DEVELOPMENT OF SOLID DOSAGE FORMS USING PLATFORM TECHNOLOGY FOR ORAL DELIVERY

Thesis Submitted for the Award of the Degree of

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2024

DECLARATION

I, hereby declared that the presented work in the thesis entitled **''DEVELOPMENT OF SOLID DOSAGE FORMS USING PLATFORM TECHNOLOGY FOR ORAL DELIVERY''** in fulfilment of degree of **Doctor of Philosophy (Ph.D)** is outcome of research work carried out by me under the supervision of **Dr. Sheetu**, working as **Associate Professor,** in the **Dept. of Pharmaceutical 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 other 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 OF SOLID DOSAGE FORMS USING PLATFORM TECHNOLOGY FOR ORAL DELIVERY''** submitted in fulfillment of the requirement for the award of degree of **Doctor of Philosophy (Ph.D.)** in the **Dept. of Pharmaceutical Sciences**, is a research work carried out by **Nikhil Gupta, 41800445** , is bonafide record of his/her 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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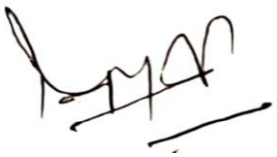

Nikhil Gupta

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List of Abbrevations

ADP: Air distribution plate

AMT: Asymmetric membrane technology

ANDA: Abbreviated new drug application

API: Active pharmaceutical ingredient

BCS: Biopharmaceutics classification

Cº: Celsius

CI: Compressibility Index

CI: Compressibility index

CMA: Critical material attributes

CPS: Centipoise

CQA: Critical quality attributes

DSC: Differential scanning calorimeter

EC: Ethyl cellulose

FBD: Fluid bed dryer

FTIR: Fourier transform infrared

GIT: Gastrointestinal tract

H: Hausner ratio

HCl: Hydrochloride

HME: Heat moisture exchanger

HPLC: High-performance liquid chromatography

HR: Hausner ratio

LOD: Loss on drying

LOQ: Limit of quantification

MS: Metoprolol succinate

MUPS: Multiple unit pellets system

NDA: New drug application

NLT: Not less than

ODT: Orodispersible tablets

PEG: Polyethylene-glycol

pH: Potential of hydrogen

PW: Purified water

PXRD: Powder x-ray diffractometry

QTPP: Quality target product profile

RPM: Revolutions per minute

SCT: Swelling technology

TEC: Tri-ethyl citrate

UV: Ultraviolet

ABSTRACT

Part A: Formulation of sustained release MUPS tablets of S (-) Metoprolol succinate using Wurster process

In this study, we use platform technology to create a new formulation. Hydrophobic polymers, hydrophilic polymers, or a mix of the two should provide the novel element of the suggested formulation. Comprehensive literature research in publications and patents revealed the research gap for the development of oral controlled release formulations employing Wurster technology with scientific explanation. S (-) Metoprolol succinate is used for hypertension, angina, and migraine prophylaxis. The beta-adrenergic receptor is inhibited by metoprolol. S (-) Metoprolol succinate half-life is only 2-7 h. For this reason, it is recommended to be administered twice it daily. The protein binding percentage is 12% and bioavailability is 50 %. S (-) Metoprolol succinate pKa is 9.68, and its hydrophilic nature makes it freely soluble in water (BCS class I). The medication is absorbed swiftly and thoroughly throughout the whole intestine. When a single dose is administered the peak plasma concentration of metoprolol occurs between two and four h after dosing. The medication is eliminated entirely in the urine within three to four h. The medication may be used up to four times daily for optimal results. Metoprolol dosage strengths range from 25 mg to 200 mg. Dosing intervals must be modified to maximise patient compliance, drug product quality, safety, efficacy and cost-effectiveness. It has always been difficult for pharmaceutical technologists to create oral sustained-release platform technology for freely water-soluble drugs with first-pass metabolism. Most of these highly water-soluble drugs are likely to reach toxic amounts after oral administration if they are not properly prepared and administered. Coated dosage forms provide a consistent, accurate, and sustained release of the drug. To ensure the steady release of an active ingredient in a pharmaceutical formulation, polymeric film coatings are frequently used. To create MUPS, the pellets containing API are combined with the powder excipients and compressed. The pellets spherical centre contains or is covered with active ingredient and in one or more outer layers mostly cellulosic and acrylic polymers are present to prevent the drug from leaking out too quickly. As an alternative to traditional immediate or modified-release tablets, MUPS technology has

