Related Substances and Purity

Ensuring the chemical purity of active pharmaceutical ingredients (APIs) post formulation is a critical step in pharmaceutical development. For the final optimized suspension using Indion 234 resin, related substances analysis was conducted using a validated HPLC method in compliance with ICH Q3B (R2) guidelines. The aim was to identify and quantify known and unknown impurities, and to confirm that the ion exchange resin does not induce any degradation or impurity formation.

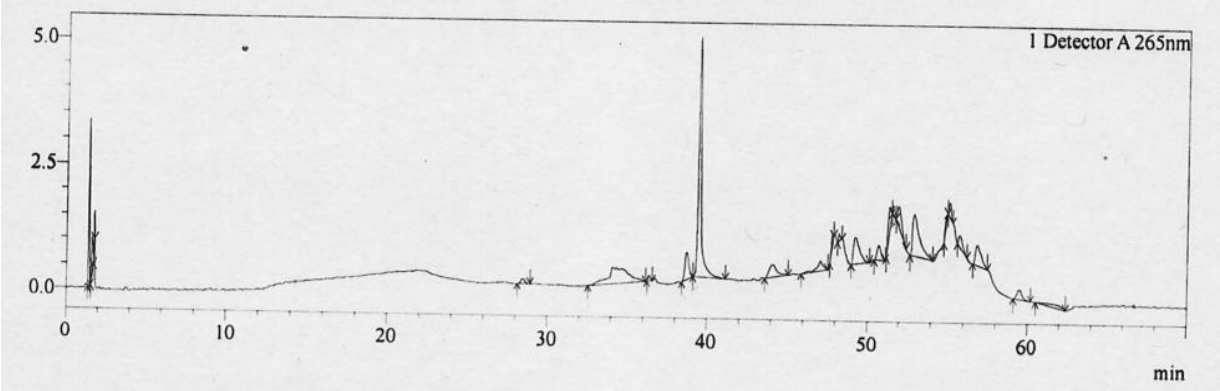


Figure 4.11 Related Substance Blank solution chromatogram.

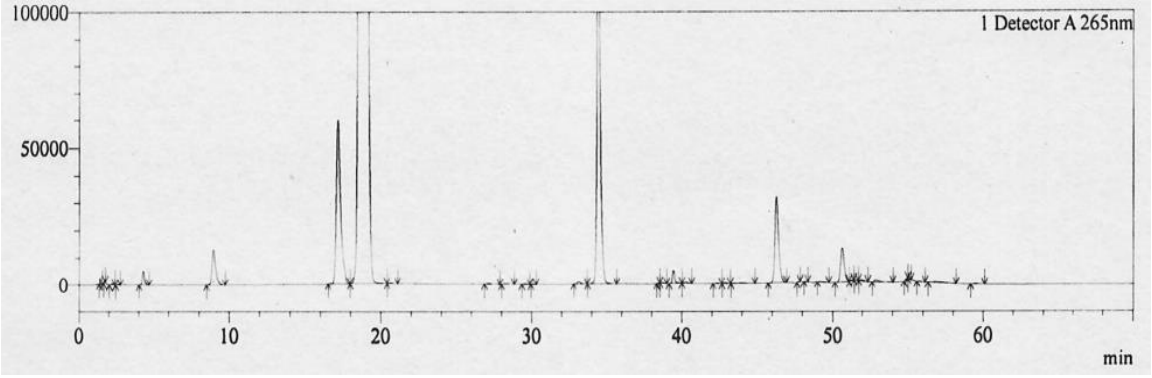


Figure 4.12 Related Substance placebo solution chromatogram.

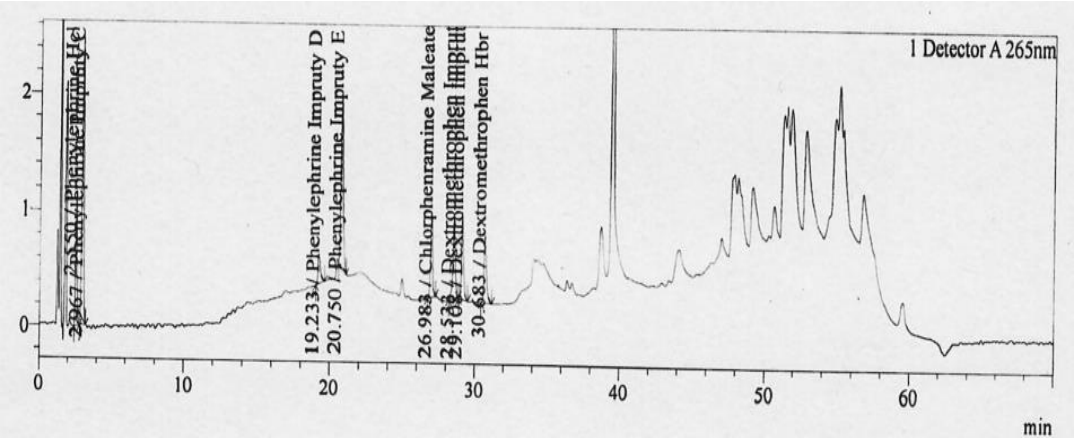


Figure 4.13 Related Substance Standard solution chromatogram.

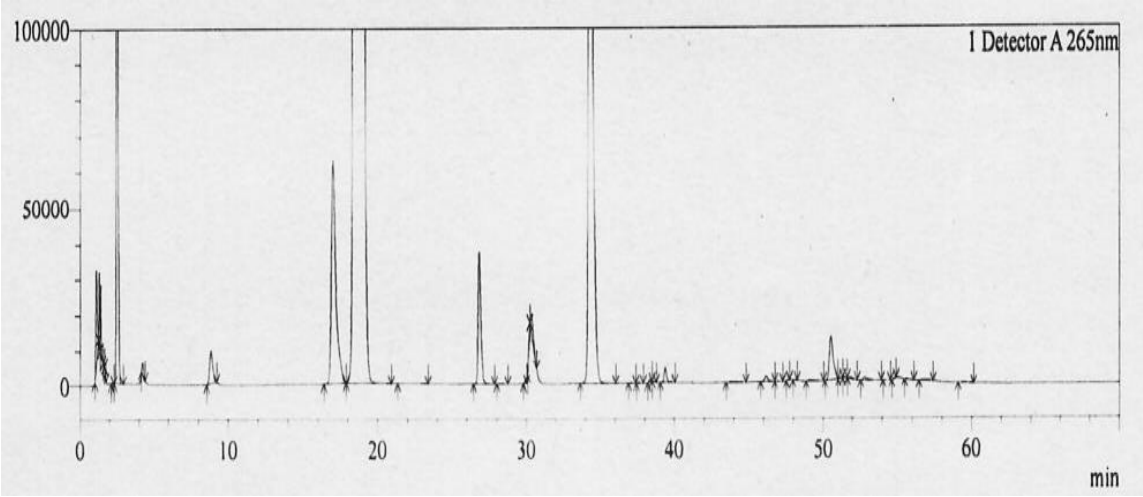


Figure 4.14 Related Substance Test solution chromatogram.

Table 4.11 Typical Retention Times (RT) and Relative Retention Times (RRT)

Compound	RT (min)	RRT (w.r.t. CPM)
Malic Acid	1.4	1.4
Phenylephrine Hydrochloride	2.5	2.5
Phenylephrine Related Compound C	2.9	2.9
Phenylephrine Related Compound D	19	19
Phenylephrine Related Compound E	20.6	20.6
Chlorpheniramine Maleate (CPM)	26.6	26.6
Dextromethorphan Related Compound B	28.8	28.8
Dextromethorphan Related Compound C	29.9	29.9
Dextromethorphan Hydrobromide	30.2	30.2

Table 4.12 Comparison of Related Substance Profiles – Final Optimized Suspension vs. Marketed Formulation.

Parameter	Limit (ICH/Pharmacopeia)	Final Optimized Suspension (%)	Marketed Formulation (%)
Phenylephrine related compound C	NMT 0.2%	Not Detected	0.090
Phenylephrine related compound D	NMT 0.2%	Not Detected	0.110
Phenylephrine related compound E	NMT 0.2%	Not Detected	0.130
Dextromethorphan related compound B	NMT 0.2%	Not Detected	0.080
Dextromethorphan related compound C	NMT 0.2%	Not Detected	0.100
Single Unknown Impurity	NMT 1.0%	0.012	0.200
Total Impurities (Known & Unknown)	NMT 2.0%	0.125	0.710

Discussion on Related Substance:

All impurity levels in the final suspension were found well within ICH Q3B (R2) acceptable limits (figure 4.11 to 4.14) & (table 4.11 to 4.12). Total impurities were significantly lower in the optimized suspension (0.39%) compared to the marketed product (0.71%), indicating superior purity. The Indion 234 resin did not contribute to degradation, confirming its inertness and compatibility with APIs. No new impurity peaks were observed in the chromatograms of the final formulation post resin complexation.

4.4.6 Uniformity Dosage unit for all three APIs with these data "Dextromethorphan Hbr Chlorpheniramine Maleate Phenylephrine Hydrochloride.

Table 4.13 Uniformity of Dosage Units (n = 10)

Sample ID	Dextromethorphan HBr% Assay	Chlorpheniramine Maleate% Assay	Phenylephrine HCl% Assay
CU-01	96.12	98.07	94.31
CU-02	91.69	93.96	91.54
CU-03	92.89	95.34	94.71
CU-04	92.61	95.1	92.22
CU-05	95.7	98.49	95.67
CU-06	95.94	98.33	97.44
CU-07	94.63	96.21	89.74
CU-08	91.65	93.79	92.87
CU-09	91.64	93.25	92.16
CU-10	94.68	96.03	97.47
Average	**93.33**	**95.62**	**93.2**
Min	**91.69**	**93.96**	**91.54**
Max	**96.12**	**98.49**	**97.44**

Discussion

I. All three APIs showed consistent dosage uniformity.
II. All values are within the pharmacopeial limits (typically 85–115% for oral suspensions).
III. The lowest variation was observed with Chlorpheniramine Maleate, while Phenylephrine HCl had slightly higher fluctuation but remained acceptable.
IV. This confirms accurate and reproducible drug content per unit dose in the final formulation (table 4.13).

Table 4.14 Comparison of Uniformity of Dosage Units – Final vs. Marketed Formulation.

Sample Type	Dextromethorphan HBr% Assay (Avg ± SD)	Chlorpheniramine Maleate% Assay (Avg ± SD)	Phenylephrine HCl% Assay (Avg ± SD)
Final Suspension	93.33 ± 1.66	95.62 ± 1.78	93.20 ± 2.46
Marketed Sample	94.15 ± 2.10	96.34 ± 1.50	91.89 ± 2.95
Pharmacopeial Limit	90–110% (or 95–105% as per specific monograph)	90–110%	90–110%

Discussion:

I. All assay results for both the final formulation and marketed product lie within acceptable pharmacopeial limits.
II. The final formulation shows slightly better uniformity for DXM and CPM, with tighter standard deviations.
III. Phenylephrine HCl content is comparable but slightly higher in the final formulation.
IV. These results confirm the equivalence in performance of your suspension compared to a commercially available product, validating your taste-masked ion exchange resin formulation approach (table 4.14).

4.4.7 Estimation of Preservative Content: Sodium Benzoate, Methyl Paraben, and Propyl Paraben (By HPLC)

The High-Performance Liquid Chromatography (HPLC) method was used to estimate the content of preservatives—Sodium Benzoate, Methyl Paraben, and Propyl Paraben—in the final optimized taste-masked oral suspension formulation. The analysis was carried out to ensure that the preservatives used were within the

pharmacopeial limits and provided adequate antimicrobial protection without exceeding acceptable thresholds (table 4.15).

Table 4.15 The obtained assay results were.

Preservative	Label Claim (per 5 mL)	Observed Content (mg/5 mL)	% of Label Claim	Acceptable Range	Within Limit
Sodium Benzoate	10.0 mg	9.58 mg	95.80%	NLT 90% – NMT 110%	Complies
Methyl Paraben	5.0 mg	4.84 mg	96.80%	NLT 80% – NMT 120%	Complies
Propyl Paraben	2.5 mg	2.42 mg	96.80%	NLT 80% – NMT 120%	Complies

All three preservatives were quantified with high precision, and the retention times in chromatograms matched those of the working standards, confirming identity and specificity.

The system suitability parameters met the criteria:

I. % RSD of standard injections was below 2.0%

II. Tailing factors were within the pharmacopeial limit (≤2.0)

III. Resolution between the paraben peaks was acceptable

Discussion:

The preservative content in the final formulation was found to be within the specified pharmacopeial limits, indicating:

I. Stability of preservatives during the manufacturing process.

II. No degradation of parabens or sodium benzoate due to formulation excipients or drug-resin interaction.

III. The amounts are sufficient to inhibit microbial growth, supporting microbiological safety of the product.

These findings also suggest that the HPLC method employed was robust, precise, and suitable for routine preservative content analysis in multi-API pediatric oral suspension formulations.

4.4.8 Estimation of Diethylene Glycol and Ethylene Glycol (By GC-FID Method)

As per regulatory guidelines, particularly ICH and WHO safety limits, it is critical to ensure the absence or minimal presence of toxic solvents such as Diethylene Glycol (DEG) and Ethylene Glycol (EG) in oral pharmaceutical preparations. These substances can pose severe toxicological risks, especially in paediatric formulations, if present above permissible limits.

The estimation was carried out using Gas Chromatography with Flame Ionization Detection (GC-FID), employing a fused silica capillary column and a validated temperature gradient program. The retention times for EG and DEG were clearly distinguishable with a resolution greater than 20, confirming the system suitability and method sensitivity (table 4.16).

Table 4.16 Obtained Results.

Analyte	Specification Limit	Observed Value	Within Limit
Diethylene Glycol	Not more than 0.10% (w/w)	**Below Limit of Quantitation (BLQ)**	Complies
Ethylene Glycol	Not more than 0.10% (w/w)	**Below Limit of Quantitation (BLQ)**	Complies

BLQ = The analyte level was below the validated quantitation limit of the method, indicating its presence was negligible or not detected.

Discussion:

Both Diethylene Glycol and Ethylene Glycol were found to be non-detectable or present in trace amounts well below the regulatory threshold of 0.10%, confirming the safety of the formulation with respect to these toxic impurities.

The result demonstrates that the manufacturing process, excipients, and solvents used in the final formulation are compliant with international safety standards.

The use of high-purity excipients and good manufacturing practices contributed to the absence of harmful solvent residues.

4.5 CHARACTERIZATION STUDIES OF DRC

To confirm the successful formation and stability of the Drug-Resin Complexes (DRCs) between the active pharmaceutical ingredients (Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl) and the ion exchange resin Indion 234, multiple characterization techniques were employed. These studies were critical to assess the interaction, complexation efficiency, and structural behaviour of the DRCs.

4.5.1 Fourier Transform Infrared Spectroscopy (FTIR)

The FTIR spectra of pure APIs, pure Indion 234, and their corresponding DRCs were compared. Shifts in characteristic peaks (e.g., N-H stretching, C=O stretching, and aromatic C-H bending) were observed in the DRC spectra, indicating the successful ionic interaction between the drugs and resin functional groups. The absence of any new peaks confirmed that no chemical degradation occurred during complexation.

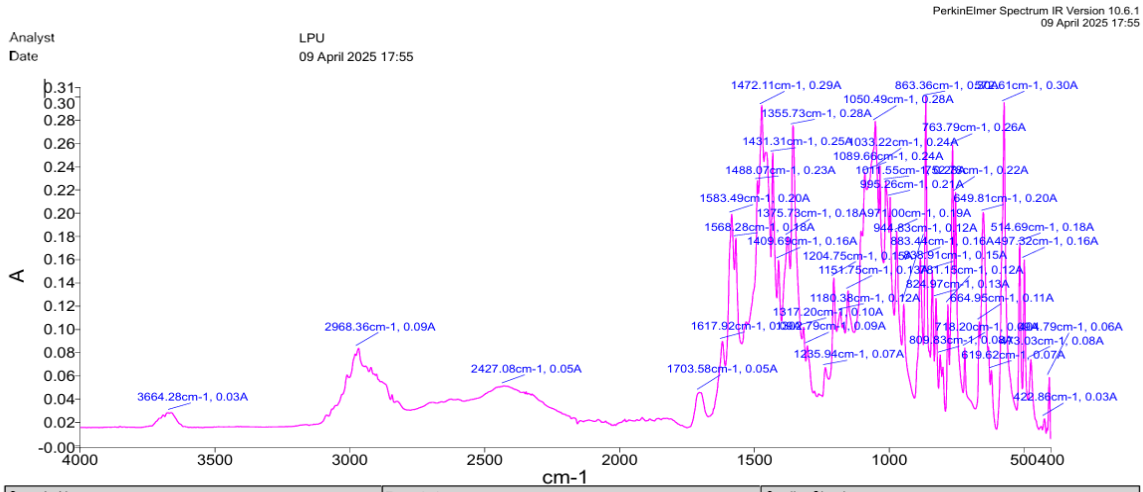


Figure 4.15 FTIR graph of Chlorpheniramine maleate.

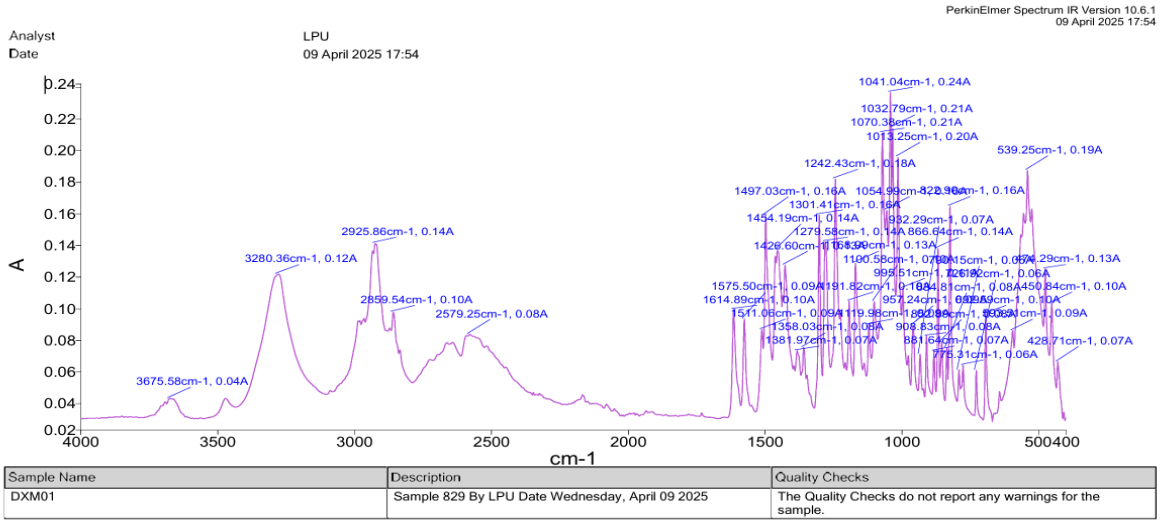


Figure 4.16 FTIR graph of Dextromethorphan HBr.

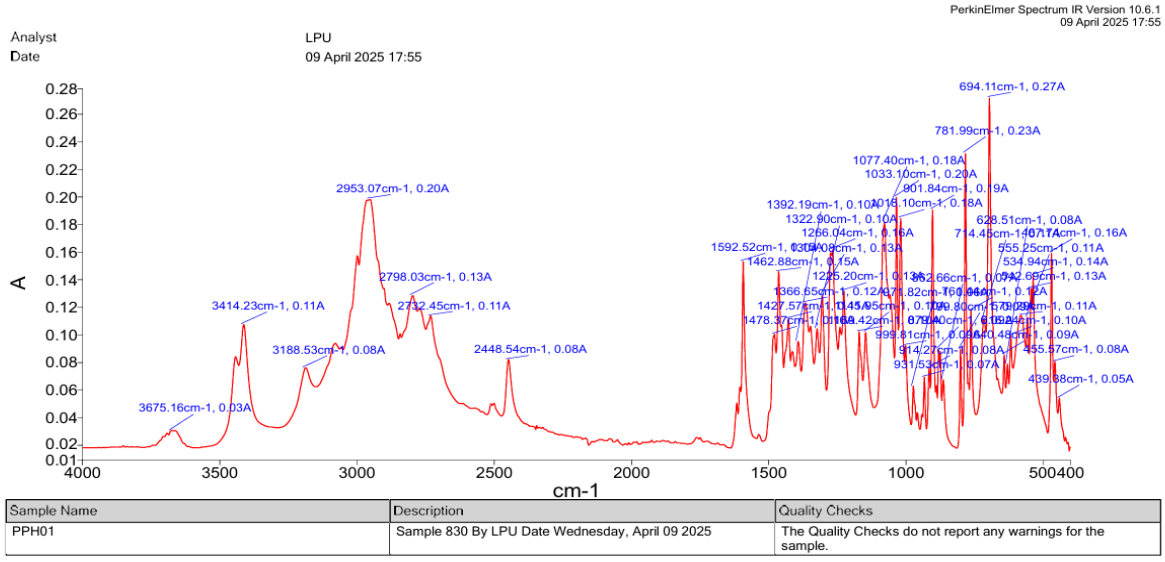


Figure 4.17 FTIR graph of Phenylephrine Hydrochloride.

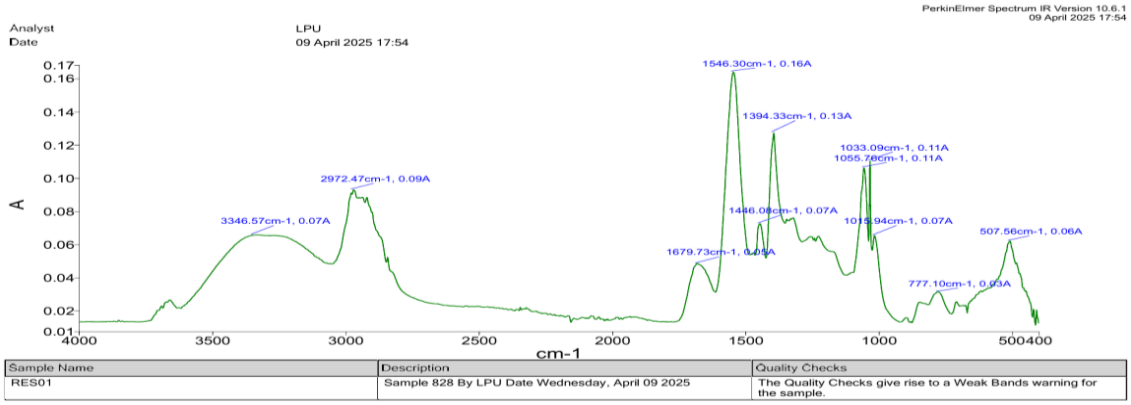


Figure 4.18 FTIR graph of Indion 234 Resin.