been adopted by the pharmaceutical sector. To prevent the API from being degraded by the acidic conditions of the stomach, it can be encapsulated in an enteric-coated pellet containing a variety of medications and then formulated as tablets. There is less potential for local discomfort and toxicity with MUPS formulations. Tablets are the most common type of pharmaceutical dosage form used in the market. The pharmaceutical business faces a significant challenge when trying to compress pellets into a tablet form. The goal of this research is to find a way to make single or double-layered tablets containg particles that disintegrate into pellets to provide the desired sustained release. S (-) Metoprolol succinate pellets with extended-release were developed using the Wurster technique. Drug coating solution containing S (-) Metoprolol succinate was used to cover the MCC spheres. For the coating of the control release polymer Methocel K4M and Methocel K100 M were used. Pellets were sprayed with a functional coating solution, drying done for 60 min, then sieved through a mesh size of 14 # and tested for various chemical and physical properties. Several trials were conducted to determine the optimal values for the process variables; spray rate: 8-20 g/min; outlet temperature: 30-40 °C; product bed temperature: 30-40 °C. Some cushioning agents were made by combining MCC PH 102, MCC PH 200, aerosil, sodium stearyl fumarate and Lubritab. Cushioning agents were combined with pellets that were coated to perform specific functions. White or off-white tablets with 250 mg weight, thickness 3.60 ± 0.40 mm, turret speed of 12 to 20 rpm, force feeder speed of 12 to 20 rpm and cylinder hydraulic pressure not more than 15 pounds are the parameters for compressing a lubricated MUPS (Multiple unit pellets system) blend in a single rotary compression machine. Micrometric characteristics, in-process parameters, drug content, content uniformity, drug assay, dissolution and stability tests were conducted on drug-coated pellets, sustained-release pellets and MUPS tablets. This optimized drug-loaded pellets formulation has a bulk density of 0.72 g/mL, a compressibility index of 12.57, an angle of repose of 27.45°, and a friability of 0.12 %. An idealised formula for functional coated pellets has a bulk density of 0.69 %, a compressibility index of 14.21 %, angle of repose of 27.21°, and a friability of 0.13%. The invitro dissolution for functional coated pellets are: For 2 h (17.77%) limit: NLT 25 %, for 4 h (33.57%) limit: 20-50 %, for 8 h (53.72 %) limit: 35 %-70 % and for 20 h (95.77 %) limit Not less than (NLT) 70 %. S (-)

Metoprolol Succinate's release from their matrices could be slowed with the use of the developed controlled release platform that includes Methocel K4M and Methocel K100. Optimized functional pellets with cushioning agents were blended. The optimal compressed MUPS tablet coated pellets formulation has the following characteristics: thickness 3.80-3.90 mm; hardness 3-4 Kg/cm^2; friability 0.13%; compression rpm 22; drug content 99.90 %; and an in vitro release profile of Metoprolol Succinate from their MUPS matrices. For 2 h (16.77%) limit: NLT 25 %, for 4 h (36.57%) limit: 20-50 %, for 8 h (54.42 %) limit: 35 %-70 % and for 20 h (95.77 %) limit NLT 70. At 0, 3 and 6 months accelerated stability study were performed and physical appearance, hardness, friability, thickness, assay and solubility of MUPS tablets were observed with in the specification limit based on samples taken at various intervals. The fact that the results meets within the specified range, makes it a stable formulation as shown in graphical abstract **Figure 1.**