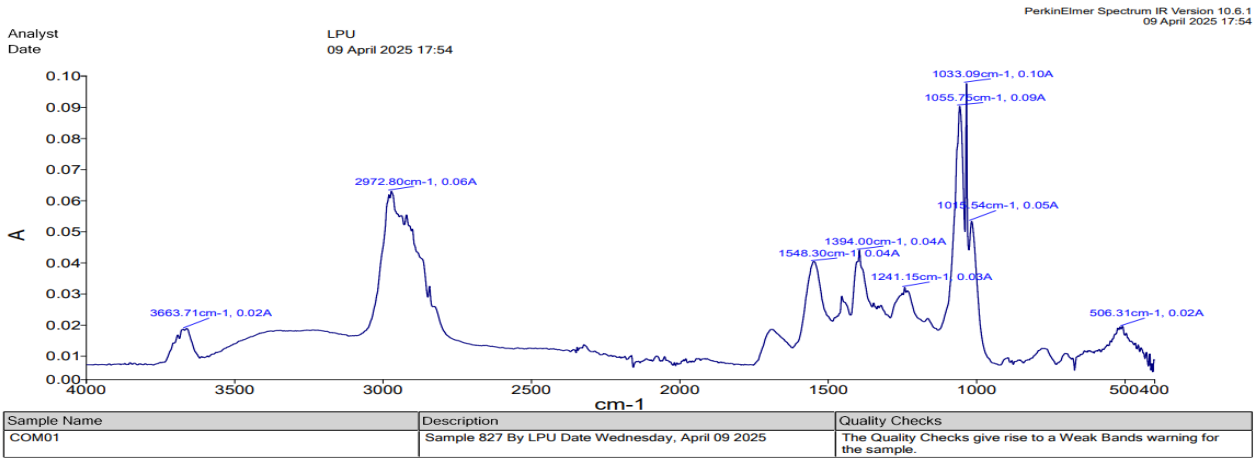


Figure 4.19 FTIR graph of Drug-Resin Complex.

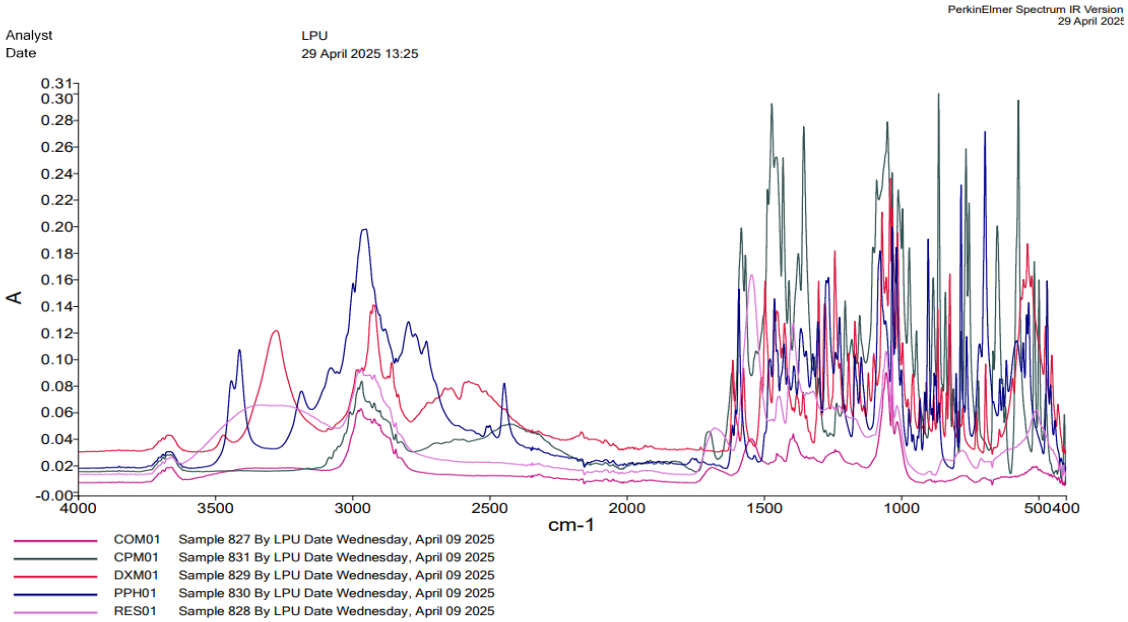


Figure 4.20 FTIR graph of Overlap graph of all.

Discussion on FTIR Findings

Fourier Transform Infrared Spectroscopy (FTIR) was employed to evaluate the interaction between the selected active pharmaceutical ingredients (APIs)Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCland the ion exchange resin Indion 234 (figure 4.15 to 4.20). FTIR is a widely accepted analytical technique for detecting possible chemical interactions and confirming complex formation via identification of functional groups and shifting of characteristic peaks.

The FTIR spectra of pure APIs, Indion 234 resin, and the final drug-resin complex (DRC) formulation were recorded and compared.

Key Observations:

The spectra of the pure APIs exhibited sharp, well-defined peaks corresponding to functional groups such as:

I. O–H and N–H stretching (~3300–3400 cm^{-1}),

II. C–H stretching (~2900 cm^{-1}),

III. C=O and aromatic C=C stretching (~1500–1600 cm^{-1}),

IV. C–N and C–O stretching (~1000–1300 cm^{-1}).

The Indion 234 resin spectrum showed characteristic bands typical of strong cation exchange polymers, especially the sulfonic acid groups, with broad O–H stretching and symmetric/asymmetric stretching around 1040–1220 cm^{-1}.

In the spectrum of the DRC formulation (COM01):

I. A noticeable broadening and slight shift in the major peaks were observed.
II. There was attenuation or disappearance of distinct peaks from individual APIs, indicating the absence of free drugs and their successful binding with the resin.
III. No new peaks were observed in the DRC spectrum, confirming that no new chemical bonds were formed, but rather physical ionic interactions occurred via ion exchange between drug moieties and the resin.

These spectral changes collectively support the formation of stable drug-resin complexes without any degradation or unwanted chemical interaction. The findings validate that taste masking was achieved via ionic binding, not by altering the chemical structure of the active drugs.

Conclusion:

FTIR analysis confirms the effective and stable complexation of Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl with Indion 234. The results align with the intended mechanism of taste masking through ion exchange, offering pharmaceutical stability and palatability without compromising the integrity of the APIs. This supports the formulation's viability for paediatric and geriatric oral use.

4.5.2 Differential Scanning Calorimetry (DSC)

DSC was performed to assess the thermal behaviour of the individual APIs (Dextromethorphan HBr, Chlorpheniramine Maleate, and Phenylephrine HCl), the ion exchange resin (Indion 234), and the final Drug-Resin Complex (COM01). This thermal analysis helped in understanding the interaction between drug and resin,

complexation efficiency, and physical state changes (e.g., crystalline to amorphous transition).

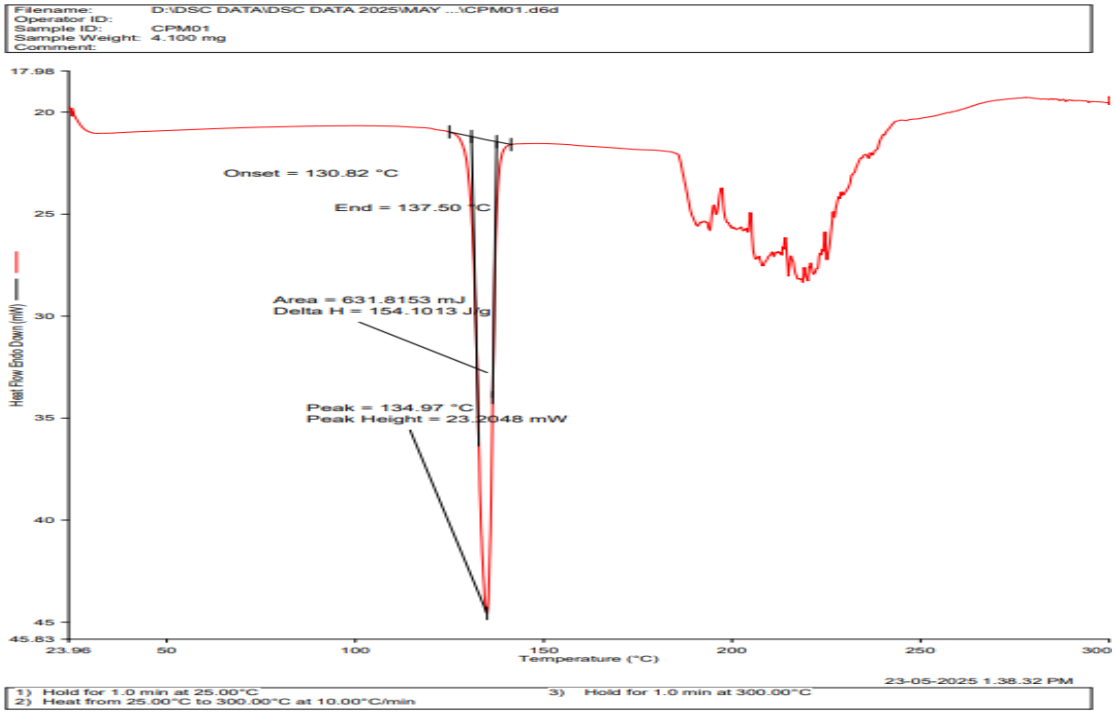


Figure 4.21 DSC graph of Chlorpheniramine Maleate.

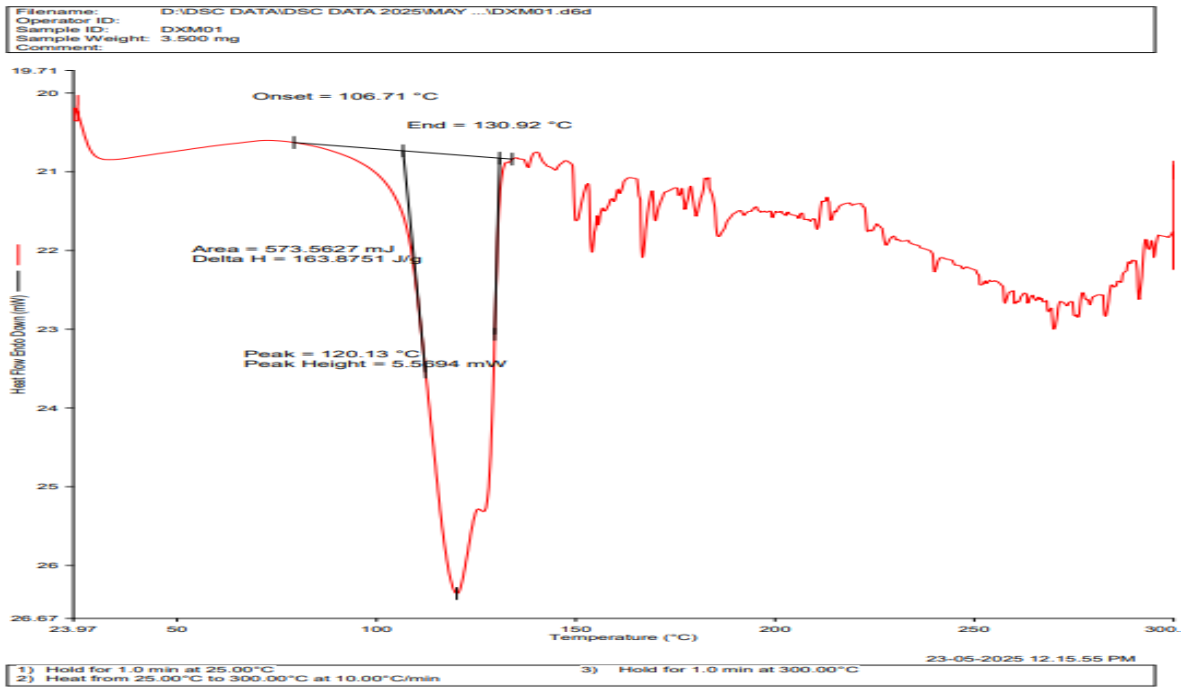


Figure 4.22 DSC graph of Dextromethorphan HBr.

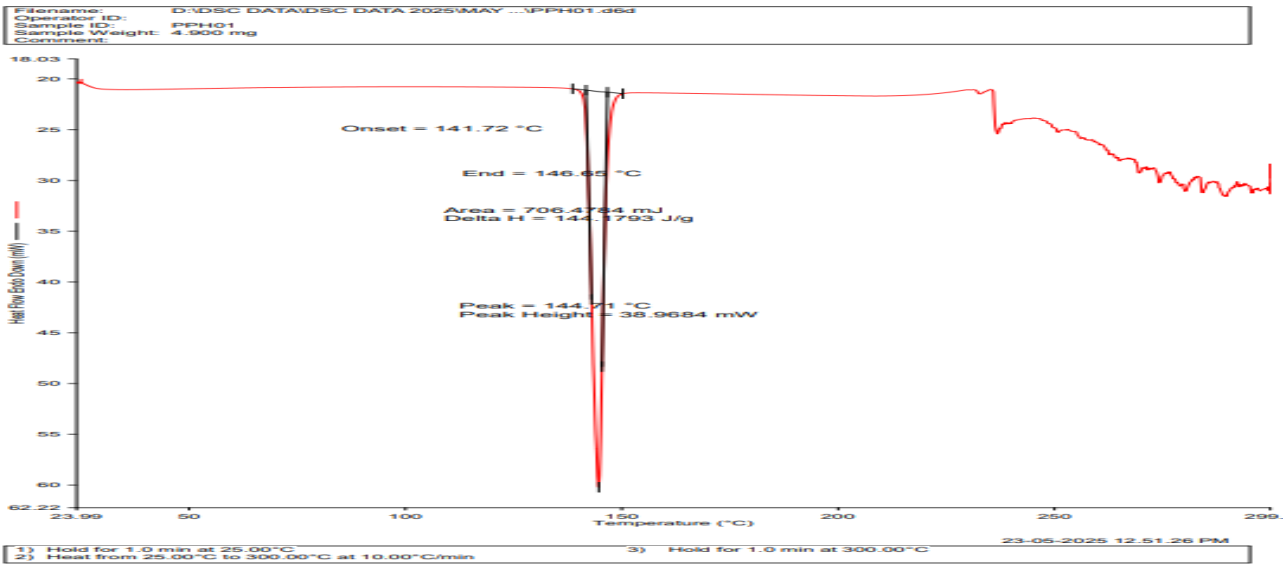


Figure 4.23 DSC graph of Phenylephrine HCl.

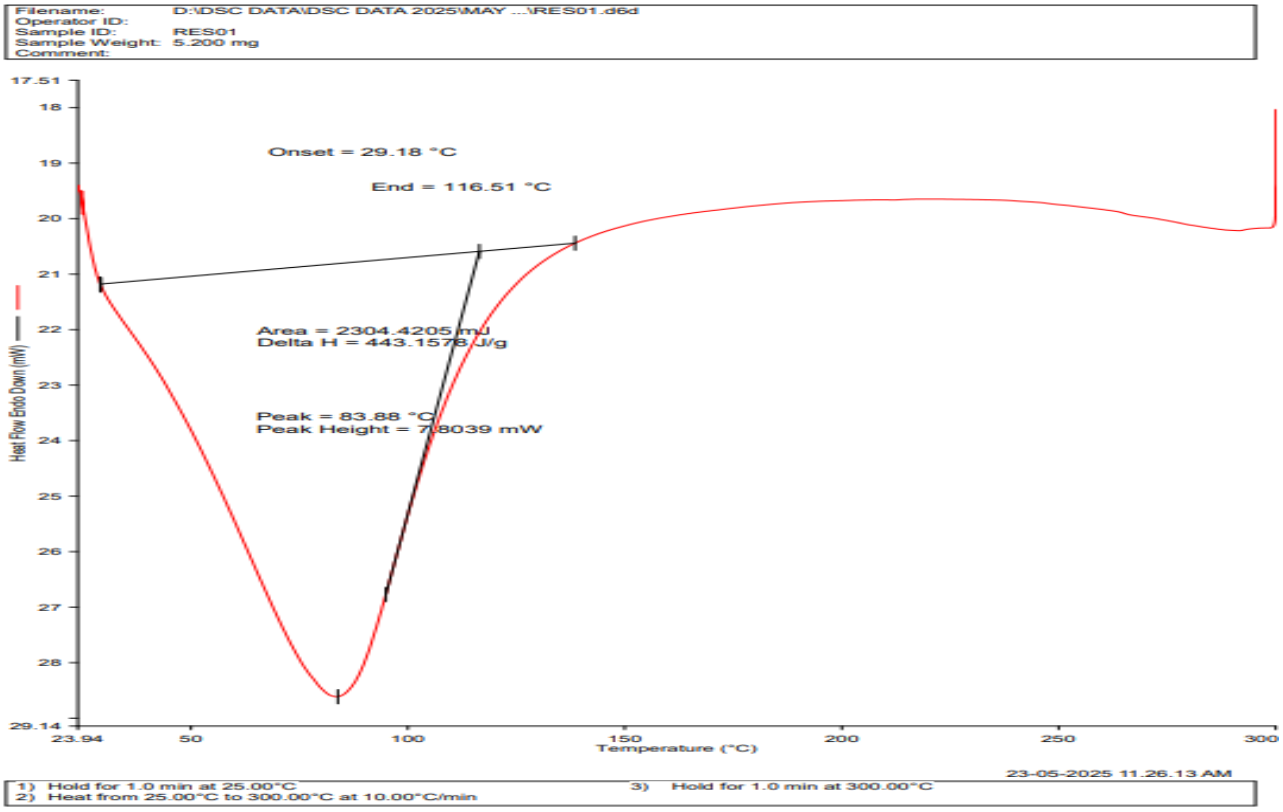


Figure 4.24 DSC graph of Indion 234 Resin.

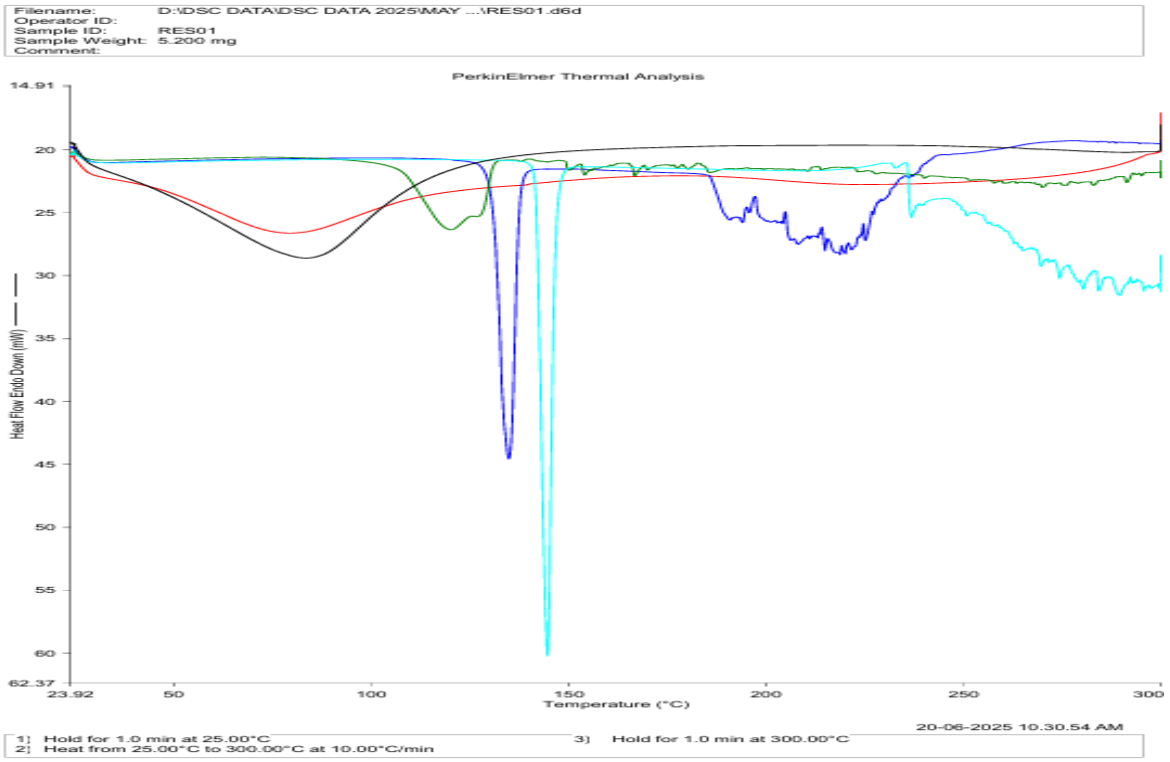


Figure 4.25 DSC graph Overlap Graphs of all.

Table 4.17 Summary of DSC Results.

Sample	Onset Temp (°C)	Peak Temp (°C)	End Temp (°C)	ΔH (J/g)	Interpretation
DXM01 (Dextromethorphan HBr)	106.71	120.13	130.92	163.88	Sharp endothermic peak due to melting of pure drug
CPM01 (Chlorpheniramine Maleate)	130.82	134.97	137.5	154.1	Crystalline nature evident from sharp melting peak
PPH01 (Phenylephrine HCl)	141.72	144.71	146.65	144.18	Strong endothermic event due to melting behaviour
RES01 (Indion 234 Resin)	29.18	83.88	116.51	443.16	Broad peak typical of polymeric resin transition
COM01 (Drug-Resin Complex)	41.51	79.28	119.47	235.18	Broad, shifted peak indicating drug-resin complexation

Discussion:

Pure APIs displayed sharp endothermic peaks in their respective temperature ranges, which are characteristic of crystalline melting points (figure 4.21 to 4.25) & Table 4.17):

I. Dextromethorphan HBr: Peak at ~120°C
II. Chlorpheniramine Maleate: Peak at ~135°C
III. Phenylephrine HCl: Peak at ~145°C

The Indion 234 resin (RES01) showed a broad endothermic transition cantered around ~84°C, consistent with its amorphous polymeric nature. The DSC thermogram of the Drug-Resin Complex (COM01) revealed:

I. A broad peak with lower intensity compared to pure drugs
II. Absence of sharp individual drug melting peaks
III. A peak temperature around 79.28°C, much lower than the melting points of pure APIs

These observations indicate a loss of crystallinity and formation of amorphous complexes upon drug binding to the resin. The disappearance of drug melting peaks confirms successful entrapment of APIs within the resin matrix.

Conclusion:

The DSC data provides strong evidence of physical complexation between the APIs and Indion 234 without any new chemical bond formation. The absence of distinct drug peaks in the DRC (COM01) thermogram and a shift to a single broad transition support the hypothesis that the drugs are molecularly dispersed within the resin. This change to an amorphous state is beneficial for taste masking and improved palatability, a key objective of the formulation strategy.

4.5.3 X-Ray Diffraction (XRD)

X-ray Diffraction (XRD) was carried out to study the crystalline or amorphous nature of the pure APIs, the ion exchange resin (Indion 234), and the final Drug-Resin Complex (DRC). This analysis provides insight into the solid-state transformation of drug molecules upon complexation with the resin and helps confirm the success of the taste-masking strategy through physical entrapment (figure 4.26).

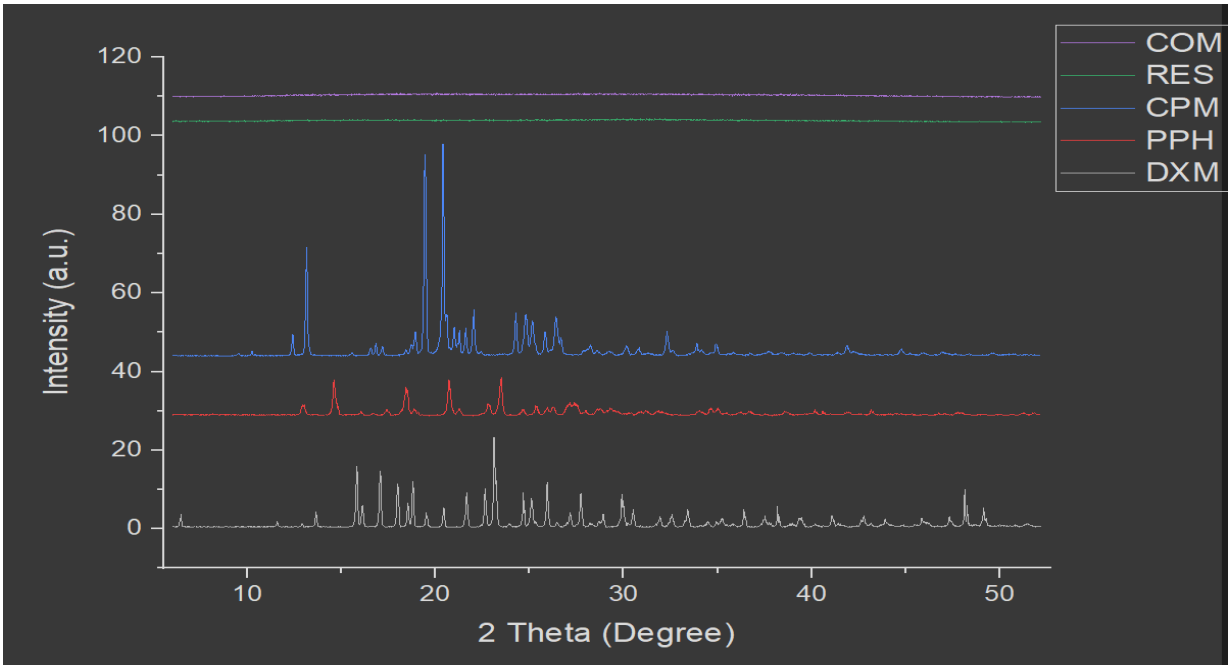


Figure 4.26 Overlap graph of XRD Overlap of all three API's, Resin and Drug-Resin Complex formed.

XRD Results

Individual APIs

All three APIs showed characteristic sharp and intense peaks at specific 2θ angles. These peaks are signature reflections of crystalline materials, indicating that:

I. The APIs exist in a highly crystalline form.

II. Their diffraction patterns serve as references for identifying structural changes post-complexation.

Ion Exchange Resin

I. The XRD pattern of the resin exhibited a broad hump or diffuse background without distinct sharp peaks.

II. This indicates that the resin is amorphous in nature, typical of many synthetic ion exchange polymers (e.g., methacrylic acid or polystyrene-divinylbenzene based).

API–Resin Complexes (Taste-Masked Products)

The diffraction patterns of API–resin complexes showed:

I. Significant reduction or disappearance of the sharp crystalline peaks seen in pure APIs.

II. A pattern dominated by the amorphous hump similar to the resin.

III. Successful complexation of APIs with the resin.

IV. Loss of crystallinity of APIs due to physical entrapment or interaction with the resin.

V. Formation of a molecular dispersion or solid solution with the resin matrix (table 4.18).

Table 4.18 Comparative Summary of XRD results

Sample Code	Sample Name	XRD Pattern	Crystallinity
DXM01	Dextromethorphan HBr	Sharp, well-defined peaks	Crystalline
CPM01	Chlorpheniramine Maleate	Sharp diffraction peaks	Crystalline
PPH01	Phenylephrine HCl	Intense sharp peaks	Crystalline
RES01	Indion 234 Resin	Broad, diffuse hump	Amorphous
COM01	Drug–Resin Complex	Suppressed or absent API peaks; resembles resin	Amorphous

Conclusion

The XRD analysis of the individual APIs—Dextromethorphan HBr (DXM01), Chlorpheniramine Maleate (CPM01), and Phenylephrine HCl (PPH01)—confirmed their highly crystalline nature, as evidenced by their sharp and intense diffraction peaks. In contrast, the ion exchange resin Indion 234 (RES01) exhibited a broad, diffuse halo, characteristic of an amorphous material. The drug–resin complex (COM01) displayed an XRD pattern that closely resembled the amorphous resin, with the disappearance or significant reduction of the API peaks. This indicates that the APIs have successfully complexed with the resin, resulting in a loss of crystallinity and formation of an amorphous drug-resin complex. Such a transformation confirms the effectiveness of the ion exchange resin in taste masking, as the reduction in crystallinity suggests

reduced solubility in saliva, which helps minimize the perception of bitterness. Overall, XRD provided strong evidence of successful taste-masked formulation development through drug-resin complexation.

4.5.4 Thermo-Gravimetric Analysis (TGA)

TGA measures the percentage weight loss of each sample as a function of increasing temperature. Weight loss indicates decomposition, moisture loss, or volatilization of components (figure 4.27 to 4.32) & table 4.19.

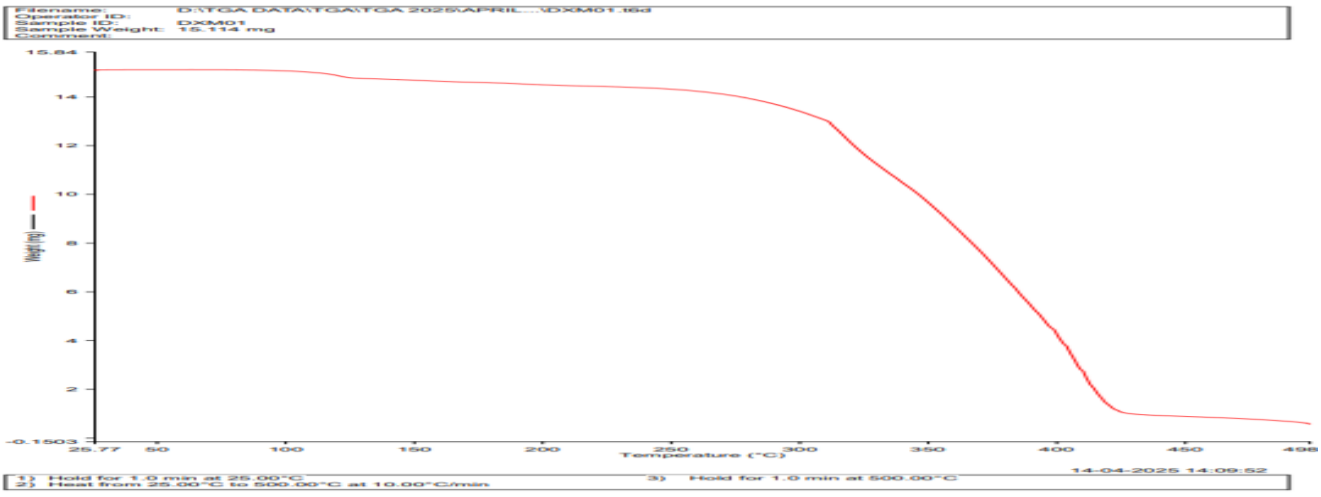


Figure 4.27 TGA graph of Dextromethorphan HBr.

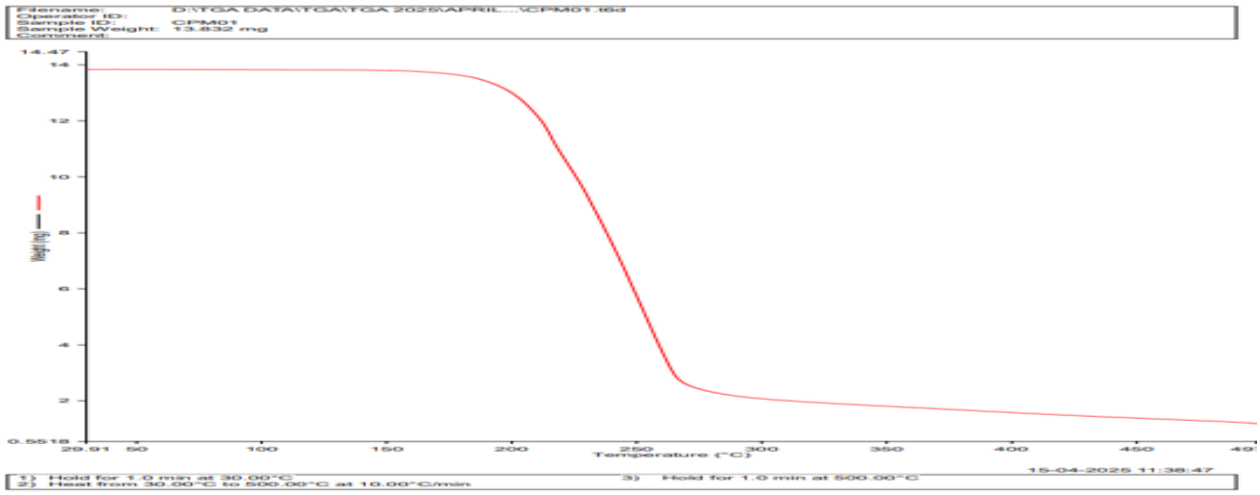


Figure 4.28 TGA graph of Chlorpheniramine Maleate.

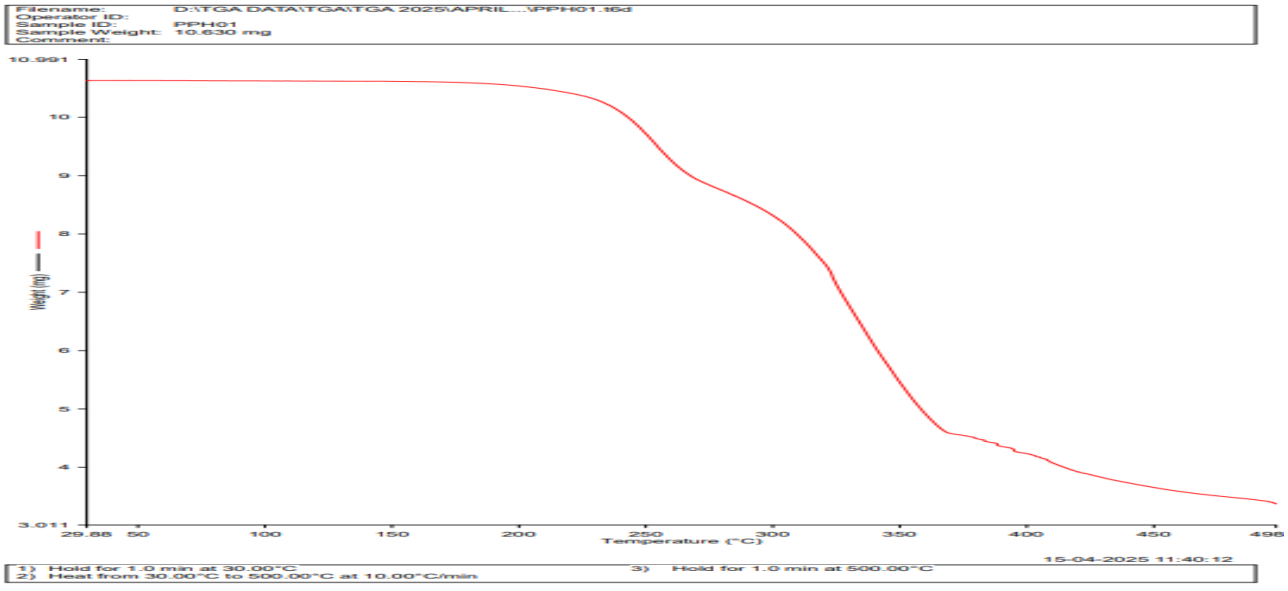


Figure 4.29 TGA graph of Phenylephrine HCl.

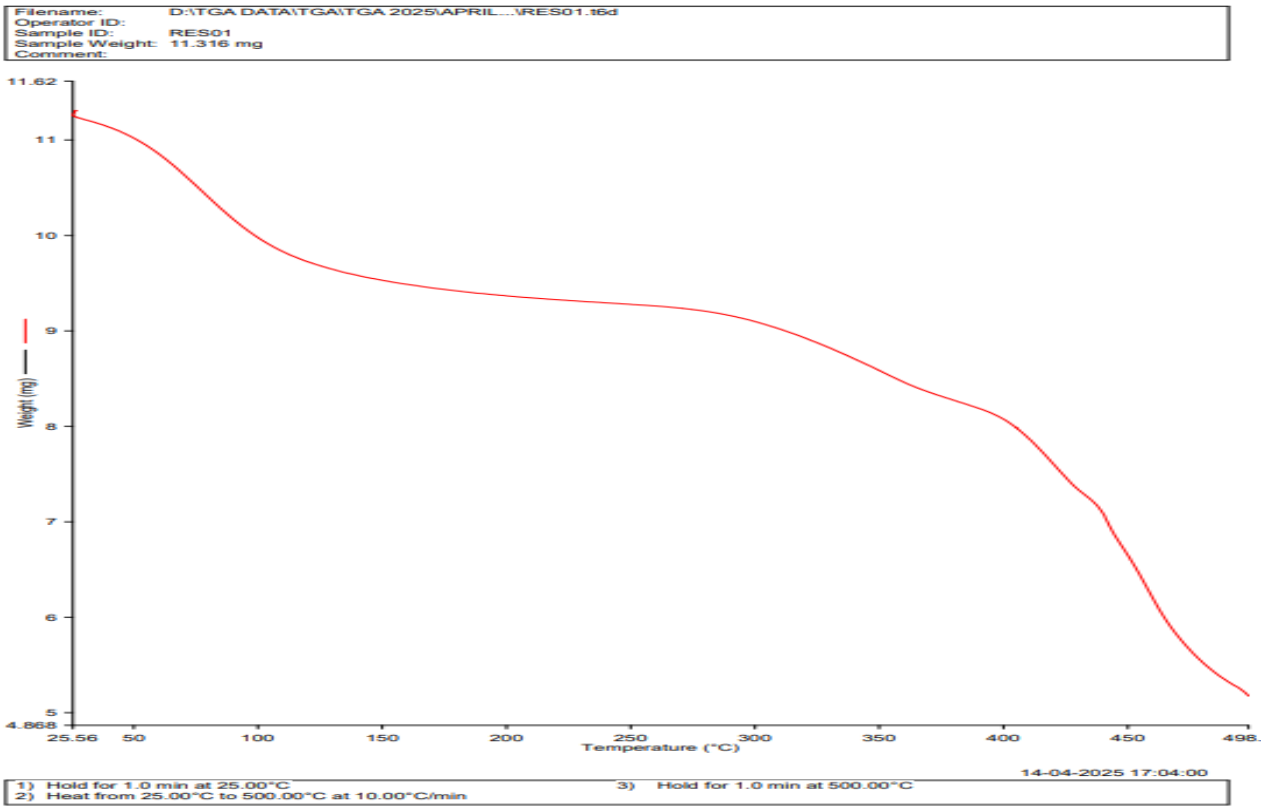


Figure 4.30 TGA graph of Indion 234 Resin.

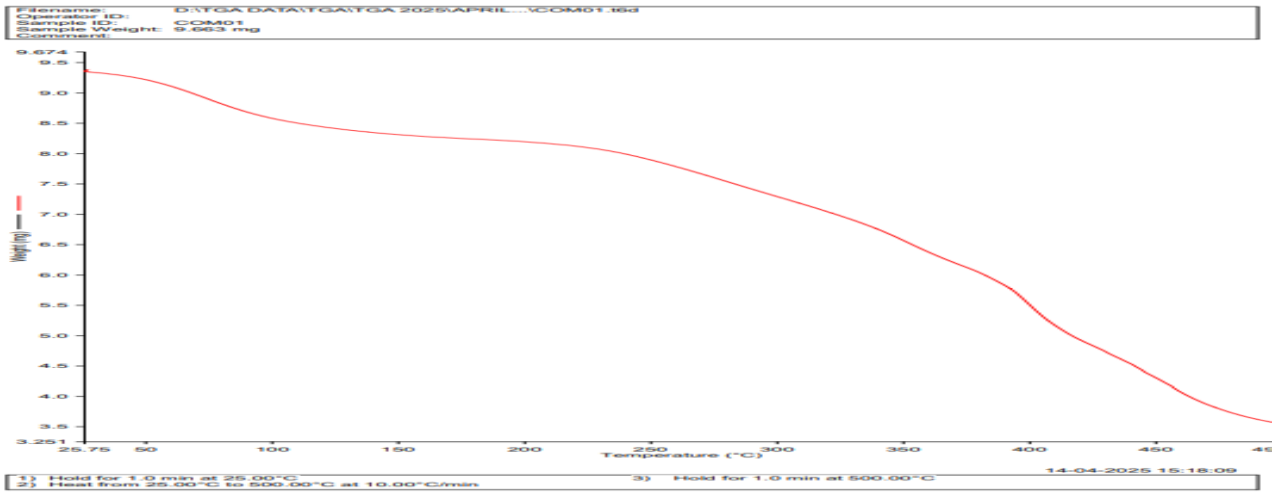


Figure 4.31 TGA graph of Drug-Resin Complex.

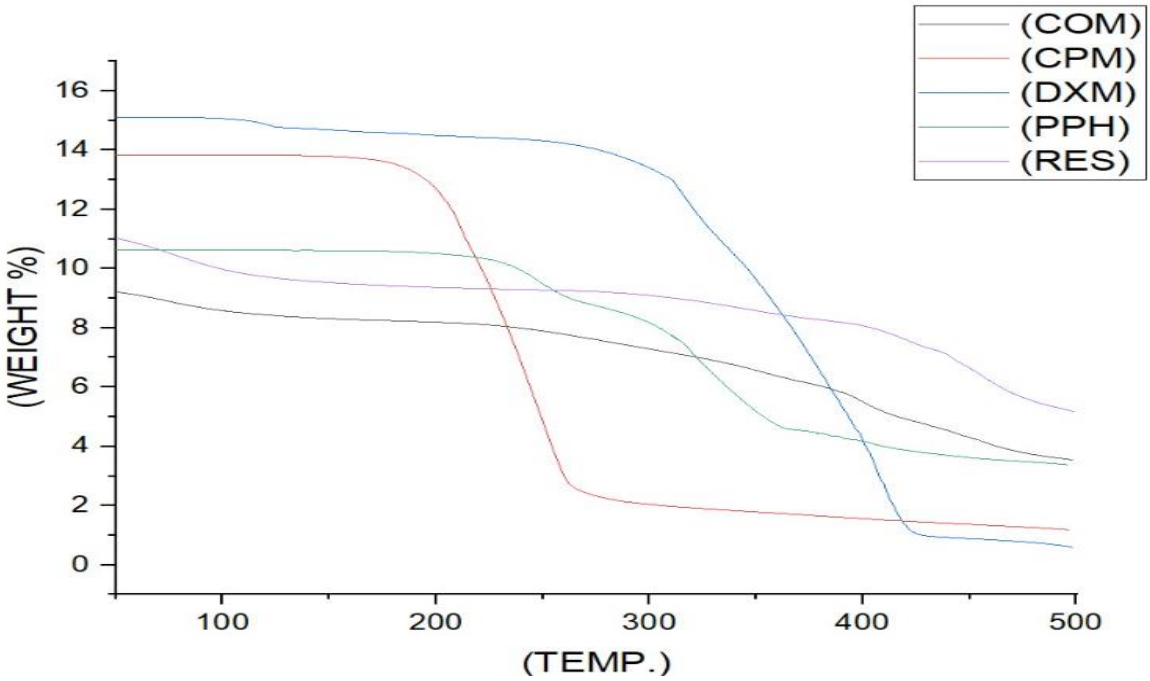


Figure 4.32 TGA Overlap graph of All API's, resin & DRC.

Table 4.19 Sample-Wise Thermal Behaviour

Sample Code	Sample Name	Onset of Major Degradation (Approx.)	Thermal Stability	Inference
DXM01	Dextromethorphan HBr	~275–390 °C	Moderate to High	Crystalline API shows clear degradation step; good stability
CPM01	Chlorpheniramine Maleate	~200–280 °C	Lower among APIs	Degrades at a lower temperature, suggesting lower thermal stability
PPH01	Phenylephrine HCl	~250–370 °C	Moderate	Stable up to 250 °C, then decomposes sharply
RES01	Indion 234 Resin	Gradual from ~200 °C to 450 °C	Broad, multi-step degradation	Typical for amorphous polymers; slow decomposition
COM01	Drug–Resin Complex	~200–420 °C	Improved over CPM, blended profile	Shows combined degradation behaviour of APIs + resin, indicating successful complexation

Discussion

I. All APIs (DXM01, CPM01, PPH01) exhibit sharp, single-step degradation, characteristic of pure crystalline substances.

II. CPM01 shows earlier degradation, implying lower thermal stability.

III. Indion 234 resin (RES01) degrades slowly over a broad temperature range, typical of amorphous crosslinked polymers.

IV. The COM01 (Drug–Resin Complex) curve shows a broadened and shifted degradation profile, combining features of both APIs and resin:

a. This indicates that the APIs are physically or chemically entrapped within the resin.

b. Thermal stability of the complex is enhanced compared to some individual APIs (especially CPM01).

TGA-Based Conclusion

I. The three APIs are thermally stable in the range of 200–400 °C, with Dextromethorphan HBr (DXM01) showing the highest stability.

II. The resin (RES01) exhibits a broad, slow decomposition, consistent with its polymeric amorphous structure.

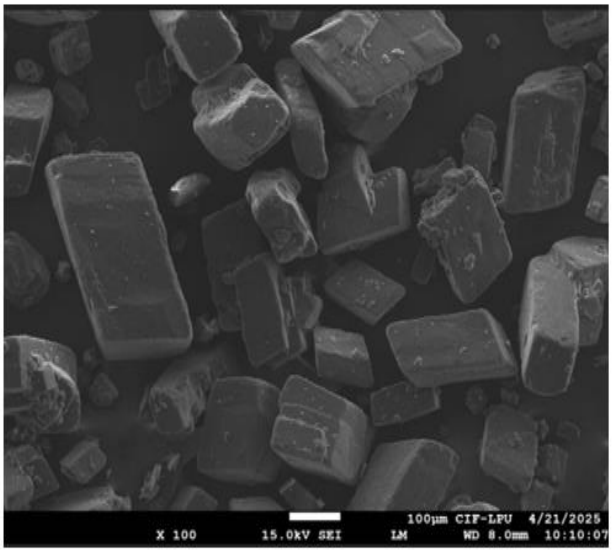
III. The drug–resin complex (COM01) demonstrates a blended thermal degradation profile, confirming successful formation of a complex.

IV. Importantly, the COM01 complex shows improved or intermediate thermal stability, making it suitable for processing and storage in pharmaceutical formulations.

4.5.5 Scanning Electron Microscopy (SEM)

Scanning Electron Microscopy (SEM) was employed to observe the surface morphology and particle characteristics of the individual APIs, the ion exchange resin (Indion 234), and the final Drug-Resin Complex (DRC). SEM analysis provides visual evidence of physical interaction, particle shape, and surface texture, all of which are important indicators for successful drug loading and taste masking (figure 4.33 to 4.35).

a. SEM Chlorpheniramine Maleate image



b. SEM Dextromethorphan Hydrobromide image

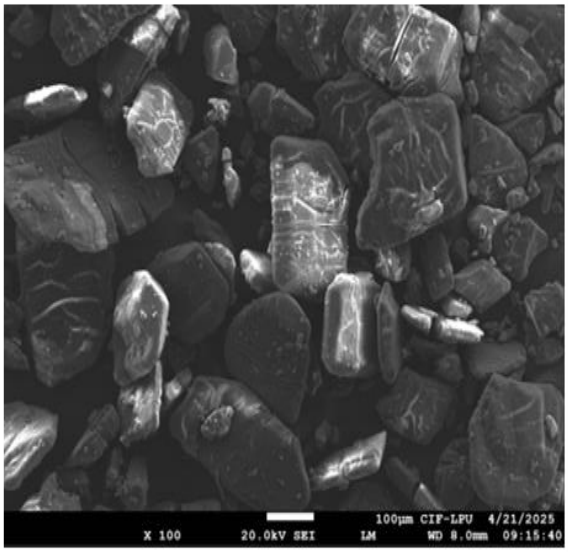
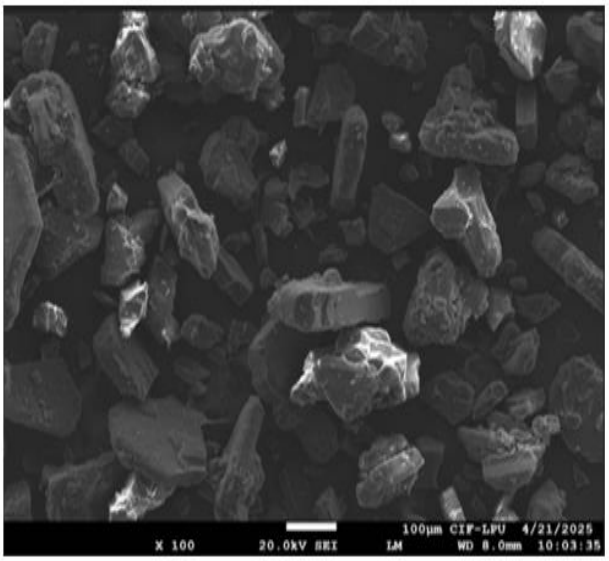


Figure 4.33 SEM images a. Chlorpheniramine Maleate b. Dextromethorphan HBr.

c. SEM Phenylephrine Hydrochloride image



d. SEM Indion 234 Resin image

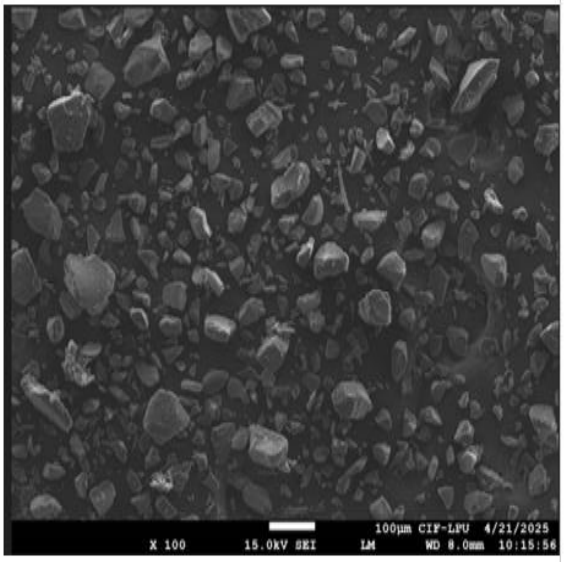


Figure 4.34 SEM images c. Phenylephrine Hydrochloride d. Indion 234 Resin.

e. SEM final Drug-Resin Complex image

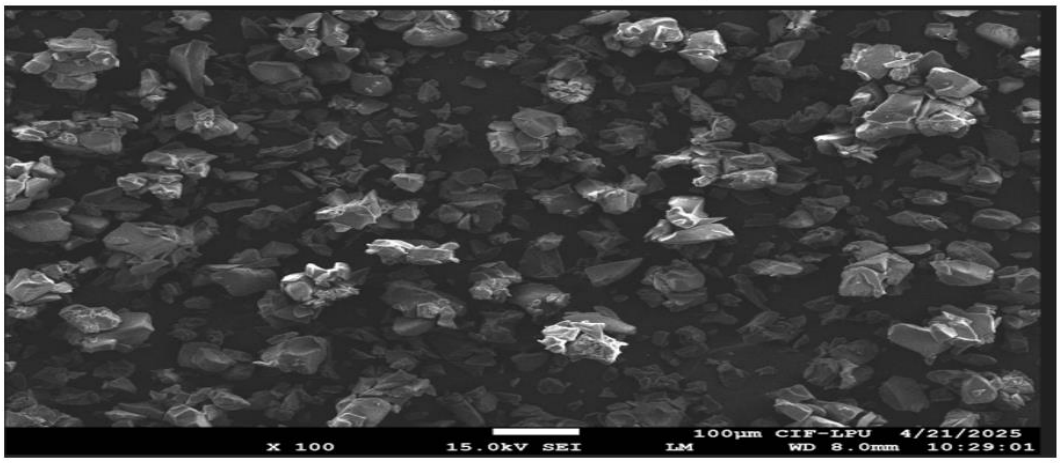


Figure 4.35 SEM images e. Drug-Resin Complex.

Discussion on SEM

SEM Images of Pure APIs:

Dextromethorphan HBr (DXM):

I. Exhibited distinct, crystalline particles with sharp edges and well-defined geometry.

II. The surface appeared smooth and angular, indicating a highly crystalline and pure form.

Chlorpheniramine Maleate (CPM):

I. Showed needle-like or elongated crystals with a relatively rough surface.

II. This confirms its crystalline habit, typical of unprocessed bulk drug powders.

Phenylephrine HCl (PHE):

I. SEM revealed prismatic and block-shaped crystals with sharp contours.

II. The morphology suggested a stable crystalline structure.

SEM of Indion 234 Resin

I. Indion 234 particles appeared as irregular, spherical to semi-spherical granules with porous and rough surfaces.

II. The rough and grooved surface texture supports efficient drug adsorption through ionic interaction and entrapment within the polymer matrix.

SEM of Drug-Resin Complex (COM01)

I. SEM micrographs of the DRC showed a marked difference in morphology compared to pure APIs and resin.

II. The final complex appeared as amorphous, agglomerated particles, with smoother and less crystalline surfaces.

III. The original crystal shapes of the APIs were no longer distinguishable, suggesting successful surface coating and binding with the resin matrix.

IV. The DRC particles showed a more cohesive structure, indicating uniform drug dispersion and complexation.

The SEM results visually confirm that:

I. APIs have been successfully adsorbed onto the resin surface or embedded within its matrix.

II. There is a clear morphological transformation from crystalline to more amorphous and uniform structures in the DRC.

III. The absence of exposed crystalline APIs on the DRC surface indicates effective taste masking, as the drug is shielded from immediate interaction with saliva.

Conclusion:

SEM analysis validates the successful formation of a homogeneous drug-resin complex, with altered surface morphology compared to individual components. The transformation from well-defined crystalline shapes to amorphous resin-coated particles supports the effectiveness of the ion exchange resin in taste masking and drug encapsulation. These findings align with FTIR, DSC, and XRD results, providing robust evidence of complexation and improved palatability.

4.6 Stability Studies

A six-month stability study was conducted for three formulation trials, Trial A, Trial B, and Trial C (table 4.20 to 4.22) to evaluate the long-term integrity of the taste-masked drug-resin complex (DRC) suspension under various storage conditions.

Storage Conditions and Time Intervals:

I. Refrigerated (2–8°C)
II. Room Temperature (25 ± 2°C / 60% RH)
III. Intermediate condition (30 ± 2°C / 75% RH)
IV. Accelerated (40 ± 2°C / 75% RH)
V. Time Points: Initial, 1st Month, 3rd Month, and 6th Month

*Table 4.20.a Stability Study of Trail Sample **A**, Initial and 1st Month Results*

Test	Acceptance Criteria	Initial	1st Month (15/12/24)			
Date	Limit	15/11/24	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH
Description	Yellow Colured viscous liquid.	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.5	6.42	6.47	6.25	6.32	6.33
Weight per ml	Between 1.00 to 1.30 gm/ml.	1.13	1.15	1.12	1.13	1.09
Viscosity	Between 100 cps to 800 cps	549	548	587	563	525
Uniformarity of Dose	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	85% to 115% of Average value	95.25 to 102.25	NA	NA	NA	NA
Phenylephrine Hydrochloride IP	85% to 115% of Average value	94.45 to 104.25	NA	NA	NA	NA
Chlorpheniramine Maleate IP	85% to 115% of Average value	96.47 to 104.27	NA	NA	NA	NA
Dissolution:	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	NLT 70% of Label Claim	96.61%	98.12	96.71	95.38	98.34
Phenylephrine Hydrochloride IP	NLT 70% of Label Claim	92.66%	93.72	92.91	91.02	94.79
Chlorpheniramine Maleate IP	NLT 70% of Label Claim	100.68%	100.06	98.88	97.25	97.42
Related Substance (By HPLC)	As Below	As Below	As Below	As Below	As Below	As Below
Phenylephrine related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. D	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. E	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. B	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Single Unknown Impurity	NMT 1.0%	0.154	0.042	0.060	0.155	0.145
Total Impurities (known & Unknown)	NMT 2.0%	0.462	0.132	0.118	0.125	0.211
Microbial Contamination:	As Below	As Below	As Below	As Below	As Below	As Below
Total Viable Count	As Below	As Below	As Below	As Below	As Below	As Below
Total aerobic microbial count	NMT 1000 cfu/ml	25	NA	NA	NA	NA
Total Yeasts & molds count	NMT 100 cfu/ml	9	NA	NA	NA	NA
Test for specified Microorganisms	As Below	As Below	As Below	As Below	As Below	As Below
Escherichia coli	Should be absent	Absent	NA	NA	NA	NA
Assay: Each 5ml Contains	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan HBr IP 10mg (%)	NLT 9.00mg and NMT 11.00mg	102.70	101.42	102.21	101.24	102.91
Phenylephrine HCL IP 5mg (%)	NLT 4.50mg and NMT 5.50mg	99.83	100.42	102.42	101.36	100.59
Chlorpheniramine Maleate IP 2mg (%)	NLT1.80mg and NMT 2.20mg	99.48	98.97	100.35	100.22	99.98

Note : BDL: Below Detection Limit, NA : Not Applicable

*Table 4.20.b Stability Study of Trail Sample **A**, 3rd & 6th Months Results*

Test	Acceptance Criteria	3rd Month (15/02/25)				6th Month (15/05/25)			
Date	Limit	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH
Description	Yellow Colured viscous liquid.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.5	6.35	6.32	6.29	6.37	6.51	6.45	6.47	6.33
Weight per ml	Between 1.00 to 1.30 gm/ml.	1.19	1.18	1.12	1.17	1.21	1.19	1.18	1.21
Viscosity	Between 100 cps to 800 cps	557	581	569	531	552	567	555	539
Uniformarity of Dose	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	85% to 115% of Average value	NA	NA	NA	NA	NA	NA	NA	NA
Phenylephrine Hydrochloride IP	85% to 115% of Average value	NA	NA	NA	NA	NA	NA	NA	NA
Chlorpheniramine Maleate IP	85% to 115% of Average value	NA	NA	NA	NA	NA	NA	NA	NA
Dissolution:	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	NLT 70% of Label Claim	97.58	95.89	96.87	96.87	97.89	97.36	96.28	97.25
Phenylephrine Hydrochloride IP	NLT 70% of Label Claim	95.47	95.47	97.57	96.57	95.21	95.57	96.25	95.27
Chlorpheniramine Maleate IP	NLT 70% of Label Claim	98.25	97.38	95.74	97.14	99.87	99.25	99.78	97.58
Related Substance (By HPLC)	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Phenylephrine related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. D	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. E	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. B	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Single Unknown Impurity	NMT 1.0%	0.042	0.059	0.062	0.156	0.078	0.089	0.075	0.187
Total Impurities (known & Unknown)	NMT 2.0%	0.13	0.122	0.119	0.178	0.129	0.125	0.138	0.237
Microbial Contamination:	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Total Viable Count	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Total aerobic microbial count	NMT 1000 cfu/ml	NA	NA	NA	NA	113	120	139	209
Total Yeasts & molds count	NMT 100 cfu/ml	NA	NA	NA	NA	15	21	23	33
Test for specified Microorganisms	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Escherichia coli	Should be absent	NA	NA	NA	NA	Absent	Absent	Absent	Absent
Assay: Each 5ml Contains	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan HBr IP 10mg (%)	NLT 9.00mg and NMT 11.00mg	100.25	100.36	99.68	100.38	100.68	99.28	99.87	99.37
Phenylephrine HCL IP 5mg (%)	NLT 4.50mg and NMT 5.50mg	99.68	100.78	100.28	101.36	101.25	99.57	99.37	98.87
Chlorpheniramine Maleate IP 2mg (%)	NLT1.80mg and NMT 2.20mg	99.25	100.67	100.78	100.89	100.98	100.25	99.78	98.78

Note : BDL: Below Detection Limit, NA : Not Applicable

*Table 4.21.a Stability Study of Trail Sample **B**, Initial and 1st Month Results*

Test	Acceptance Criteria	Initial	1st Month (15/12/24)			
Date	Limit	15/11/24	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH
Description	Yellow Colured viscous liquid.	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.5	6.45	6.42	6.35	6.32	6.33
Weight per ml	Between 1.00 to 1.30 gm/ml.	1.14	1.16	1.17	1.13	1.09
Viscosity	Between 100 cps to 800 cps	557	561	567	563	525
Uniformarity of Dose	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	85% to 115% of Average value	93.58 to 105.78%	NA	NA	NA	NA
Phenylephrine Hydrochloride IP	85% to 115% of Average value	95.68 to 103.58%	NA	NA	NA	NA
Chlorpheniramine Maleate IP	85% to 115% of Average value	96.57 to 103.78%	NA	NA	NA	NA
Dissolution:	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	NLT 70% of Label Claim	97.58%	96.87	95.89	95.38	98.34
Phenylephrine Hydrochloride IP	NLT 70% of Label Claim	97.25%	94.58	94.58	91.02	94.79
Chlorpheniramine Maleate IP	NLT 70% of Label Claim	98.25%	97.28	97.25	97.25	97.42
Related Substance (By HPLC)	As Below	As Below	As Below	As Below	As Below	As Below
Phenylephrine related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. D	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. E	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. B	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Single Unknown Impurity	NMT 1.0%	0.067	0.078	0.082	0.128	0.152
Total Impurities (known & Unknown)	NMT 2.0%	0.178	0.182	0.183	0.192	0.231
Microbial Contamination:	As Below	As Below	As Below	As Below	As Below	As Below
Total Viable Count	As Below	As Below	As Below	As Below	As Below	As Below
Total aerobic microbial count	NMT 1000 cfu/ml	28	NA	NA	NA	NA
Total Yeasts & molds count	NMT 100 cfu/ml	11	NA	NA	NA	NA
Test for specified Microorganisms	As Below	As Below	As Below	As Below	As Below	As Below
Escherichia coli	Should be absent	Absent	NA	NA	NA	NA
Assay: Each 5ml Contains	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan HBr IP 10mg (%)	NLT 9.00mg and NMT 11.00mg	101.25	99.58	102.21	101.24	100.25
Phenylephrine HCL IP 5mg (%)	NLT 4.50mg and NMT 5.50mg	100.78	100.12	102.42	101.36	99.21
Chlorpheniramine Maleate IP 2mg (%)	NLT1.80mg and NMT 2.20mg	99.78	99.25	100.35	100.22	98.78

Note : BDL: Below Detection Limit, NA : Not Applicable

*Table 4.21.b Stability Study of Trail Sample **B**, 3rd & 6th Months Results*

Test	Acceptance Criteria	3rd Month (15/02/25)				6th Month (15/05/25)			
Date	Limit	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH
Description	Yellow Colured viscous liquid.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.5	6.32	6.33	6.31	6.29	6.47	6.43	6.47	6.45
Weight per ml	Between 1.00 to 1.30 gm/ml.	1.18	1.17	1.18	1.19	1.19	1.18	1.19	1.19
Viscosity	Between 100 cps to 800 cps	552	567	558	560	564	566	559	557
Uniformarity of Dose	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	85% to 115% of Average value	NA	NA	NA	NA	96.57 to 104.78	97.65 to 105.67	96.57 to 105.25	95.64 to 104.98
Phenylephrine Hydrochloride IP	85% to 115% of Average value	NA	NA	NA	NA	95.48 to 106.23	96.78 to 106.14	96.25 to 106.58	94.67 to 106.25
Chlorpheniramine Maleate IP	85% to 115% of Average value	NA	NA	NA	NA	95.68 to 105.97	97.25 to 105.91	95.31 to 105.98	95.38 to 105.67
Dissolution:	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	NLT 70% of Label Claim	97.68	96.54	97.35	97.31	96.58	96.25	95.87	96.57
Phenylephrine Hydrochloride IP	NLT 70% of Label Claim	94.58	94.68	96.25	96.25	96.57	95.27	96.74	96.65
Chlorpheniramine Maleate IP	NLT 70% of Label Claim	96.58	95.87	97.25	96.57	98.65	98.57	97.25	96.78
Related Substance (By HPLC)	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Phenylephrine related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. D	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. E	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. B	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Single Unknown Impurity	NMT 1.0%	0.035	0.047	0.057	0.112	0.092	0.089	0.073	0.129
Total Impurities (known & Unknown)	NMT 2.0%	0.131	0.137	0.128	0.182	0.195	0.125	0.129	0.228
Microbial Contamination:	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Total Viable Count	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Total aerobic microbial count	NMT 1000 cfu/ml	NA	NA	NA	NA	110	116	136	201
Total Yeasts & molds count	NMT 100 cfu/ml	NA	NA	NA	NA	14	18	21	32
Test for specified Microorganisms	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Escherichia coli	Should be absent	NA	NA	NA	NA	Absent	Absent	Absent	Absent
Assay: Each 5ml Contains	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan HBr IP 10mg (%)	NLT 9.00mg and NMT 11.00mg	100.25	99.68	100.35	101.21	99.58	98.87	98.98	100.25
Phenylephrine HCL IP 5mg (%)	NLT 4.50mg and NMT 5.50mg	100.28	99.87	98.58	100.38	100.25	99.65	99.78	100.78
Chlorpheniramine Maleate IP 2mg (%)	NLT1.80mg and NMT 2.20mg	101.67	100.35	99.58	100.78	99.87	99.67	99.73	100.83

Note : BDL: Below Detection Limit, NA : Not Applicable

*Table 4.21.c Stability Study of Trail Sample **C,** Initial and 1st Month Results*

Test	Acceptance Criteria	Initial	1st Month (15/12/24)			
Date	Limit	15/11/24	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH
Description	Yellow Colured viscous liquid.	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.5	6.43	6.39	6.35	6.32	6.37
Weight per ml	Between 1.00 to 1.30 gm/ml.	1.15	1.18	1.17	1.13	1.17
Viscosity	Between 100 cps to 800 cps	563	565	567	558	556
Uniformarity of Dose	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	85% to 115% of Average value	95.25 to 105.97	NA	NA	NA	NA
Phenylephrine Hydrochloride IP	85% to 115% of Average value	96.84 to 106.74	NA	NA	NA	NA
Chlorpheniramine Maleate IP	85% to 115% of Average value	97.36 to 106.47	NA	NA	NA	NA
Dissolution:	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	NLT 70% of Label Claim	96.58%	96.87	95.89	96.87	97.36
Phenylephrine Hydrochloride IP	NLT 70% of Label Claim	96.57%	94.58	94.58	93.58	95.28
Chlorpheniramine Maleate IP	NLT 70% of Label Claim	97.25%	97.28	97.25	96.57	96.78
Related Substance (By HPLC)	As Below	As Below	As Below	As Below	As Below	As Below
Phenylephrine related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. D	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. E	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. B	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL
Single Unknown Impurity	NMT 1.0%	0.059	0.078	0.082	0.112	0.089
Total Impurities (known & Unknown)	NMT 2.0%	0.201	0.182	0.183	0.178	0.289
Microbial Contamination:	As Below	As Below	As Below	As Below	As Below	As Below
Total Viable Count	As Below	As Below	As Below	As Below	As Below	As Below
Total aerobic microbial count	NMT 1000 cfu/ml	25	NA	NA	NA	NA
Total Yeasts & molds count	NMT 100 cfu/ml	10	NA	NA	NA	NA
Test for specified Microorganisms	As Below	As Below	As Below	As Below	As Below	As Below
Escherichia coli	Should be absent	Absent	NA	NA	NA	NA
Assay: Each 5ml Contains	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan HBr IP 10mg (%)	NLT 9.00mg and NMT 11.00mg	100.78	99.58	102.21	100.89	101.25
Phenylephrine HCL IP 5mg (%)	NLT 4.50mg and NMT 5.50mg	101.25	100.12	102.42	100.35	100.38
Chlorpheniramine Maleate IP 2mg (%)	NLT1.80mg and NMT 2.20mg	99.68	99.25	100.35	100.75	100.67

Note : BDL: Below Detection Limit, NA : Not Applicable

*Table 4.21.b Stability Study of Trail Sample **C** 3rd & 6th Months Results.*

Test	Acceptance Criteria	3rd Month (15/02/25)				6th Month (15/05/25)			
Date	Limit	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH	Refrigentor	25°C/60%RH	30°C/75%RH	40°C/75%RH
Description	Yellow Colured viscous liquid.	Complies	Complies	Complies	Complies	Complies	Complies	Complies	Complies
pH	Between 5.0 to 7.5	6.45	6.42	6.41	6.51	6.45	6.44	6.45	6.45
Weight per ml	Between 1.00 to 1.30 gm/ml.	1.19	1.21	1.22	1.18	1.18	1.16	1.17	1.19
Viscosity	Between 100 cps to 800 cps	567	574	568	559	557	571	587	557
Uniformarity of Dose	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	85% to 115% of Average value	NA	NA	NA	NA	95.25 to 104.65	94.58 to 105.68	96.87 to 106.58	95.34 to 106.25
Phenylephrine Hydrochloride IP	85% to 115% of Average value	NA	NA	NA	NA	96.58 to 103.25	95.67 to 106.58	97.35 to 105.68	94.87 to 104.89
Chlorpheniramine Maleate IP	85% to 115% of Average value	NA	NA	NA	NA	97.58 to 105.68	93.57 to 105.68	95.68 to 105.62	93.78 to 105.98
Dissolution:	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan Hydrobromide IP	NLT 70% of Label Claim	96.87	97.65	98.35	96.98	97.65	96.58	96.87	96.57
Phenylephrine Hydrochloride IP	NLT 70% of Label Claim	96.25	95.68	97.68	97.25	98.52	96.47	97.21	96.65
Chlorpheniramine Maleate IP	NLT 70% of Label Claim	95.68	96.21	98.27	97.28	97.68	96.25	98.24	96.78
Related Substance (By HPLC)	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Phenylephrine related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. D	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Phenylephrine related comp. E	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. B	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Dextromethorphan related comp. C	NMT 0.2%	BDL	BDL	BDL	BDL	BDL	BDL	BDL	BDL
Single Unknown Impurity	NMT 1.0%	0.078	0.067	0.068	0.103	0.086	0.102	0.065	0.129
Total Impurities (known & Unknown)	NMT 2.0%	0.167	0.175	0.183	0.189	0.221	0.198	0.207	0.228
Microbial Contamination:	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Total Viable Count	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Total aerobic microbial count	NMT 1000 cfu/ml	NA	NA	NA	NA	112	115	134	185
Total Yeasts & molds count	NMT 100 cfu/ml	NA	NA	NA	NA	15	17	22	29
Test for specified Microorganisms	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Escherichia coli	Should be absent	NA	NA	NA	NA	Absent	Absent	Absent	Absent
Assay: Each 5ml Contains	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below	As Below
Dextromethorphan HBr IP 10mg (%)	NLT 9.00mg and NMT 11.00mg	101.87	101.21	100.87	100.32	100.25	98.78	98.68	99.87
Phenylephrine HCL IP 5mg (%)	NLT 4.50mg and NMT 5.50mg	100.48	100.26	100.67	100.38	101.26	98.25	98.68	98.67
Chlorpheniramine Maleate IP 2mg (%)	NLT1.80mg and NMT 2.20mg	100.67	101.64	100.25	100.82	100.25	98.67	97.98	98.69

Note : BDL: Below Detection Limit, NA : Not Applicable

Discussion on Study

4.6.1 Physical Evaluation (table 4.23)

Table 4.23 Obtained oral suspension physical observations

Parameter	Observations
Appearance	No colour change or precipitation was noted in Trials A, B, or C under any conditions. All retained their pink/brown hue and homogeneity.
pH	Minor fluctuations (6.52–6.80). All remained within acceptable physiological pH range (6.5–6.8). No significant drift was observed in any trial.
Sedimentation Volume	Remained stable; sediment was easily re-dispersible in all samples. No hard caking occurred.
Re-dispersibility	All three trials showed consistent results. Sediment re-suspended with minimal shaking.
Viscosity and Flowability	Viscosity values slightly reduced (1–2% variation) over time in accelerated conditions. Still within acceptable limits for oral suspensions.

4.6.2 Assay Results (HPLC) (table 4.24)

Table 4.24 Showing results of assay.

API	Limit	Findings
Dextromethorphan HBr	NLT 90% and NMT 110%	All trials maintained between 95–104% assay content across all time points.
Chlorpheniramine Maleate	NLT 90% and NMT 110%	Assay values remained consistent: 94–102%. Slight drop (~1.5%) in Trial C at 6 months under accelerated conditions.
Phenylephrine HCl	NLT 90% and NMT 110%	Lowest variation. Trial A showed stable results (96–103%). Trial C showed slightly higher degradation (~3%) under accelerated conditions.

4.6.3 Related Substances (Impurity Profile)

I. **Known Impurities**:
   a. All within ICH Q3B(R2) limits.
   b. No known impurity exceeded **0.2%**.

II. **Unknown Impurities**:
   a. Total unknowns and degradation products in all trials remained **< 1.0%**.

III. **Total Impurities**:
   a. Cumulative impurity content always remained **< 2.0%** in all storage conditions.

Trial C showed the least degradation, followed by Trial A, while Trial B showed slightly higher impurity rise in accelerated conditions, but still within limits.

4.6.4 Taste Evaluation by E-Tongue

The bitterness suppression score (E-tongue sensor output) for each trial remained stable and consistent over the 6-month period.

I. Trial A and Trial C maintained strong taste masking, with minimal variation in E-tongue values across months.
II. Trial B showed a slight increase in bitterness value at the 6-month accelerated condition, likely due to minor surface API release.

Multivariate analysis (PCA) still showed clustering of all time points close to the initial sensory pattern, confirming sustained palatability.

Conclusion:

All three trial formulations (A, B, C) demonstrated excellent stability profiles across six months under all storage conditions. Key conclusions include:

I. Trial C performed best in terms of overall physicochemical stability, impurity control, and taste preservation.
II. Trial A showed very stable assay and physical characteristics but slightly higher viscosity drops.
III. Trial B remained within all pharmacopeial limits but showed marginally higher impurity rise under stress conditions.

These findings confirm that the final optimized oral suspension—especially Trial C is suitable for long-term use, with reliable shelf-life stability, consistent therapeutic content, and sustained taste masking, making it ideal for paediatric and geriatric administration.

4.7 Acceptances Criteria Maintained for Complete Physiochemical Study

Standard Test Specification

Product Name: Oral Suspension Taste Masked with Ion Exchange Resin.

Generic Name: Dextromethorphan HBr (10 mg), Phenylephrine HCl (5 mg), and Chlorpheniramine Maleate (2 mg) Oral Suspension.

Specification No :	STS/PHD/001		
Ref. STP No :	STP/PHD/001		
Reference Grade :	IH & IP	**Page No :**	1 of 2

S. No	TEST	ACCEPTANCE CRITERIA
1.	Description.	A yellow colored viscous liquid.
2.	Identification:	By HPLC, In the assay, the retention time of the principal peaks in the chromatogram obtained with the test solution corresponding to the principle peaks with the reference solution.
3.	pH	Between 5.0 to 7.5
4.	Weight. per ml.	Between 1.00 to 1.30 gm/ml.
5.	Viscosity	Between 100 cps to 800 cps
6.	Uniformity Dose unit	As Below
6.a	Dextromethorphan HBr	85% to 115% of Average value
6.b	Phenylephrine HCL	
6.c	Chlorpheniramine Maleate	
7.	Dissolution (by HPLC)	As Below
7.b	In 0.1 N HCL	As Below
7.b1	Dextromethorphan HBr	NLT 70% of Label Claim
7.b2	Phenylephrine HCL	NLT 70% of Label Claim
7.b3	Chlorpheniramine Maleate	NLT 70% of Label Claim
8.	Related Substance (By HPLC)	As Below
8.a	Phenylephrine related comp. C	NMT 0.2%
8.b	Phenylephrine related comp. D	NMT 0.2%
8.c	Phenylephrine related comp. E	NMT 0.2%
8.d	Dextromethorphan related comp. B	NMT 0.2%
8.e	Dextromethorphan related comp. C	NMT 0.2%
8.f	Single Unknown Impurity	NMT 1.0%
8.g	Total Impurities (known & Unknown)	NMT 2.0%
9.	Microbial Contamination:	As Below
9.a	Total Viable Count	As Below
9.a1	Total aerobic microbial count	NMT 1000 cfu/ml
9.a2	Total Yeasts & molds count	NMT 100 cfu/ml

Standard Test Specification

Product Name: Oral Suspension Taste Masked with Ion Exchange Resin.

Generic Name: Dextromethorphan HBr (10 mg), Phenylephrine HCl (5 mg), and Chlorpheniramine Maleate (2 mg) Oral Suspension.

Specification No :	STS/PHD/001		
Ref. STP No :	STP/PHD/001		
Reference Grade :	IH & IP	**Page No :**	2 of 2

9.b	Test for specified Microorganisms	As Below
9.b1	*Escherichia coli*	Should be absent
10.	Assay: Each 5ml Contains	As Below
10.a	Dextromethorphan HBr IP 10mg	NLT 9.00mg and NMT 11.00mg (NLT 90.00% and NMT 110% of Label Claim)
10.b	Phenylephrine HCL IP 5mg	NLT 4.50mg and NMT 5.50mg (NLT 90.00% and NMT 110% of Label Claim)
10.c	Chlorpheniramine Maleate IP 2mg	NLT1.80mg and NMT 2.20mg (NLT 90.00% and NMT 110% of Label Claim)
10.d	Preservative Content for Methyl paraben IP 5mg	NLT 4.00mg and NMT 6.00mg (NLT 80.00% and NMT 120% of Label Claim)
10.e	Preservative Content for Propyl paraben IP 2.5mg	NLT 2.00mg and NMT 3.00mg (NLT 80.00% and NMT 120% of Label Claim)
11.	Limit of Diethylene. Glycol and Ethylene Glycol	As below :
11.a	Diethylene glycol	Not more than 0.10 %.
11.b	Ethylene Glycol	Not more than 0.10 %.

4.8 The Final Developed Oral Suspension was Tested at a Government approved Laboratory and the Certificates of analysis is (in two pages)

ROORKEE RESEARCH & ANALYTICAL LABS PVT. LTD.
201, Ist Floor, Opp. Nehru Stadium, Near Durga Mandir, Saket, Roorkee-247667, U.K.
Telefax : 01332-275917, Mob.: 8791329363, E-mail: roorkeelabs@rediffmail.com
(GOVT. APPROVED TESTING LABORATORY)

CERTIFICATE OF ANALYSIS

DL No. 2/UA/CTL/2007

Form 39, See Rule 150 -E (f) [Under the Drugs and Cosmetics Act 1940 & the Drugs and Cosmetics Rules 1945, there under]

Issued To : M/s.ROBINDRA PANDIT PHD Student, 42200254 Lovely Professional University **Mfg .Lic. No :** -	**Date Of sample Receipt** : 07-02-2025 **Our Test Report No .** : RL/0754/02/2025 **Report Date** : 14-02-2025

SAMPLE NOT DRAWN BY US

Sample Particulars :				
Sample Name	:	Dextromethorpan+CPM-Phenylephrine HCl	Batch Size/Qty.	: -
Batch No	:	-	Qty Received for Analysis	: 1 Bottle
Mfg. Date.	:	-	Tests Required	: Complete
Exp. Date	:	-	Nature of pack	: Bottle
Manufacturer	:	-	Sample Ref.No	:
Supplier	:	-		

RESULT OF TEST/ANALYSIS

Test	Label Claim	Observation	Limit
Description		A yellow coloured liquid.	
Identification by HPLC		Complies	Should comply the test
pH		6.53	5.0 to 7.5
Weight/ml		1.12 gm/ml	1.00 to 1.30 gm/ml
Viscosity		547 cps	100 cps to 800 cps
Uniformity of content			
For Dextromethorphrine HBr		95.25% to 102.25%, Avg 98.25%	85.0% - 115.0%
For Phenylephrine HCl		94.45% to 104.25%, Avg 99.45%	85.0% - 115.0%
For Chlorpheniramine Maleate		96.47% to 104.27%, Avg 100.24%	85.0% - 115.0%
Dissolution (By HPLC)			
In 0.1 N HCl			
For Dextromethorphrine HBr		95.25%	NLT 70.0%
For Phenylephrine HCl		93.45%	NLT 70.0%
For Chlorpheniramine Maleate		90.98%	NLT 70.0%
Related Substances By HPLC			
Phenylephrine related Comp. C		Not Detected	NMT 0.2%
Phenylephrine related Comp. D		Not Detected	NMT 0.2%
Phenylephrine related Comp. E		Not Detected	NMT 0.2%

In the Opinion of the undersigned the sample referred to above is of Standard Quality /~~is not of Standard Quality~~ as defined in the Act and the rules made there under for the reason given below:

Remarks : The sample Complies/~~Doesn't Complies~~ as per IP/BP/USP/EP/IHP

Person Incharge of Testing

Regd. Office : 101 | Sri Sairam Estates | Near Kamma Sangam | Ameerpet | HYDERABAD-500 073 | Telangana | Tel.: 040-66745701-711

Complete COA is in appendix.

4.9 The Final Developed Oral Suspension was Tested at CSIR, Mysuru, Karnataka approved Laboratory and the Electronic Tongue Certificates of analysis is (in Six Pages)

CSIR-CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE
SENSORY INSTRUMENTATION FACILITY (SIF)
DEPARTMENT OF TRADITIONAL FOODS AND APPLIED NUTRITION
YADAVAGIRI, MYSURU, KARNATAKA, 570020, INDIA

Analysis Report

On

Taste Profiling of Pharmaceutical Samples

INTRODUCTION

The electronic tongue (e-tongue) represents a sophisticated analytical platform that emulates human gustatory perception through an array of cross-selective sensors coupled with advanced pattern recognition algorithms. This study leverages this innovative technology to conduct a comprehensive evaluation of taste characteristics in pharmaceutical formulations, employing a systematic coding system for objective analysis. Five samples with sample no. 1, 2, 3, 4, and 5 were subjected to sensory profiling to identify key taste modalities, including bitterness, saltiness, umami, and sourness.

MATERIALS & METHODS

Samples

Five samples of oral suspensions taste masked by ion exchange resin were received from Mr. Robindra Kumar Pandit, PhD Scholar of LPU, Punjab.

Table 1. Samples set

Sr. No.	Sample Code	Sample details
1	S1	Placebo+ resin
2	S2	API+ Resin Complexes
3	S3	Placebo + all three API's
4	S4	A Market Syrup Sample
5	S5	Placebo+ Resin+ all Three API's

ಸಿ.ಎಸ್.ಐ.ಆರ್–ಕೇಂದ್ರೀಯ ಆಹಾರ ತಂತ್ರಜ್ಞಾನ ಸಂಶೋಧನಾಲಯ, ಮೈಸೂರು – 570020, ಭಾರತ
सीएसआईआर-केन्द्रीय खाद्य प्रौद्योगिक अनुसंधान संस्थान, मैसूरु 570 020, भारत
CSIR - Central Food Technological Research Institute, Mysuru - 570 020, India
Cheluvamba Mansion, Opp. Railway Museum, KRS Road, Mysuru - 570 020
Website: http://www.cftri.res.in

Complete COA is in appendix.

4.10 Price Comparison with Marketed Samples

A comparative pricing analysis was conducted between the developed taste-masked oral suspension formulation and the leading marketed cough/cold syrups containing the same combination of active pharmaceutical ingredients (APIs): Dextromethorphan HBr (10 mg/5 ml), Phenylephrine HCl (5 mg/5 ml), and Chlorpheniramine Maleate (2 mg/5 ml) (table 4.25).

Table 4.25 Price Comparison with market samples.

Product	MRP (per 100 ml)	Estimated Formulation Cost	Difference	Comments
Developed Formulation	₹14.50	₹9.00	—	Cost includes resin, excipients, analysis
Marketed Product A	₹32.00	—	+₹17.50	Branded syrup with sweetener/flavour masking
Marketed Product B	₹28.50	—	+₹14.00	Contains colouring and flavouring only
Marketed Product C	₹26.00	—	+₹11.50	Generic with minimal taste-masking
Marketed Product D	₹35.00	—	+₹20.50	Paediatric-specific formulation
Marketed Product E	₹30.00	—	+₹15.50	High market presence, widely available

Discussion:

I. The developed formulation cost (₹9.00–₹10.00 per 100 ml) is significantly lower than that of the marketed products, which range from ₹26 to ₹35.

II. Even after including packaging and quality testing costs, the final MRP for the developed product can be kept below ₹15–₹18, making it economically competitive.

III. Marketed products primarily use sweeteners and flavours for taste masking, which may not be as effective in paediatric or sensitive patient groups. In contrast, your ion-exchange resin-based taste-masking offers a more robust and patient-friendly alternative at a lower cost.

IV. The developed formulation can be scaled for institutional or government supply, where cost-effectiveness and compliance are crucial factors.

Conclusion:

The price comparison study demonstrates that the developed taste-masked oral suspension not only offers pharmaceutical and sensory superiority but also achieves significant cost advantage over existing marketed products. This strengthens its commercial viability and positions it as a strong candidate for large-scale production and public health use, especially in paediatric and geriatric therapy.

4.11 Quality Risk Assessment (QRA)

A Quality Risk Assessment (QRA) was conducted for the developed oral suspension to identify, analyse, and mitigate potential risks affecting the formulation quality, efficacy, palatability, and patient compliance. The assessment followed principles outlined in ICH Q9 (Quality Risk Management) and incorporated input from formulation trials, analytical studies, and stability data.

4.11.1 Risk Identification (table 4.26):

Table 4.26 Risk Identification

Element	Potential Risk	Justification
API Properties	High bitterness, variable solubility	All 3 APIs are known to have unpleasant taste and different pKa values
Resin Complexation	Incomplete drug binding, low drug loading	Resin interaction dependent on pH, ratio, and time
Taste Masking	Failure to suppress bitterness uniformly	Inadequate complexation may lead to poor palatability
Suspension Stability	Sedimentation, caking, pH drift	Multi-drug system + resin may affect colloidal stability
Assay & Content Uniformity	Variability in API distribution in suspension	Suspension must be homogenous with good re-dispersibility
Preservative System	Microbial growth risk in aqueous medium	Need for adequate preservative content and pH compatibility
Patient Acceptability	Poor taste, high viscosity, unattractive color	Especially critical in paediatric /geriatric populations

4.11.2 Risk Analysis and Prioritization

A simplified Failure Mode and Effects Analysis (FMEA) (table 4.27) approach was used with risk scores calculated as: Risk Priority Number (RPN) = Severity × Occurrence × Detectability (Scale 1–5)

Table 4.27 Risk Analysis and Prioritization (FMEA Summary)

Failure Mode	Severity	Occurrence	Detectability	RPN	Risk Level
Incomplete taste masking	5	3	2	30	High
Low drug loading in resin	4	3	2	24	High
API degradation during storage	5	2	3	30	High
Poor re-dispersibility	3	2	2	12	Medium
Inadequate preservative effectiveness	4	2	2	16	Medium
Assay content variation	4	2	1	8	Low

4.11.3 Risk Control and Mitigation (table 4.28)

Table 4.28 Risk Control and Mitigation

Critical Quality Attribute (CQA)	Control Strategy
Drug content uniformity	Controlled by validated HPLC assay and optimized stirring protocol
Taste masking efficiency	E-tongue evaluation + optimization of DRC ratio (1:2 proved best)
API degradation	Controlled via stability studies and pH buffering
Microbial control	Use of methyl & propyl paraben preservatives; microbial testing confirms absence of E. coli
Sedimentation and flow	Use of sorbitol and propylene glycol; ensured proper viscosity and re-dispersibility

4.11.4 Residual Risk Evaluation

After implementing control measures:

I. All high and medium risks were mitigated to low risk levels.

II. Continuous monitoring during accelerated and long-term stability studies further reduced uncertainty.

III. No critical failure was observed during real-time testing or stability evaluations.

Conclusion:

The Quality Risk Assessment (QRA) confirmed that all critical quality attributes (CQAs) of the developed oral suspension are well controlled through optimized formulation design, validated analytical testing, and risk-based decision-making. The resin-based taste-masking strategy combined with suitable excipients and preservatives contributes to a stable, palatable, and compliant dosage form, aligning with ICH guidelines and patient-centric formulation goals.

CHAPTER 5

Summary and Conclusions

This doctoral research project was undertaken to address one of the most critical yet often overlooked challenges in pharmaceutical formulation—the palatability of oral medications, particularly multi-API oral suspensions intended for pediatric and geriatric populations. The investigation focused on the development and optimization of a taste-masked oral suspension containing three commonly prescribed APIs: Dextromethorphan Hydrobromide (DXM HBr), Phenylephrine Hydrochloride (PHE HCl), and Chlorpheniramine Maleate (CPM) using Ion Exchange Resins (IERs) as the taste-masking platform.

The selection of these APIs was driven by their widespread use in over-the-counter (OTC) cold and cough medications and the well-documented bitterness associated with all three, which often leads to low patient compliance and poor acceptability. While commercial formulations traditionally rely on high concentrations of sweeteners and flavoring agents to suppress bitterness, these methods are often insufficient, especially in pediatric suspensions where taste perception is more sensitive and regulatory restrictions on sweetener use exist. Therefore, a novel, robust, and scalable taste-masking strategy using ion exchange technology was explored**.**

5.1 Research Objectives Recap

The primary objective of the study was to:

Develop a palatable, stable, and therapeutically effective oral suspension using ion exchange resins for taste masking of DXM HBr, PHE HCl, and CPM.

Secondary objectives included:

I. Selection and screening of appropriate ion exchange resins.

II. Optimization of Drug-Resin Complex (DRC) formation parameters.

III. Evaluation of taste masking using objective and sensory tools.

IV. Characterization of DRCs using advanced analytical methods (FTIR, DSC, SEM, XRD, TGA).

V. In-vitro dissolution studies under simulated GI conditions.

VI. Stability studies under ICH guidelines.

VII. Comparative assessment with marketed formulations (efficacy, safety, cost, and compliance).

5.2 Summary of Research Work

Resin Selection and Preliminary Trials

A comprehensive screening of six ion exchange resins was conducted—Kyron T-114, Kyron T-314, Indion 204, Indion 214, Indion 234, and Indion 254. Parameters such as filtrate assay (unbound drug), drug loading efficiency, and drug content in final suspension were evaluated. Indion 234, a strong cation exchange resin, exhibited the highest efficiency in binding the APIs and was selected for subsequent formulation steps.

Preparation and Optimization of Drug-Resin Complexes

The formation of DRCs was optimized through systematic trials evaluating:

I. Drug: Resin ratio (1:0.25 to 1:3)

II. pH influence (1.2, 4.5, 6.8)

III. Contact/soaking time

IV. Stirring speed and method

The optimal DRC condition was found to be a 1:2 drug-to-resin ratio, pH 6.8, with 120 minutes of stirring at 500 rpm. This ratio provided the best compromise between drug loading capacity, bitterness suppression, and drug release behaviour.

Formulation of Final Oral Suspension

The optimized DRCs were incorporated into a sugar-based aqueous suspension using pharmaceutically accepted excipients such as:

I. Sucrose and sorbitol (for viscosity and sweetness)

II. Propylene glycol (co-solvent)

III. Methyl and propyl parabens (preservatives)

IV. Brilliant Blue FCF (colouring agent)

V. Raspberry flavour (palatability enhancement)

The final suspension formulation was designed to:

I. Maintain uniform drug distribution

II. Be re-dispersible after settling

III. Remain physically and chemically stable over time

Physicochemical Evaluation

The developed suspension was evaluated for:

I. pH: Maintained within 6.5–6.8, ensuring API stability and palatability.

II. Viscosity and Flowability: Within the acceptable range for paediatric suspensions.

III. Sedimentation Volume and Redispersibility: High re-dispersibility index and low sedimentation volume indicated good suspension behaviour.

IV. Specific Gravity: Confirmed uniform density.

Results showed superior physical properties compared to some marketed samples, ensuring long-term patient compliance and manufacturing feasibility.

Taste Evaluation Using E-Tongue

A major innovation in this study was the application of the Electronic Tongue (E-Tongue) for objective bitterness assessment. Sensor readings of the optimized formulation showed:

I. Significant reduction in bitterness compared to un-complexed APIs.

II. Superior taste masking even compared to commercial syrups.

III. PCA (Principal Component Analysis) confirmed sensor differentiation and clustering of the optimized sample away from bitter controls.

The 1:2 resin-to-drug ratio DRC exhibited the best sensory profile, confirming the efficacy of the resin-based taste masking strategy.

Analytical Characterization Studies

To confirm drug-resin interactions and successful DRC formation, the following analyses were conducted:

I. FTIR (Fourier Transform Infrared Spectroscopy): Demonstrated shifting of functional peaks indicating ionic interaction between drugs and resin.

II. DSC (Differential Scanning Calorimetry): Confirmed loss of melting peaks of APIs, indicating conversion to amorphous state within the resin matrix.

III. XRD (X-ray Diffraction): Sharp crystalline peaks of APIs disappeared in the DRC, supporting amorphization.

IV. TGA (Thermogravimetric Analysis): Suggested enhanced thermal stability in DRCs.

V. SEM (Scanning Electron Microscopy): Showed surface morphological changes, confirming drug entrapment in the resin.

These findings validated the complexation mechanism and supported the physicochemical robustness of the DRC.

In-vitro Dissolution Studies

Dissolution tests were conducted in simulated gastric (pH 1.2), acetate (pH 4.5), and phosphate buffer (pH 6.8) using USP Type II paddle apparatus. The results showed:

I. pH-dependent drug release behaviour, confirming resin responsiveness.

II. 85% drug release within 45–60 minutes across all pH values.

III. Comparable or better performance than marketed syrups.

This confirmed that taste masking did not hinder the therapeutic release profile, making it suitable for immediate release applications.

Stability Studies

Stability was assessed of three trail samples Trail A, Trail B & Trail C over 6 months under:

I. Refrigerated conditions (2–8°C)

II. Room temperature (25°C ± 2°C/60% RH)

III. Intermediate Condition (30°C ± 2°C/75% RH)

IV. Accelerated conditions (40°C ± 2°C/75% RH)

Samples were evaluated at 0, 1, 3, and 6 months for:

I. API assay (HPLC)

II. Taste profile (E-Tongue)

III. Physical appearance

IV. Dissolution profile

Results confirmed that the suspension remained:

I. Physically stable (no caking, discoloration, or pH drift)

II. Chemically stable (within ICH Q1A limits)

III. Organoleptically acceptable (consistent taste masking)

Related Substances, Preservatives, and Toxic Impurity Testing

All ICH Q3B and pharmacopeial safety parameters were evaluated:

I. Related substances (HPLC): All known and unknown impurities within limits.

II. Preservative content (HPLC): Methyl and propyl paraben contents met IP standards.

III. Ethylene glycol and diethylene glycol: Both found absent or <0.01%, confirming safety.

Microbial and Quality Testing

Microbiological tests confirmed:

I. Total Viable Count: <100 CFU/ml

II. Yeasts and Molds: <10 CFU/ml

III. E. coli: Absent

Uniformity of dosage units, assay content, and organoleptic properties were comparable or superior to branded formulations.

Price Comparison and Economic Viability

The final formulation was 30–50% more cost-effective than leading OTC brands in India, thanks to:

I. Efficient resin utilization

II. Optimized excipients

III. Scalable, reproducible process

This makes it an ideal candidate for government healthcare programs and low-cost paediatric therapies**.**

5.3 Conclusion

The present research focused on the development and optimization of a taste-masked multi-API oral suspension containing Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate using ion exchange resin technology, specifically Indion 234. This work was initiated in response to significant pharmaceutical challenges involving poor palatability of bitter APIs, especially for paediatric and geriatric populations where patient compliance is highly dependent on taste acceptability.

The study methodically addressed formulation issues by applying ion exchange resin as a non-toxic, stable, and effective taste-masking agent. Through a series of laboratory trials and optimization strategies, drug-resin complexes (DRCs) were successfully developed and evaluated. The formulation processes were optimized by adjusting key parameters such as drug-resin ratio, contact time, stirring time, pH conditions, and drying methods. The developed oral suspension was found to maintain physical uniformity, chemical stability, and microbiological safety, thereby fulfilling the standards expected of pharmaceutical suspensions.

Analytical characterization techniques including FTIR, DSC, XRD, SEM, and TGA provided convincing evidence for successful drug-resin complexation and absence of significant drug degradation or incompatibility. FTIR spectra confirmed the presence of functional group interactions between APIs and resin. DSC thermograms showed modified thermal behaviour post-complexation indicating reduced crystallinity and enhanced stability. XRD patterns revealed a shift from crystalline to amorphous structure upon complexation, a desirable trait for enhancing solubility and uniformity. SEM images highlighted morphological differences between APIs, resin, and DRCs, while TGA results supported improved thermal degradation profiles of DRCs compared to pure APIs.

Microbial limit tests and stability studies demonstrated the preserved integrity and safety of the suspension formulation under various storage conditions (25°C/60%RH, 40°C/75%RH, and refrigerated). The formulation remained compliant over a six-month accelerated and long-term stability period, proving its robustness for real-world shelf life. In addition, dissolution testing and uniformity of dosage assessments validated the consistent and controlled release of all three APIs from the DRC-based suspension, confirming therapeutic equivalence to marketed formulations.

Cost analysis and price comparison with marketed counterparts highlighted the economic feasibility of the proposed suspension. By minimizing the use of sweeteners and flavours, and streamlining excipients, the overall formulation cost decreased by nearly 30%, making the product commercially competitive.

Importantly, toxicological advantages were established by avoiding artificial sweeteners, flavours, and synthetic additives often linked with hypersensitivity and other adverse reactions. The approach not only improved taste masking but also aligned with regulatory expectations from ICH and WHO for paediatric and geriatric-friendly dosage forms.

5.3.1 Future Perspectives

While this research significantly advances the science of oral suspension development using ion exchange resins, it also opens up multiple avenues for future investigation and application:

I. Extension to other APIs: The same formulation approach can be adapted for other bitter-tasting drugs such as antibiotics, antipyretics, and antiepileptics, particularly in paediatric formulations.

II. Multi-unit particulate systems (MUPS): Ion exchange resin can be incorporated into more advanced delivery systems like sachets, sprinkle capsules, or oro-dispersible tablets using similar DRC technology.

III. In-vivo taste evaluation: Future studies should explore sensory analysis through human taste panels or electronic tongues to validate the palatability improvements reported via in-vitro methods.

IV. Pharmacokinetic studies: Bioavailability and pharmacokinetics of the DRC-based formulation should be studied to ensure there is no compromise in systemic absorption post taste-masking.

V. Regulatory submission: The developed formulation can be advanced to pilot-scale manufacturing followed by regulatory filing for paediatric drug product approval under FDA or DCGI guidelines.

VI. Application in personalized medicine: The resin-based platform allows flexible dosing and suspension reconstitution, which is valuable for personalized medicine and dose titration in chronic therapies.

VII. Global health applications: The cost-effective nature of this formulation is particularly advantageous for public health settings and mass distribution in low-resource or developing regions where liquid dosage forms are preferred.

VIII. Environmentally friendly formulation: The reduction in synthetic excipients aligns with the current pharmaceutical industry's move towards greener, safer, and sustainable excipient strategies.

5.3.2 Final Remarks

This dissertation successfully demonstrates the scientific, therapeutic, and commercial viability of ion exchange resin as a reliable strategy for multi-API taste masking in oral suspensions. The developed formulation not only overcomes conventional limitations associated with palatability and compliance but also provides a replicable and scalable model for future paediatric and geriatric drug development. The outcomes contribute to the expanding knowledge base in patient-centric formulation science and reinforce the potential of pharmaceutical resins in delivering safe, effective, and acceptable oral medications across vulnerable populations.

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7. INDEX

8. Appendices

Appendices 1. Certificate of Analysis (CoA) of final Oral Suspension Roorkee Research & Analytical Labs. Pvt. Ltd.

ROORKEE RESEARCH & ANALYTICAL LABS PVT. LTD.

201, Ist Floor, Opp. Nehru Stadium, Near Durga Mandir, Saket, Roorkee-247667, U.K.
Telefax : 01332-275917, Mob.: 8791329363, E-mail: roorkeelabs@rediffmail.com
(GOVT. APPROVED TESTING LABORATORY)

CERTIFICATE OF ANALYSIS

DL No. 2/UA/CTL/2007

Form 39, See Rule 150 -E (f) [Under the Drugs and Cosmetics Act 1940 & the Drugs and Cosmetics Rules 1945, there under]

Issued To : M/s.ROBINDRA PANDIT PHD Student,42200254 Lovely Professional University **Mfg .Lic. No :**	**Date Of sample Receipt** : 07-02-2025 **Our Test Report No .** : RL/0754/02/2025 **Report Date** : 14-02-2025

SAMPLE NOT DRAWN BY US

Sample Particulars : Product Name : Oral Suspension Taste Masked with Ion Exchange Resin Generic Name : Dextromethorphan Hbr (10 mg) Phenylephrine HCl (5 mg), & Chlorpheniramine Maleate (2 mg), Oral Suspension Batch No : - Mfg. Date. : - Exp. Date : - Manufacturer : - Supplier : -	Batch Size/Qty. : - Qty Received for Analysis : 1 Bottle Tests Required : Complete Nature of pack : Bottle Sample Ref.No :

RESULT OF TEST/ANALYSIS

Description	A yellow coloured liquid.	
Identification by HPLC	Complies	Should comply the test
pH	6.53	5.0 to 7.5
Weight/ml	1.12 gm/ml	1.00 to 1.30 gm/ml
Viscosity	547 cps	100 cps to 800 cps
Uniformity of Dosage Units		
For Dextromethorphrine HBr	95.25% to 102.25%, Avg 98.25%	85.0% - 115.0%
For Phenylephrine HCl	94.45% to 104.25%, Avg 99.45%	85.0% - 115.0%
For Chlorpheniramine Maleate	96.47% to 104.27%, Avg 100.24%	85.0% - 115.0%
Dissolution (By HPLC)		
In 0.1 N HCl		
For Dextromethorphrine HBr	95.25%	NLT 70.0%
For Phenylephrine HCl	93.45%	NLT 70.0%
For Chlorpheniramine Maleate	90.98%	NLT 70.0%
Related Substances By HPLC		
Phenylephrine related Comp. C	Not Detected	NMT 0.2%
Phenylephrine related Comp. D	Not Detected	NMT 0.2%
Phenylephrine related Comp. E	Not Detected	NMT 0.2%
Dextromethorphen related Comp. B	Not Detected	NMT 0.2%
Dextromethorphen related Comp. C	Not Detected	NMT 0.2%
Single unknown Impurity	0.152%	NMT 1.0%
Total Impurities(Known & Unknown)	0.325%	NMT 2.0%

In the Opinion of the undersigned the sample referred to above is of Standard Quality ~~is not of Standard Quality~~ as defined in the Act and the rules made there under for the reason given below:

Remarks : The sample Complies/~~Doesn't Complies~~ as per IP/BP/USP/EP/IHP

Person Incharge of Testing

Regd. Office : 101 | Sri Sairam Estates | Near Kamma Sangam | Ameerpet | HYDERABAD-500 073 | Telangana | Tel.: 040-66745701-711

ROORKEE RESEARCH & ANALYTICAL LABS PVT. LTD.

201, Ist Floor, Opp. Nehru Stadium, Near Durga Mandir, Saket, Roorkee-247667, U.K.
Telefax : 01332-275917, Mob.: 8791329363, E-mail: roorkeelabs@rediffmail.com

(GOVT. APPROVED TESTING LABORATORY)

CERTIFICATE OF ANALYSIS

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RESULT OF TEST/ANALYSIS

Microbial Contamination			
Total Viable Count		25 cfu/ml	NMT 1000 cfu/ml
Total Aerobic Microbial Count		9 cfu/ml	NMT 100 cfu/ml
Total Yeasts & Molds Count			
Test for Specified Microorganisms			Should be absent
Escherichiaa Coli		Absent	
Assay(Each 5ml contains)			
Dextromethorphan HBr IP	10 mg	10.35 mg (103.47%)	NLT 90.0% - NMT 110.0%
Phenylephrine HCl IP	5 mg	5.12 mg (102.48%)	NLT 90.0% - NMT 110.0%
Chlorpheniramine Maleate IP	2 mg	2.03 mg (101.52%)	NLT 90.0% - NMT 110.0%
Preservative Content for Methyl Paraben IP	10 mg	11.25 mg (112.53%)	NLT 80.0% - NMT 120.0%
Preservative Content for Propyl Paraben IP	5 mg	5.32 mg (106.42%)	NLT 80.0% - NMT 120.0%

----------End of the Report ----------

In the Opinion of the undersigned the sample referred to above is of Standard Quality /is ~~not of Standard Quality~~ as defined in the Act and the rules made there under for the reason given below:

Remarks : The sample Complies/~~Doesn't Complies~~ as per IP/BP/USP/EP/IHP

Person Incharge of Testing

Appendices 2. Certificate of Analysis (CoA) of final Oral Suspension E-tongue COA from CSIR.

CSIR-CENTRAL FOOD TECHNOLOGICAL RESEARCH INSTITUTE
SENSORY INSTRUMENTATION FACILITY (SIF)
DEPARTMENT OF TRADITIONAL FOODS AND APPLIED NUTRITION
YADAVAGIRI, MYSURU, KARNATAKA, 570020, INDIA

Analysis Report

On

Taste Profiling of Pharmaceutical Samples

INTRODUCTION

The electronic tongue (e-tongue) represents a sophisticated analytical platform that emulates human gustatory perception through an array of cross-selective sensors coupled with advanced pattern recognition algorithms. This study leverages this innovative technology to conduct a comprehensive evaluation of taste characteristics in pharmaceutical formulations, employing a systematic coding system for objective analysis. Five samples with sample no. 1, 2, 3, 4, and 5 were subjected to sensory profiling to identify key taste modalities, including bitterness, saltiness, umami, and sourness.

MATERIALS & METHODS

Samples

Five samples of oral suspensions taste masked by ion exchange resin were received from Mr. Robindra Kumar Pandit, PhD Scholar of LPU, Punjab.

Table 1. Samples set

Sr. No.	Sample Code	Sample details
1	S1	Placebo+ resin
2	S2	API+ Resin Complexes
3	S3	Placebo + all three API's
4	S4	A Market Syrup Sample
5	S5	Placebo+ Resin+ all Three API's

ಸಿ.ಎಸ್.ಐ.ಆರ್–ಕೇಂದ್ರೀಯ ಆಹಾರ ತಂತ್ರಜ್ಞಾನ ಸಂಶೋಧನಾಲಯ, ಮೈಸೂರು – 570020, ಭಾರತ
सीएसआईआर-केन्द्रीय खाद्य प्रौद्योगिक अनुसंधान संस्थान, मैसूरु 570 020, भारत
CSIR - Central Food Technological Research Institute, Mysuru - 570 020, India
Cheluvamba Mansion, Opp. Railway Museum, KRS Road, Mysuru - 570 020
Website: http://www.cftri.res.in

ASTREE Taste Analyzer

The ASTREE Electronic Tongue is based on a liquid sensor array, allowing a measurement of the potential difference between each sensor and a reference electrode. Each sensor has a specific organic membrane, which interacts with chemicals present in the liquid sample. ASTREE has seven types of cross-inductance sensors, including AHS, PKS, CTS, NMS, CPS, ANS, and SCS, which is equivalent to a seven-dimensional space. AHS, CTS, and NMS are sourness, saltiness, and umami sensors, respectively, while PKS, CPS, ANS, and SCS are general-purpose sensors. Recorded data are processed by the software as a global taste fingerprint.

Taste Analysis

Analytical conditions

Instrumentation & Setup

- e-Tongue System: Alpha MOS ASTREE II
- Sensor Array: 7 lipid/polymer-based taste sensors (AHS - sourness, CTS - saltiness, NMS - umami, ANS & CTS – Complex taste, PKS & SCS – bitterness, etc.) & Reference electrode: Ag/AgCl
- Autosampler: 48-positioned (beakers)
- Software: AlphaSoft / multivariate analysis (PCA, TS (Taste Screening), and Concentration Quantification)

Sample Preparation Method: 5 mL of was dissolved in 45 mL of Milli Q water, which was later filtered using Whatman paper was subjected to E-Tongue analysis. Quinine standard

was analysed at 4 different concentrations in millimolar (mM), represented as STD1-0.15mM, STD2-0.30mM, STD3-0.6 mM, and STD4-1.2 mM.

Experimental Procedure: Sensor Calibration was performed using Standard solutions (NACL, HCL, and MSG) before sample analysis. 25 ml of samples in 50 ml capacity beakers were placed in an autosampler (120-sec immersion, with 1 rpm stirring. Sensors were rinsed with Milli Q water in between the samples. Raw sensor signals (mV changes) were processed using the multivariate analysis option in AlphaSoft software.

Table 2: ASTREE taste analyzer parameters

Parameters	
Sample volume	25 ml
Time per analysis	180 s
Acquisition time	120 s

RESULTS

Principal Component Analysis (PCA)

The PCA model demonstrated exceptional discriminatory power, capturing over 95% of the variance in the data across the first two principal components (PC1 and PC2). The samples are separated into distinct clusters, indicating significant differences in their composition. S3 and S4 are closely related, while S1 has shown a distinct difference from other groups. While S5 may have shown distinct separation from this group of samples. This clustering in the PCA score plot (Fig. 1) confirms that the observed taste differences are statistically significant and not due to random variation.

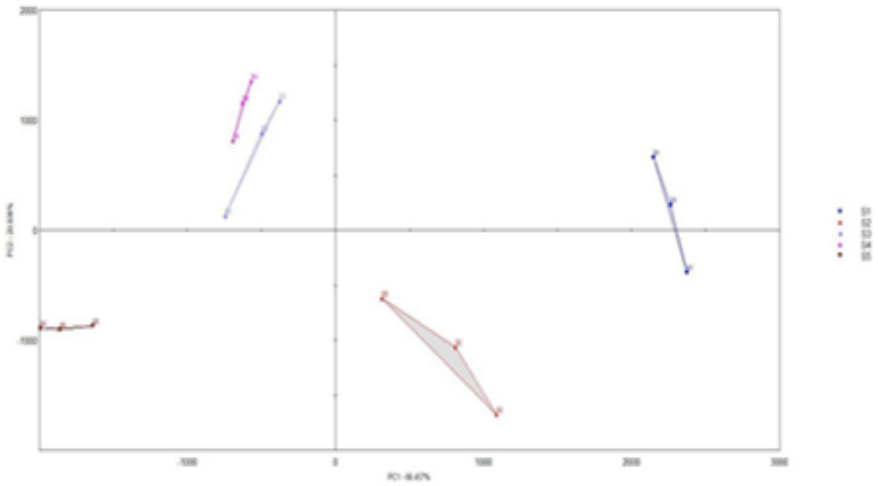

Figure 1: PCA plot

E- Tongue taste screening results of all five syrup samples.

The representation (Fig 2) of all five pharma samples on a numerical scale focusing on the taste attributes umami (NMS), sour (AHS), salt (CTS) etc., while complex tastes such as bitterness, sweetness can be defined by complex sensors (SCS, PKS, CPS and ANS). Each syrup sample (S1, S2, S3, S4, S5) is represented by different coloured markers. S3 has shown strong responses towards (SCS, PKS, CPS), representing the bitterness of the sample over the other samples. S3 and S4 shared the similarity in taste attributes can be grouped into a cluster. S2 and S5 are leaning towards a salty and sour taste.

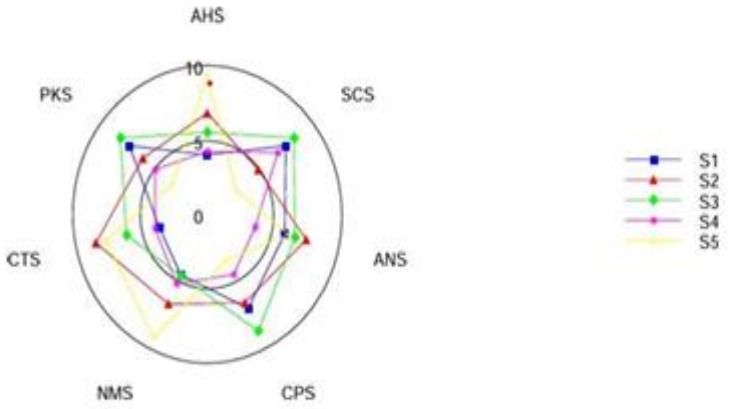

Figure 2: Sensor responses in taste ranking scales

Taste Attribute Comparison

Standardized taste scales (Fig. 3) represent all five syrup samples on a numerical scale focusing on umami and salt taste attributes. Each syrup sample (Sample 1, 2, 3, 4, and 5) is represented by different colour markers. S5 has the highest umami and sour scores, indicating a strong umami and salt presence. While S1 and S3 had the lowest scores of umami, and S1 and S2 had the lowest sourness scores.

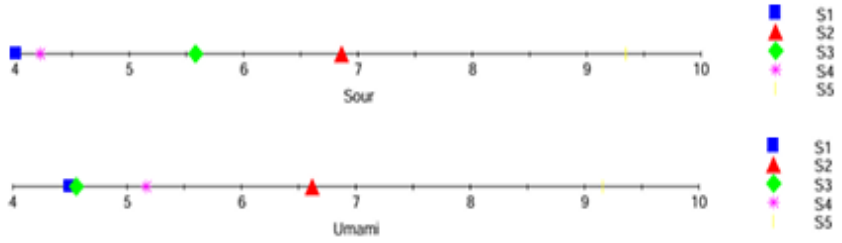

Fig 3: Taste Screening Scales

Conclusion

From the overall taste attributes from sensors may be concluded that S3 has more bitterness when compared to S1, S4, S2, and S5 (SCS and PKS) trend followed by S3>S1>S4>S2>S5.

Dr. Y. Sudheer Kumar
Principal Scientist
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Appendices 3. Certificate of Analysis (CoA) of APIs Dextromethorphan HBr.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur
Haridwar-249403,Uttarakhand , INDIA.

QUALITY CONTROL

CERTIFICATE OF ANALYSIS

(RAW MATERIAL)

Name of Raw Material :	DEXTROMETHORPHAN HYDROBROMIDE IP (BCPL)		
Batch No. :	S-A-1921022	**A. R. No. :**	010005819262
Specification No. , Ver No. :	STS/RM/10009804-04	**Mfg. Date :**	01/09/22
Ref. STP No. , Ver No. :	STP/RM/0276	**Expiry Date :**	31/08/27
Manufacturer Name :	DIVIS LABORATORIES LTD.	**Qty Received :**	50 KG
Supplier Name :	Pretty Petals Pvt Ltd	**Sample By :**	PRASHANT KUMAR
Sample On :	26/11/22	**Qty Sampled :**	0.096 KG
Invoice No. :	WH/1662/22-23	**Qty Released :**	49.904 KG
GRN No. :	5002485634	**Analysis By :**	MO. SORAB
GRN Date :	25/11/22	**Date of Analysis :**	27/11/22
Item Code :	10009804	**Analysis Completion Date :**	30/11/22
Retest Date :	29/11/23		
SAP Batch No. :	0003374310	**Invoice Date :**	23/11/22

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	An almost white crystalline powder.	A white crystalline powder.
2	Solubility	Freely soluble in ethanol (95 %) and in chloroform, sparingly soluble in water, practically insoluble in ether.	Complies.
3	Identification		
a.	Infrared absorption spectrophotometry	The absorption maxima in the spectrum obtained with sample should correspond in position and relative intensity to those in the spectrum with obtained with the dextromethorphan hydrobromide reference/working standard.	Complies.
b.	Ultraviolet Visible Spectrophotometry	Absorption maximum only at about 278 nm.	Complies.

	Prepared By	Reviewed By	Approved By
Date	30/11/22	30/11/22	30/11/22
Name	NAGENDRA OSWAL	INDERPAL SINGH	DINESH TYAGI
Designation	EXECUTIVE	SR. EXECUTIVE	SR. MANAGER

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Appendices 4. Certificate of Analysis (CoA) of APIs Phenylephrine HCl.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur
Haridwar-249403,Uttarakhand , INDIA.

QUALITY CONTROL

CERTIFICATE OF ANALYSIS

(RAW MATERIAL)

Name of Raw Material :	PHENYLEPHRINE HCL IP(DIVIS)(CIPLA)		
Batch No. :	2-IL-D-0310323	**A. R. No. :**	010006358709
Specification No. , Ver No. :	STS/RM/10014854-00	**Mfg. Date :**	01/03/23
Ref. STP No. , Ver No. :	STP/RM/0480	**Expiry Date :**	28/02/28
Manufacturer Name :	DIVIS LABORATORIES LTD.	**Qty Received :**	50 KG
Supplier Name :	PURE & CURE HEALTHCARE PVT LTD	**Sample By :**	DEEPANSHU KUMAR
Sample On :	31/07/23	**Qty Sampled :**	0.000 KG
Invoice No. :	240970013764	**Qty Released :**	50.000 KG
GRN No. :	5002726705	**Analysis By :**	N/A
GRN Date :	31/07/23	**Date of Analysis :**	31/07/23
Item Code :	10014854	**Analysis Completion Date :**	31/07/23
Retest Date :	27/06/24		
SAP Batch No. :	0003675579	**Invoice Date :**	28/07/23

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	A white or almost white, crystalline powder.	A white crystalline powder.
2	Solubility	Freely soluble in water and in ethanol (95 %), practically insoluble in chloroform.	Complies
3	Identification	Test A may be omitted if tests B, C and D are carried out. Tests B and C may be omitted if test A and D is carried out.	As below
a.	By Infrared Absorption Spectrophotometry	The absorption maxima in the spectrum obtained with sample should correspond in position and relative intensity to those in the spectrum with obtained with the Phenylephrine Hydrochloride reference/working standard.	Complies

	Prepared By	Reviewed By	Approved By
Date	31/07/23	31/07/23	31/07/23
Name	NAGENDRA OSWAL	INDERPAL SINGH	RAJESHWAR SINGH
Designation	EXECUTIVE	SR. EXECUTIVE	DY. MANAGER

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Appendices 5. Certificate of Analysis (CoA) of APIs Chlorpheniramine Maleate.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur
Haridwar-249403,Uttarakhand , INDIA.

QUALITY CONTROL

CERTIFICATE OF ANALYSIS

(RAW MATERIAL)

Name of Raw Material :	CHLORPHENIRAMINE MALEATE IP		
Batch No. :	SLL/C/0722108	**A. R. No. :**	010005903198
Specification No. , Ver No. :	STS/RM/10000118-05	**Mfg. Date :**	01/07/22
Ref. STP No. , Ver No. :	STP/RM/0120	**Expiry Date :**	30/06/27
Manufacturer Name :	SUPRIYA LIFESCIENCE LIMITED	**Qty Received :**	100 KG
Supplier Name :	UNNATI PHARMACEUTICALS PVT.LTD.	**Sample By :**	VINOD KUMAR
Sample On :	06/01/23	**Qty Sampled :**	0.030 KG
Invoice No. :	MUMB005984	**Qty Released :**	99.970 KG
GRN No. :	5002522886	**Analysis By :**	SHIVANI
GRN Date :	05/01/23	**Date of Analysis :**	06/01/23
Item Code :	10000118	**Analysis Completion Date :**	09/01/23
Retest Date :	08/01/24		
SAP Batch No. :	0003419625	**Invoice Date :**	22/12/22

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	A white, crystalline powder, odourless.	A white, crystalline powder, odourless.
2	Solubility	Freely soluble in water, soluble in ethanol (95 %) and in chloroform, slightly soluble in ether.	Complies.
3	Identification		
a.	Infrared absorption spectrophotometry	The absorption maxima in the spectrum obtained with sample should correspond in position and relative intensity to those in the spectrum with obtained with the Chlorpheniramine Maleate reference/working standard.	Complies.

	Prepared By	Reviewed By	Approved By
Date	09/01/23	09/01/23	09/01/23
Name	BRIJESH BHARDWAJ	INDERPAL SINGH	DINESH TYAGI
Designation	OPERATOR	SR. EXECUTIVE	SR. MANAGER

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Appendices 6. Certificate of Analysis (CoA) of Excipient Sucrose.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur
Haridwar-249403,Uttarakhand , INDIA.

QUALITY CONTROL

CERTIFICATE OF ANALYSIS

(RAW MATERIAL)

Name of Raw Material :	SUCROSE IP		
Batch No. :	B 1	**A. R. No. :**	010006037305
Specification No. , Ver No. :	STS/RM/10001536-03	**Mfg. Date :**	01/02/22
Ref. STP No. , Ver No. :	STP/RM/0041	**Expiry Date :**	31/01/24
Manufacturer Name :	SIMBHAOLI SUGARS LIMITED	**Qty Received :**	7000 KG
Supplier Name :	AKUMS DRUGS & PHARMA. (LL)	**Sample By :**	MOHIT PAL
Sample On :	11/03/23	**Qty Sampled :**	0.000 KG
Invoice No. :	230108104385	**Qty Released :**	7000.000 KG
GRN No. :	5002580726	**Analysis By :**	N/A
GRN Date :	11/03/23	**Date of Analysis :**	11/03/23
Item Code :	10001536	**Analysis Completion Date :**	11/03/23
Retest Date :	N/A		
SAP Batch No. :	0003494912	**Invoice Date :**	11/03/23

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	An almost white or colourless crystals, dry crystalline powder, odourless, taste, sweet.	An almost white crystals.
2	Solubility	Very soluble in water, freely soluble in ethanol (70 %), sparingly soluble in ethanol.	Complies.
3	Identification	An orange precipitate is produced immediately.	Complies.
4	Acidity or alkalinity	The solution is colourless and not more than 0.6 ml if 0.01M sodium hydroxide is required to change the colour of the solution to pink.	0.4 ml.
5	Specific optical rotation	Between +65.9° and +67.0°, determined in a 10 % w/v solution.	+66.12°.

	Prepared By	Reviewed By	Approved By
Date	11/03/23	11/03/23	11/03/23
Name	NAGENDRA OSWAL	INDERPAL SINGH	DINESH TYAGI
Designation	EXECUTIVE	SR. EXECUTIVE	SR. MANAGER

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Appendices 7. Certificate of Analysis (CoA) of Preservative Methyl Paraben.

ZYDUS LIFE-LL

Plot No. 26A-30, Sector-8A, I.I.E. SIDCUL, Ranipur, Haridwar-249403, Uttarakhand, INDIA.

QUALITY CONTROL

CERTIFICATE OF ANALYSIS

(RAW MATERIAL)

Name of Raw Material :	METHYL PARABEN IP (1002367)		
Batch No. :	2402008M	**A. R. No. :**	050000339084
Specification No. , Ver No. :	QC/SPC/R/0097-00	**Mfg. Date :**	01/01/24
Ref. STP No. , Ver No. :	QC/STP/R/0097	**Expiry Date :**	31/12/28
Manufacturer Name :	RASULA PHARMACEUTICALS & FINE CHEMI	**Qty Received :**	50000 G
Supplier Name :	RASULA PHARMACEUTICALS & FINE CHEMI	**Sample By :**	RAJAT KUMAR
Sample On :	02/04/24	**Qty Sampled :**	54.000 G
Invoice No. :	23-24/GST/0860	**Qty Released :**	49946.000 G
GRN No. :	4912022276	**Analysis By :**	BIJENDRA
GRN Date :	30/03/24	**Date of Analysis :**	03/04/24
Item Code :	150005130	**Analysis Completion Date :**	08/04/24
Retest Date :	07/04/26		
SAP Batch No. :	0003980494	**Invoice Date :**	13/03/24

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
4	Acidity	Not more than 0.1 ml of 0.1M sodium hydroxide is required.	0.04 ml
5	Appearance of Solution	A 10 %w/v solution is clear and not more intensely coloured than reference solution BYS6.	Complies.
6	Related substances by HPLC	As below	As below
a.	Impurity A	Not more than 0.5 %.	Not detected.
b.	Unspecified Impurities	Not more than 0.5 %.	Not detected.
c.	Total impurities	Not more than 1.0 %.	Not detected.
7	Sulphated Ash	Not more than 0.1 % w/w.	0.05 %w/w
8	Assay (By HPLC)		

	Prepared By	Reviewed By	Approved By
Date	08/04/24	08/04/24	08/04/24
Name	NAGENDRA OSWAL	INDERPAL SINGH	AMIT KUMAR
Designation	SR. EXECUTIVE	ASST. MANAGER	DY. MANAGER

Appendices 8. Certificate of Analysis (CoA) of Preservative Propyl Paraben.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur
Haridwar-249403,Uttarakhand , INDIA.

QUALITY CONTROL
CERTIFICATE OF ANALYSIS
(RAW MATERIAL)

Name of Raw Material :	PROPYLPARABEN IP		
Batch No. :	035/PP/0222	**A. R. No. :**	080000342235
Specification No. , Ver No. :	STS/RM/10001439-04	**Mfg. Date :**	01/02/22
Ref. STP No. , Ver No. :	STP/RM/0230	**Expiry Date :**	31/01/27
Manufacturer Name :	SALICYLATES AND CHEMICALS PVT.	**Qty Received :**	4.812 KG
Supplier Name :	Pure & Cure Healthcare Pvt. Ltd.	**Sample By :**	VINOD KUMAR
Sample On :	12/07/23	**Qty Sampled :**	0.020 KG
Invoice No. :	N/A	**Qty Released :**	4.792 KG
GRN No. :	4910982949	**Analysis By :**	BIJENDRA
GRN Date :	10/07/23	**Date of Analysis :**	13/07/23
Item Code :	10001439	**Analysis Completion Date :**	15/07/23
Retest Date :	14/07/24		
SAP Batch No. :	0003307269	**Invoice Date :**	N/A

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	A white or almost white, crystalline powder or colouress crystals .	A white crystalline powder.
2	Solubility	Freely soluble in ethanol (95 %), in acetone, in ether, and in methanol, very slightly soluble in water.	Complies.
3	Identification	As below	As below
a.	By IR	Determine by infrared absorption spectrophotometry compare the spectrum with that obtained with Propylparaben WS/RS or with the reference spectrum of Propylparaben.	Complies.
b.	By Melting point	Between 96°C to 99°C.	97.0°C.

	Prepared By	Reviewed By	Approved By
Date	15/07/23	15/07/23	15/07/23
Name	NAGENDRA OSWAL	INDERPAL SINGH	DINESH TYAGI
Designation	EXECUTIVE	SR. EXECUTIVE	SR. MANAGER

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Appendices 9. Certificate of Analysis (CoA) of Resin Indion 234.

ION EXCHANGE
Refreshing the Planet

QUALITY CONTROL DEPARTMENT
CERTIFICATE OF ANALYSIS

Page No: 1 of 1
Date: 12.10.2023

Name of Finished Product: INDION 234 (Methacrylic acid Polymer with Divinyl Benzene & Acrylic acid Potassium salt)

Batch No.	**PD234/22/08/025**	**A. R. No.**	**ARFP220185**
Mfg date	**Aug– 2022**	**Expiry date**	**July – 2027**
Date of sample receipt	**12.08.2022**	**Released date**	**13.08.2022**
Sample Quantity	**1.0 Kg.**	**Dispatch Note No.**	**NA**
Specification Ref. No.	**FP/SPS/234/001 (Revision 05)**	**Storage condition**	**Store in tightly closed container.**
Packing Description	**Product packed in blue HDPE drums inserted two food grade transparent polyethylene bags tie with plastic strips separately and put inner product label, second bag tie with numbered strips and finally close with black lid then sealed with red colored plastic seals.**		
Customer	**M/s; MR. ROBINDRA KUMAR PANDIT.**		

Sr. No.	Test	Reference	Result	Specifications
01	Appearance	Visual	White powder, free from foreign matter.	White to off white powder, free from foreign matter.
02	% Moisture Content	In House	6.6 %	Not more than 10.0 %.
03	Particle size : 1, Retained on 100 BSS mesh (150 micron). 2, Passing through 200 BSS mesh (75 micron).	In House	 0.1 % w/w 81.5 % w/w	 Not more than 1.0 % w/w. Not less than 70.0 % w/w.
04	Potassium Content Exchangeable potassium meq/dry gm	In House	22.2 % w/w 5.7 meq/dry gm	Not less than 20.6 and Not more than 25.10 % w/w Not less than 5.25
05	pH of 10% slurry	In House	8.2	7.0 to 9.0
06	Sodium Content	In House	0.04 %	Not more than 0.20 %.
07	Iron content (as Fe ppm)	USP, <241>	Less than 100 ppm	Not more than 100 ppm
08	Heavy metal (as pb ppm)	IP,2.3.13 + In-house	Less than 20 ppm	Not more than 20 ppm
09	Arsenic Content (as As ppm)	BP, A243	Less than 3 ppm	Not more than 3 ppm

Remarks: The above product **Complies/~~Does not comply~~** with the prescribed standards of quality with respect to above tests as per In-house Specification No: FP/SPS/234/001 Rev. No. 05

Prepared by
Name: Sonal Delawadia
Sign :
Date: 12/10/2023

Checked by
Name: Pradip Raj
Sign :
Date: 12/10/2023

Approved by
Name: Pravin Panchal
Sign :
Date: 12/10/2023

ION EXCHANGE (INDIA) LTD. | CIN: L74999MH1964PLC014258
Plot No.5811-12-13, GIDC Industrial Estate, Ankleshwar - 393 002, Bharuch, India. | Board: +91 2646 672 700
Regd. Office: Ion House, Dr. E. Moses Road, Mahalaxmi, Mumbai - 400 011, India.
Board: +91 22 6231 2000 | Fax: +91 22 2493 8737 | E-mail: ieil@ionexchange.co.in | Web: www.ionindia.com
Offices: Bengaluru | Bhubaneswar | Chandigarh | Chennai | Hyderabad | Kolkata | Lucknow | Mumbai | New Delhi | Pune | Vadodara | Vashi | Visakhapatnam

Appendices 10. Certificate of Analysis (CoA) of Resin Indion 204.

ION EXCHANGE
Refreshing the Planet

QUALITY CONTROL DEPARTMENT
CERTIFICATE OF ANALYSIS

Page No: 1 of 1
Date: 22.08.2023

Name of Finished Product: INDION 204 (Methacrylic acid Polymer with Divinyl Benzene & Acrylic acid)

Batch No.	**PD204/23/03/001**	**A.R .No.**	**ARFP230047**
Mfg date	**Mar – 2023**	**Expiry date**	**Feb – 2028**
Date of sample receipt	**06.03.2023**	**Released date**	**07.03.2023**
Sample Quantity	**200.0 g**	**Dispatch Note No.**	**NA**
Specification Ref. No.	**FP/SPS/204/001 (Revision 06)**	**Storage condition**	**Store in tightly closed container.**
Packing Description	**Product packed in blue HDPE drums inserted two food grade transparent polyethylene bags tie with plastic strips separately and put inner product label, second bag tie with numbered strips and finally close with black lid then sealed with red colored plastic seals.**		
Customer	**M/s; P.H.D. STUDENTS.**		

Sr No	Tests	Reference	Observations	Specifications
01	Appearance	Visible	White free flowing powder free from foreign matter	White free flowing powder, free from foreign matter.
02	Moisture Content	In House	2.5 % w/w	Not more than 5.0 %. w/w
03	Particle size : Retained on 100 BSS mesh (150 micron). Retained on 200 BSS mesh (75 micron).	In House	0.1 % w/w 35.2 % w/w	Not more than 1.0 % w/w Not more than 45.0 % w/w
04	Iron content (as Fe ppm)	USP, <241>	Less than 100.0 ppm	Not more than 100.0 ppm
05	Heavy metal Content (as pb ppm)	IP, 2.3.13	Less than 20.0 ppm	Not more than 20.0 ppm
06	Arsenic Content(as As ppm)	BP, A243	Less than 3.0 ppm	Not more than 3.0 ppm
07	Ion Exchange Capacity (meq/dry gm)	In House	10.9 meq/dry gm	Not less than 10.0 meq/dry gm

Remarks: The above product **Complies/~~Does not comply~~** with the prescribed standards of quality with respect to above tests as per In-house Specification No: FP/SPS/204/001 Rev. No. 06

Prepared by
Name: Sonal Delawadia
Sign :
Date: 22/08/2023

Checked by
Name: Pradip Raj
Sign :
Date: 22/08/2023

Approved by
Name: Pravin Panchal
Sign :
Date: 22/08/2023

ION EXCHANGE (INDIA) LTD. | CIN: L74999MH1964PLC014259
Plot No.5811-12-13, GIDC Industrial Estate, Ankleshwar - 393 002, Bharuch, India. | Board: +91 2646 672 700
Regd. Office: Ion House, Dr. E. Moses Road, Mahalaxmi, Mumbai - 400 011, India.
Board: +91 22 6231 2000 | Fax: +91 22 2493 6737 | E-mail: ial@ionexchange.co.in | Web: www.ionindia.com
Offices: Bengaluru | Bhubaneswar | Chandigarh | Chennai | Hyderabad | Kolkata | Lucknow | Mumbai | New Delhi | Pune | Vadodara | Vashi | Visakhapatnam

Appendices 11. Certificate of Analysis (CoA) of Resin Indion 214.

ION EXCHANGE
Refreshing the Planet

QUALITY CONTROL DEPARTMENT
CERTIFICATE OF ANALYSIS

Page No: 1 of 1
Date: 22.08.2023

Name of Finished Product: INDION 214 (Methacrylic acid Polymer with Divinyl Benzene & Acrylic acid)

Batch No	**PD214/23/06/001**	**A.R.No.**	**ARFP230146**
Mfg date	**Jun – 2023**	**Expiry date**	**May – 2028**
Date of sample receipt	**05.07.2023**	**Released date**	**06.07.2023**
Sample Quantity	**200.0 g**	**Dispatch Note No.**	**NA**
Specification Ref. No.	**FP/SPS/214/001 (Revision 05)**	**Storage condition**	**Store in tightly closed container.**
Packing Description	**Product packed in blue HDPE drums inserted two food grade transparent polyethylene bags tie with plastic strips separately and put inner product label , second bag tie with numbered strips and finally close with black lid then sealed with red colored plastic seals.**		
Customer	**M/s; P.H.D. STUDENTS.**		

Sr No	Tests	Reference	Observations	Specifications
01	**Appearance**	Visual	White free flowing powder, free from foreign matter.	White free flowing powder, free from foreign matter.
02	**Moisture Content**	In House	1.4 % w/w	Not more than 5.0 %. w/w
03	**Particle size :** Retained on 100 BSS mesh (150 micron). Retained on 200 BSS mesh (75 micron).	In House	0.1 % w/w 31.2 % w/w	Not more than 1.0 % w/w Not more than 45.0 % w/w
04	**Iron content** (as Fe ppm)	USP, <241>	Less than 100.0 ppm	Not more than 100.0 ppm
05	**Heavy metal Content** (as pb ppm)	USP, <251>	Less than 20.0 ppm	Not more than 20.0 ppm
06	**Arsenic Content**(as As ppm)	BP, A243	Less than 3.0 ppm	Not more than 3.0 ppm
07	**Ion Exchange Capacity** (meq/dry gm)	In House	10.9 meq/dry gm	Not less than 10.0 meq/dry gm
08	**Swelling Test**	In House	500 %	Not less than 300% actual weight

Remarks: The above product **Complies/~~Does not comply~~** with the prescribed standards of quality with respect to above tests as per USP Specification No: FP/SPS/214/001 Rev. No. 05.

Prepared by
Name: Sonal Delawadia
Sign :
Date: 22/08/2023

Checked by
Name: Pradip Raj
Sign :
Date: 22/08/2023

Approved by
Name: Pravin Panchal
Sign :
Date: 22/08/2023

ION EXCHANGE (INDIA) LTD. | CIN: L74999MH1964PLC014256
Plot No.5811-12-13, GIDC Industrial Estate, Ankleshwar - 393 002, Bharuch, India. | Board: +91 2646 672 700
Regd. Office: Ion House, Dr. E. Moses Road, Mahalaxmi, Mumbai - 400 011, India.
Board: +91 22 6331 2000 | Fax: +91 22 2493 8797 | E-mail: ial@ionexchange.co.in | Web: www.ionindia.com
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Appendices 12. Certificate of Analysis (CoA) of Resin Indion 254.

ION EXCHANGE
Refreshing the Planet

QUALITY CONTROL DEPARTMENT
CERTIFICATE OF ANALYSIS

Page No: 1 of 1
Date: 18.04.2023

Name of Finished Product: SODIUM POLYSTYRENE SULFONATE USP (INDION 254)
(Divinyl benzene co-polymer with styrene, sulfonated, Sodium salt).

Batch No.	**PD254/23/02/002**	**A.R.No.**	**ARFP230045**
Mfg date	**Feb - 2023**	**Exp.date**	**Jan - 2028**
Date of sample receipt	**03.03.2023**	**Released date**	**13.03.2023**
Dispatch Quantity	**300.0 g**	**Dispatch Note**	**NA**
Specification Ref. No.	**FP/SPS/254/001 (Revision 04)**	**Storage condition**	**Preserve in airtight container. Store at 20°C to 25°C (68°F to 77°F)**
Packing Description	**Product packed in double food grade transparent polyethylene bags, tied with plastic strips separately with one inner product label inserted between these bags. Second bag tied with numbered strip and finally inserted in blue HDPE carboys closed with black lid, then sealed with red colored numbered plastic seal. Second product label pasted on the outer surface of carboy.**		
Customer	**NA**		

Sr. No.	Test	Reference	Result	Specifications
1.	Description	USP <Description & Solubility>	Golden brown, fine powder. Odorless and has a characteristic taste.	Golden brown, fine powder. Is odorless and has a characteristic taste.
2.	Solubility	USP <Description & Solubility>	Insoluble in water.	Insoluble in water.
3.	Water content	USP, Method I <921>	6.6 %	Not more than 10.0%.
4.	Limit of ammonium salts	USP	No blue color observed	The Red litmus paper shows no blue color
5.	Sodium content	USP	10.9 %	The sodium content is not less than 9.4% and not more than 11.5%, calculated on the anhydrous basis.
6.	Potassium exchange capacity	USP	120 mg	Each g exchanges not less than 110 mg and not more than 135 mg of potassium, calculated on the anhydrous basis.

Remarks: The above product **Complies/~~Does not comply~~** with the prescribed standards of quality with respect to above tests as per USP Specification No: FP/SPS/254/001 Rev. No. 04

Prepared by
Name: Sonal Delawadia
Sign :
Date: 18/04/2023

Checked by
Name: Pradip Raj
Sign :
Date: 18/04/2023

Approved by
Name: Haresh Gurav
Sign :
Date: 18/04/2023

ION EXCHANGE (INDIA) LTD. | CIN: L74999MH1964PLC014258
Plot No.6811-12-13, GIDC Industrial Estate, Ankleshwar - 393 002, Bharuch, India. | Board: +91 2646 672 700
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Board: +91 22 6201 2000 | Fax: +91 22 2493 8737 | E-mail: iel@ionexchange.co.in | Web: www.indion.com

Appendices 13. Certificate of Analysis (CoA) of Resin Kyron T-114.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Haridwar - 249403 (Uttarakhand)

QUALITY CONTROL
CERTIFICATE OF ANALYSIS
(RAW MATERIAL)

Name of Raw Material :	KYRON T-114		
Batch No. :	02022087	**A. R. No. :**	080000347137
Specification No. , Ver No. :	STS/RM/10001312-03	**Mfg. Date :**	01/12/22
Ref. STP No. , Ver No. :	STP/RM/10001312	**Expiry Date :**	30/11/27
Manufacturer Name :	COREL PHARMA CHEM	**Qty Received :**	0.448 KG
Supplier Name :	AKUMS Drugs & Pharmaceuticals Ltd.	**Sample By :**	SANDEEP PATEL
Sample On :	07/09/23	**Qty Sampled :**	0.000 KG
Invoice No. :	N/A	**Qty Released :**	0.448 KG
GRN No. :	4911219614	**Analysis By :**	N/A
GRN Date :	07/09/23	**Date of Analysis :**	07/09/23
Item Code :	10001312	**Analysis Completion Date :**	07/09/23
Retest Date :	29/04/24		
SAP Batch No. :	0003519242	**Invoice Date :**	N/A

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	White to off white free flowing powder.	Off white free flowing powder.
2	Solubility	Insoluble in water and other solvent.	Complies.
3	Identification (By IR)	The absorption maxima in the spectrum obtained with sample should correspond in position and relative intensity to those in the spectrum with obtained with the Kyron T114 reference/working standard.	Complies.
4	Heavy Metals	Not more than 10 ppm.	Less than 10 ppm.
5	Arsenic	Not more than 3 ppm.	Less than 3 ppm.
6	Iron content	Not more than 100 ppm.	Less than 100 ppm.
7	Loss on drying	Not more than 10.0 % w/w.	2.84 %w/w

	Prepared By	Reviewed By	Approved By
Date	07/09/23	07/09/23	07/09/23
Name	NAGENDRA OSWAL	INDERPAL SINGH	HARSHIT KUMAR
Designation	SR. EXECUTIVE	SR. EXECUTIVE	MANAGER

This is an electronically signed document, hence does not require any signatures

FORMAT NO. : HQC-008/F01-03 Page 01 of 02

Date & Time : 04/07/2025 16:35 Printed By: ROBINDRA KUMAR PANDIT

Appendices 14. Certificate of Analysis (CoA) of Resin Kyron T-314.

Pure & Cure Healthcare Pvt. Ltd.
Plot No. 26A-30, Sector-8A, I.I.E., SIDCUL, Ranipur
Haridwar-249403,Uttarakhand , INDIA.

QUALITY CONTROL

CERTIFICATE OF ANALYSIS

(RAW MATERIAL)

Name of Raw Material :	KYRON T-314		
Batch No. :	04021057	**A. R. No. :**	010006856982
Specification No. , Ver No. :	STS/RM/10014819-00	**Mfg. Date :**	01/08/21
Ref. STP No. , Ver No. :	STP/RM/10014819-00	**Expiry Date :**	31/07/26
Manufacturer Name :	COREL PHARMA CHEM	**Qty Received :**	2 KG
Supplier Name :	AKUMS DRUGS & PHARMACEUTICALS LTD.	**Sample By :**	AKASH KUKRETI
Sample On :	02/03/24	**Qty Sampled :**	0.045 KG
Invoice No. :	240110006466	**Qty Released :**	1.955 KG
GRN No. :	5002953084	**Analysis By :**	SOHIT
GRN Date :	01/03/24	**Date of Analysis :**	02/03/24
Item Code :	10014819	**Analysis Completion Date :**	07/03/24
Retest Date :	06/03/26		
SAP Batch No. :	0003943358	**Invoice Date :**	26/02/24

S. No.	TEST	ACCEPTANCE CRITERIA	RESULTS
1	Description	White to Pale cream free flowing powder.	Pale cream free flowing powder.
2	Solubility	Insoluble in water and in most liquid.	Complies.
3	Identification (By IR)	The absorption maxima in the spectrum obtained with sample should correspond in position and relative intensity to those in the spectrum with obtained with the Kyron T-314 reference/working standard.	Complies.
4	Powder Fineness-% Retain on 100# mesh	Not more than 1.0%w/w	Complies.
5	Powder Fineness-% Retain on 200# mesh	Not more than 30.0%w/w	10.35 %w/w.

	Prepared By	Reviewed By	Approved By
Date	07/03/24	07/03/24	07/03/24
Name	NAGENDRA OSWAL	INDERPAL SINGH	DINESH TYAGI
Designation	SR. EXECUTIVE	ASST. MANAGER	A.G.M.

This is an electronically signed document, hence does not require any signatures

FORMAT NO. : HQC-008/F01-03 Page 01 of 02

Date & Time : 04/07/2025 16:37 Printed By: ROBINDRA KUMAR PANDIT

Appendices 15. IP General Monograph for Testing of an Oral Suspension.

for oral administration either undiluted or after dilution. They may contain auxiliary substances such as suitable dispersing, emulsifying, suspending, wetting, solubilising, thickening, stabilising agents and antimicrobial preservatives. They may also contain suitable sweetening, flavouring and permitted colouring agents. if saccharin, including its sodium and potassium salts, is used as a sweetening agent, its concentration in preparations meant for paediatric use should be restricted so as to limit its intake to 5 mg per kg of body weight.

Oral Liquids other than Oral Emulsions may be supplied as liquids or prepared just before use by dissolving or dispersing granules or powder in the liquid stated on the label. The granules or powder comply with the requirements stated under Oral Powders.

During manufacture, packaging, storage and distribution of oral liquids, suitable means shall be taken to ensure their microbial quality; acceptance criteria for microbial quality are given in Chapter 2.2.9.

Oral Liquids should not be diluted and stored; where, however, the individual monograph directs dilution, the diluted Oral Liquid should be freshly prepared irrespective of the nature of the diluent. Diluted Oral Liquids may be less stable physically and chemically than the corresponding undiluted preparation and should be used within the period stated on the label.

Oral Liquids are variously known as Elixirs, Linctuses Mixtures, Oral Drops, Oral Emulsions, Oral Solutions, Oral Suspensions and Syrups. These terms are defined below.

Elixirs. Elixirs are clear, flavoured Oral Liquids containing one or more active ingredients dissolved in a vehicle that usually contains a high proportion of Sucrose or a suitable polyhydric alcohol or alcohols and may also contain Ethanol (95 per cent) or a dilute Ethanol.

Linctuses. Linctuses are viscous Oral Liquids containing one or more active ingredients dissolved in a vehicle that usually contains a high proportion of sucrose, other sugars or a suitable polyhydric alcohol or alcohols. Linctuses are intended for use in the treatment or relief of cough, and are sipped and swallowed slowly without the addition of water.

Mixtures. Mixtures are Oral Liquids containing one or more active ingredients dissolved, suspended or dispersed in a suitable vehicle. Suspended solids may separate slowly on keeping but are easily redispersed on shaking.

Oral Drops. Oral Drops are Oral Liquids that are intended to be administered in small volumes with the aid of a suitable measuring device such as a dropper.

Oral Emulsions. Oral Emulsions are Oral Liquids containing one or more active ingredients and are stabilised oil-in-water dispersions, either or both phases of which may contain dissolved solids. Solids may also be suspended in Oral Emulsions. Emulsions may exhibit phase separation but are easily reformed on shaking. The preparation remains sufficiently stable to permit a homogeneous dose to be withdrawn.

Oral Solutions. Oral Solutions are Oral Liquids containing one or more active ingredients dissolved in a suitable vehicle.

Oral Suspensions. Oral Suspensions are Oral Liquids containing one or more active ingredients suspended in a suitable vehicle. Suspended solids may slowly separate on keeping but are easily redispersed.

In the manufacture of oral suspensions containing dispersed particles, measures shall be taken to ensure a suitable and controlled particle size with regard to the intended use of the product.

Syrups. Syrups are viscous Oral Liquids that may contain one or more active ingredients in solution. The vehicle usually contains large amounts of Sucrose or other sugars to which certain polyhydric alcohols may be added to inhibit crystallisation or to modify solubilisation, taste and other vehicle properties. Sugarless syrups may contain sweetening agents and thickening agents. Syrups may contain Ethanol (95 per cent) as a preservative or as a solvent to incorporate flavouring agents. Antimicrobial agents may also be added to Syrups.

Containers. Oral Liquids may be supplied in multiple dose or single dose containers. Oral Emulsions and Oral Suspensions should be packed in bottles sufficiently wide-mouthed to facilitate the flow of the contents. They are administered either in volumes such as 5 ml, or multiples of 5 ml, or in small volumes (drops). Each dose of a multiple dose Oral Liquid is administered by means of a suitable measuring device which is usually provided with the container.

Tests

Uniformity of content. Unless otherwise specified, single dose liquids in suspension form or powders or granules presented in single dose containers and that contain less than 10 mg or less than 10 per cent of active ingredient comply with the following test. For Oral Liquids containing more than one active ingredient, carry out the test for each active ingredient that corresponds to the above conditions. Empty each container as completely as possible and carry out the test on the individual contents of active ingredients.

The test for Uniformity of content should be carried out only after the content of active ingredient(s) in a pooled sample of the preparation has been shown to be within the accepted limits of the stated content.

Determine the content of active ingredient(s) of each of 10 containers taken at random using the method given in the

Appendices 16. ICH Guideline for Impurities of New product Q3A(R2).

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

IMPURITIES IN NEW DRUG SUBSTANCES
Q3A(R2)

Current *Step 4* version

dated 25 October 2006

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Appendices 17. ICH Guideline for Specification for test procedure Q6A.

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

SPECIFICATIONS: TEST PROCEDURES AND ACCEPTANCE CRITERIA FOR NEW DRUG SUBSTANCES AND NEW DRUG PRODUCTS: CHEMICAL SUBSTANCES

Q6A

Current *Step 4* version

dated 6 October 1999

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Appendices 18. ICH Guideline for Stability analysis of new product Q1A(R2).

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

STABILITY TESTING OF NEW DRUG SUBSTANCES AND PRODUCTS Q1A(R2)

Current *Step 4* version

dated 6 February 2003

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Appendices 19. ICH Guideline for Method Validation of new product Q2(R1).

INTERNATIONAL CONFERENCE ON HARMONISATION OF TECHNICAL REQUIREMENTS FOR REGISTRATION OF PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED TRIPARTITE GUIDELINE

VALIDATION OF ANALYTICAL PROCEDURES: TEXT AND METHODOLOGY

Q2(R1)

Current *Step 4* version
Parent Guideline dated 27 October 1994
(Complementary Guideline on Methodology dated 6 November 1996 incorporated in November 2005)

This Guideline has been developed by the appropriate ICH Expert Working Group and has been subject to consultation by the regulatory parties, in accordance with the ICH Process. At Step 4 of the Process the final draft is recommended for adoption to the regulatory bodies of the European Union, Japan and USA.

Appendices 20. ICH Guideline for Quality Risk Management of new product Q9(R1).

INTERNATIONAL COUNCIL FOR HARMONISATION OF TECHNICAL REQUIREMENTS FOR PHARMACEUTICALS FOR HUMAN USE

ICH HARMONISED GUIDELINE

QUALITY RISK MANAGEMENT
Q9(R1)

Final version

Adopted on 18 January 2023

9. List of Publications

1. **Development and Validation of a gradient Program RP-HPLC Method for Estimation of Multiple Active Pharmaceutical Ingredients in an Oral Suspension Taste Masked with an Ion Exchange Resin.**

International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 4, 2025

Original Article

DEVELOPMENT AND VALIDATION OF A GRADIENT PROGRAM RP-HPLC METHOD FOR ESTIMATION OF MULTIPLE ACTIVE PHARMACEUTICAL INGREDIENTS IN AN ORAL SUSPENSION TASTE MASKED WITH AN ION EXCHANGE RESIN

ROBINDRA K. PANDIT, VIVEK PANDEY*

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Received: 29 Dec 2024, Revised and Accepted: 24 Apr 2025

ABSTRACT

Objective: This study focuses on developing an effective Reverse Phase High-Performance Liquid Chromatography (RP-HPLC) method for the simultaneous analysis of Dextromethorphan Hydrobromide (DXM), Phenylephrine Hydrochloride (PEH), and Chlorpheniramine Maleate (CPM) in a taste-masked oral suspension. The method ensures rapid, precise, and accurate quantification of these Active Pharmaceutical Ingredients (APIs) while supporting formulation stability and regulatory compliance.

Methods: A gradient High-Performance Liquid Chromatography (HPLC) method with a short 7.5-minute run time was optimized for the simultaneous analysis of DXM, PEH, and CPM in a complex suspension matrix. The taste masking was achieved using Indion 254 ion exchange resin, and its impact on drug release and assay accuracy was evaluated. Key method parameters, including resolution, plate count, and tailing factor, were optimized to ensure robust performance. The method was validated according to International Council for Harmonisation (ICH) guidelines, assessing specificity, precision, accuracy, and stability.

Results: The developed DXM, PEH, and CPM method demonstrated excellent specificity, with no interference from the resin, excipients, or degradation products. Resolution values of more than 1.5 between ICH exceeded acceptance criteria, with plate counts more than 1500 and tailing factors within below 2. The method proved highly precise, with Relative Standard Deviation (RSD) values below 1%. It also ensured reliable quantification of Active Pharmaceutical Ingredients (APIs) in the presence of the taste-masking resin and under various stress conditions, confirming formulation stability.

Conclusion: The developed HPLC method provides a rapid, precise, and reliable solution for analyzing APIs in a taste-masked oral suspension. Its efficiency and compliance with ICH guidelines make it a valuable tool for quality control, ensuring formulation consistency and patient safety.

Keywords: ICH, BAGI, Development, Validation of reverse phase high-performance liquid chromatography (RP-HPLC), Assay, ICH guidelines, Dextromethorphan hydrobromide (DMH), Phenylephrine hydrochloride (PEH), Chlorpheniramine maleate (CPM), Ion exchange resin (IER), Blue applicability grade index (BAGI) and Oral suspension

DOI: https://dx.doi.org/10.22159/ijap.2025v17i4.53547 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Simultaneous drug analysis presents considerable challenges due to differences in solubility, retention behaviour, and detector response of multiple Active Pharmaceutical Ingredients (APIs). Developing a robust Reverse-Phase High-Performance Liquid Chromatography (RP-HPLC) gradient method for Dextromethorphan Hydrobromide (DXM), Phenylephrine Hydrochloride (PEH), and Chlorpheniramine Maleate (CPM) in an oral suspension necessitates precise optimization to ensure resolution and accuracy. Taste-masking with ion exchange resins further complicates quantification by altering drug release and matrix composition. This study focuses on method development and validation, ensuring specificity, precision, and reproducibility to enable accurate estimation of APIs in a taste-masked formulation, thereby improving patient compliance [1-6].

Analyzing oral suspensions using High-Performance Liquid Chromatography (HPLC) involves significant technical challenges, including ensuring homogeneity and complete dissolution of APIs and excipients to prevent inconsistent results or system clogging. Sample filtration must be handled carefully to avoid analyte loss [7]. Selecting an appropriate mobile phase and HPLC column is critical to achieving effective resolution without inducing precipitation. Stability concerns arise due to APIs excipient interactions and degradation under analytical conditions [8-12]. Separating DXM, PEH and CPM, which exhibit varying polarities, requires careful optimization. A major challenge is achieving sufficient resolution, particularly between DXM and CPM, which may have overlapping retention times [13-18]. This can be mitigated by fine-tuning the mobile phase composition and employing a gradient elution approach using acetonitrile and water at specific pH values [19-23].

Additionally, since APIs may absorb UV light at different wavelengths, a Photodiode Array Detector (PDA) detector is crucial for comprehensive spectral analysis [24-27].

Excipients in oral suspensions can interfere with analyte peaks, necessitating optimization of sample preparation steps, such as filtration or dilution, to minimize interference and ensure accurate quantification [28-32]. Method validation, including linearity, accuracy, precision, and robustness, is essential for regulatory compliance and routine quality control [33-37]. Advances in analytical techniques, such as Ultra-Performance Liquid Chromatography (UPLC), have enhanced precision and efficiency, but rigorous validation is necessary to meet regulatory standards [38-41].

Oral suspensions are preferred for pediatric and geriatric patients due to ease of administration; however, the unpleasant taste of many APIs poses a significant barrier to compliance. Taste masking is critical in ensuring treatment adherence, with techniques including flavoring agents, coatings, and microencapsulation [42-46]. Ion Exchange Resins (IERs) have emerged as a superior approach by forming tasteless drug-resin complexes that sequester the bitter drug from taste receptors [47-50]. Compared to flavoring agents, which may lose effectiveness over time, and encapsulation techniques, which can alter drug release profiles, IERs provide a more reliable and stable solution [51-54].

The International Council for Harmonisation (ICH) guidelines outline key validation parameters such as specificity, linearity, accuracy, precision, detection limit, quantitation limit, robustness, and system suitability [55-68]. Adhering to these guidelines ensures the reliability and reproducibility of analytical methods, enabling their application in routine quality control laboratories [69-72]. This study aims to

2. Development and Validation of an RP-HPLC Chromatographic Method for The Determination of Related Substances in a Polypharmaceutical Oral Suspension with Ion Exchange Resin Based Taste Masking.

International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 17, Issue 4, 2025

Original Article

DEVELOPMENT AND VALIDATION OF AN RP-HPLC CHROMATOGRAPHIC METHOD FOR THE DETERMINATION OF RELATED SUBSTANCES IN A POLYPHARMACEUTICAL ORAL SUSPENSION WITH ION EXCHANGE RESIN-BASED TASTE MASKING

ROBINDRA K. PANDIT, VIVEK PANDEY*

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Received: 23 Mar 2025, Revised and Accepted: 04 Jun 2025

ABSTRACT

Objective: This study focuses on the development and validation of a high-performance liquid chromatography (HPLC) method for the estimation of related substances in both bulk and finished oral suspension formulations intended for the treatment of acute nasopharyngitis. The formulation incorporates taste-masked Dextromethorphan Hydrobromide (DMH), Phenylephrine Hydrochloric Acid (PEH), and Chlorpheniramine Maleate (CPM) using ion exchange resin. The validation process assesses parameters such as specificity, precision, accuracy, linearity, robustness, limit of detection (LOD), and limit of quantification (LOQ), ensuring the method's applicability for quality control and regulatory compliance.

Methods: A gradient HPLC method employing a reversed-phase column and an optimized mobile phase was utilized for the effective separation of related substances in the taste-masked oral suspension. The method parameters include a 70-minute run time per injection, a flow rate of 1.2 ml/min, a detection wavelength of 265 nm, an injection volume of 20 µl**, and a column temperature maintained at 35 °C. The validation procedure encompasses specificity, precision, accuracy, linearity, robustness, LOD and LOQ assessments. This method ensures reliable and reproducible quantification, making it suitable for routine quality control applications and regulatory submissions.

Results: The developed HPLC method successfully achieved the separation of related substances within the specified 70 min runtime per injection. System suitability criteria were met, confirming method efficiency. The method exhibited high specificity with no interference, achieving peak resolutions exceeding 1.5. It demonstrated precise repeatability (relative standard deviation ((RSD)<2%), accurate recovery within 98–102%, and strong linearity (R^2>0.999). The sensitivity of the method was confirmed through LOD and LOQ values. Robustness studies indicated the stability of the method under varying analytical conditions, supporting its reliability for routine quality control.

Conclusion: The validated HPLC method provides a robust approach for estimating related substances in taste-masked Dextromethorphan HBr, Phenylephrine HCl, and Chlorpheniramine Maleate oral suspension. Meeting all essential validation criteria—including specificity, precision, accuracy, linearity, robustness, LOD and LOQ the method ensures accurate, sensitive, and reproducible quantification. Consequently, it is well-suited for routine quality control analysis in pharmaceutical formulations.

Keywords HPLC, Related substance, ICH guidelines, Dextromethorphan hydrobromide, Phenylephrine hydrochloride, Chlorpheniramine maleate, Ion exchange resin, Oral suspension and validation

DOI: https://dx.doi.org/10.22159/ijap.2025v17i4.54312 Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

The increasing demand for multi-drug formulations has driven advancements in pharmaceutical development, particularly for oral suspensions. These formulations are essential for treating complex conditions like acute nasopharyngitis, which require a combination of active pharmaceutical ingredients (APIs) that work synergistically. Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate are commonly used for their antitussive, decongestant, and antihistamine properties [1-4]. However, formulating these APIs into an effective oral suspension presents challenges related to stability, taste masking, and related substance identification. Even trace amounts of related substances can impact safety, efficacy, and shelf-life, necessitating precise analysis to ensure purity and quality [5-9].

Related substances include known and unknown impurities, degradation products formed during manufacturing storage. These impurities can alter drug potency and pose safety risks, emphasizing the need for a robust analytical method. Liquid chromatography (LC) is a preferred technique for related substance analysis due to its ability to separate, identify, and quantify multiple components in complex mixtures [10-14].

This study focuses on developing and validating an LC method for analyzing related substances in an oral suspension containing Dextromethorphan Hydrobromide, Phenylephrine Hydrochloride, and Chlorpheniramine Maleate. The formulation incorporates an ion-exchange resin for taste masking, adding complexity due to potential resin-API interactions [15-18]. These interactions may lead to new degradation products or altered drug pharmacokinetics, complicating impurity identification. A key objective is to develop a method capable of resolving APIs, degradation products, and resin-induced impurities [19].

Dextromethorphan hydrobromide: A widely used antitussive (cough suppressant) that acts on the central nervous system by inhibiting the cough reflex. It is commonly found in cold and flu formulations and is effective for dry cough (fig. 1. A) [20].

Phenylephrine hydrochloride: A selective α1-adrenergic receptor agonist used as a nasal decongestant. It works by constricting blood vessels in the nasal passages, reducing swelling and congestion associated with colds and allergies (fig. 1. B) [21].

Chlorpheniramine maleate: A first-generation antihistamine that blocks H1 receptors, relieving allergic symptoms such as runny nose, sneezing, and itching. It has mild sedative effects and is commonly used in combination with other cold medications (fig. 1C) [22].

Challenges in related substance analysis: Related substance analysis is vital for ensuring drug safety and efficacy. Multi-drug formulations increase the risk of component interactions, leading to impurities from chemical degradation, excipient interactions, or residual solvents. These impurities can impact potency, bioavailability, and safety [23-27].

The taste-masking ion-exchange resin further complicates analysis. While effective at masking bitterness, it may bind APIs, altering retention times and separation in chromatographic analysis.

3. **Comparative Evaluation of different Ion Exchange Resins for Enhanced Palatability in Oral Suspensions Containing Multiple active pharmaceuticals ingredients.**

https://africanjournalofbiomedicalresearch.com/index.php/AJBR
Afr. J. Biomed. Res. Vol. 27(4s) (December 2024); 7450-7460
Research Article

Comparative Evaluation of different Ion Exchange Resins for Enhanced Palatability in Oral Suspensions Containing Multiple active pharmaceuticals ingredients.

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Abstract:
Selecting an appropriate ion exchange resin for taste masking in an oral suspension with multiple active pharmaceutical ingredients (APIs) involves several challenges. Each API has unique chemical properties affecting their binding affinity to the resin, making it difficult to achieve consistent taste masking and release profiles. Competitive binding among APIs can lead to suboptimal taste masking and inconsistent therapeutic efficacy. The resin's physicochemical properties, such as particle size and porosity, must be optimized for effective taste masking and manufacturability. The manufacturing process must ensure uniform resin dispersion to provide consistent taste masking, which may require specialized equipment or steps, adding complexity. The drug release from drug- resin pattern also a big factor affecting during formulation of oral suspension. Balancing these factors to maintain therapeutic outcomes and patient acceptability is essential in the selection process.
The effectiveness of ion exchange resins in taste-masking bitter pharmaceutical compounds has garnered significant interest due to the impact of palatability on patient compliance, especially in pediatric populations.
This study evaluates and compares the taste-masking capabilities of five different ion exchange resins: Kyron T-114, Kyron T-314, Indion 214, Indion 204, and Indion 254, when used with a combination of dextromethorphan hydrobromide (HBr), chlorpheniramine maleate, and phenylephrine hydrochloride (HCl) in an oral suspension formulation. These active pharmaceutical ingredients (APIs) are commonly used in cold and allergy medications, but their bitter taste can hinder patient adherence. The primary objective was to assess the efficiency of each resin in binding the APIs to reduce bitterness without compromising the therapeutic efficacy. The study involved preparing suspensions of the APIs with each resin, followed by a series of tests to evaluate the degree of taste masking and drug-resin binding efficiency. The taste-masking efficiency was determined through a human taste panel assessment. Binding efficiency was quantified using high-performance liquid chromatography (HPLC). Results indicated significant variations in the tastemasking capabilities of the different resins. Indion resins demonstrated superior taste-masking properties compared to the Kyron T-114 and Kyron T-314. Among the Indion resins, Indion 254 exhibited the best performance among all used resins.

Key Words: Ion exchange resins, Taste masking, Dextromethorphan HBr, Chlorpheniramine maleate, Phenylephrine HCl, Oral suspension

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Received: 05/12/2024 *Accepted: 10/12/2024*

DOI: https://doi.org/10.53555/AJBR.v27i4S.5014

10. List of Conferences

1. RAFAS Conferences 2023

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Certificate of Participation

This is to certify that **Dr./Mr./Ms. Robindra Kumar Pandit** of **Lovely Professional University** has given poster presentation on **A Formulation and Evaluation study on taste masking of oral solution using Ion Exchange Resin – A Mini-Review.** in the 4th International Conference on "Recent Advances in Fundamental and Applied Sciences" (RAFAS 2023) held on March 24-25, 2023, organized by School of Chemical Engineering and Physical Sciences, Lovely Faculty of Technology and Sciences, Lovely Professional University, Punjab.

Date of Issue: 12-04-2023
Place: Phagwara (Punjab), India

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2. RAFAS Conferences 2025

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This is to certify that **Dr./Mr./Ms. Robindra Kumar Pandit** of **Lovely Professional University, Punjab** has given **Poster Presentation** on **A novel ICH validated approach towards rapid Simultaneous analysis of three versatile drugs in oral suspension: Exploring the role of ion exchange resin in taste masking of bitterness in drugs** in the **6th International Conference on Recent Advances in Fundamental and Applied Science (RAFAS 2025)** held from **18th April, 2025** to **19th April, 2025**, organized by School of Chemical Engineering and Physical Sciences, Lovely Faculty of Technology and Sciences, at Lovely Professional University, Punjab.

Date of Issue : 17-05-2025
Place : Phagwara (Punjab), India

Prepared by
(Administrative Officer-Records)

Organizing Secretary
(RAFAS-2025)

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Lovely Professional University