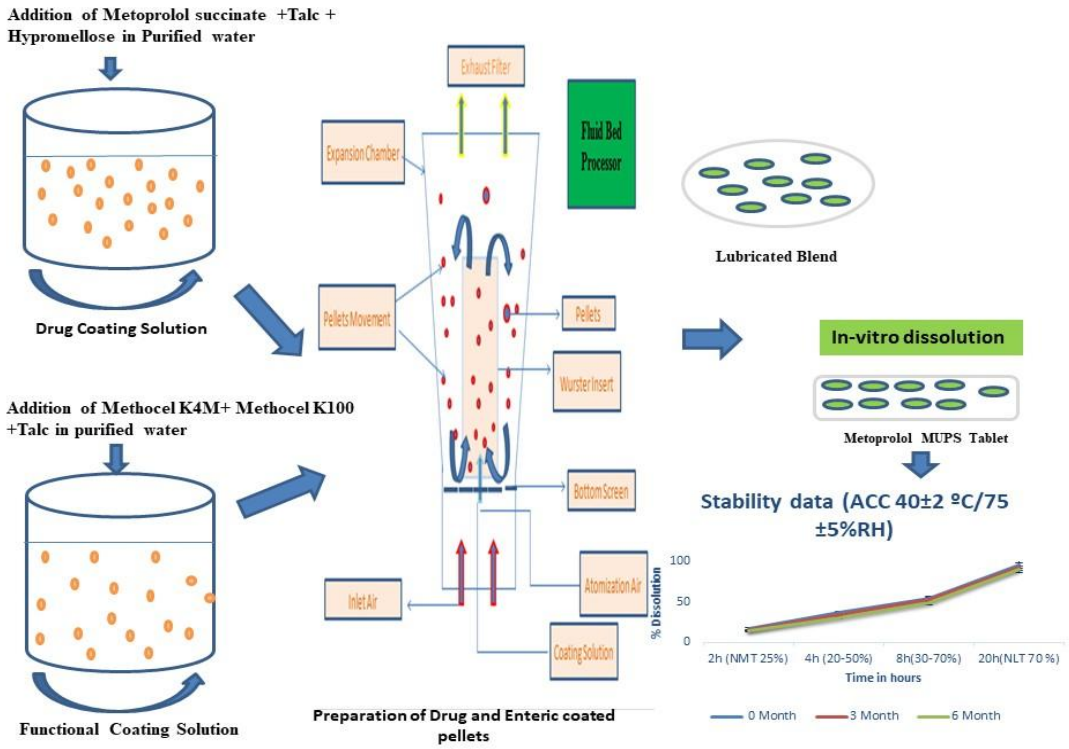

Figure 1: Graphical abstract of S (-) Metoprolol succinate MUPS tablets

Part B: Development and evaluation of spray-dried fluid bed processed orodispersible tablet of Levocetirizine HCl

The focus of this research is to develop a novel formulation of orodispersbile tablets of Levocetirizine HCl by means of platform technology. Allergic rhinitis has common occurrence, the detrimental effects on professional, academic performance and healthcare expenditures are substantial. Water solubility is very high for Levocetirizine HCl (Charoo *et.al.*,2023). The investigation of already-formulated pharmaceuticals is of great scientific interest, as there are a lot of problems with the way drugs are typically made.

Novel drug delivery is the subject of exciting new research. The effectiveness, safety, and convenience for the patient is enhanced. For competitive advantage, patent ease, and a larger slice of the market, these drug delivery firms are busy expanding their efforts to develop numerous platform technologies. Tablets that disintegrate quickly in the mouth are called orodispersible. Traditional dose forms, such as pills, might be difficult to swallow in situations of motion sickness (kinetosis) and quick bouts of coughing due to the common cold, allergy condition, or bronchitis, especially in the absence of water. This is why there is so much focus on developing orally disintegrating tablets (ODT) that dissolve or disintegrate rapidly in the mouth.

Orodispersible tablets are good candidates for patients who have trouble in swallowing. Orodispersible tablets are also great for those who lead active lifestyles. When placed on the tongue, orodispersible tablets instantly dissolve the medicament in the mouth's saliva. The faster a tablet dissolves, the sooner it will take effect clinically. A few medications can be absorbed from the oral cavity, thoat, and oesophagus into the bloodstream and then the stomach via saliva. The aims of this research was to develop an ODT of Levocetirizine HCl by directly compressing the drug with the aid of superdisintegrants. The density, thickness, hardness, friability, disintegration time, wetting time, drug content, and in-vitro dissolving time of the prepared tablets were all evaluated. The primary goal of this study is to create dispersible tablet that may be taken orally and quickly dissolve when placed under the tongue. The newly designed formulation has a quick onset of action.

Levocetirizine hydrochloride orodispersible tablets were created utilising the direct compression process, with the addition of the superdisintegrants i.e crospovidone

and L-HPC, as well as the binders i.e PVPK-30 and sucralose. The new prepared Levocetirizine HCl tablets are quick to dissolve and provide rapid onset of action. Additionally, physical and chemical characteristics of Levocetirizine HCl tablets were analyzed. Post-compression metrics included wetting time, water absorption ratio, in-vitrodisintegration, drug content, and in-vitrodissolution. The optimized orodispersible tablets have the following inprocess parameters i.e thickness 3.80 ± 0.08 mm; hardness 4 ± 0.34 Kp; friability 0.16 %; disintegration time: 28.50 ± 2.50 sec; wetting time 30 ± 1.90 sec; assay 100.60 ± 0.50 % and in *vitro* release profile of Levocetirizine HCl from their matrices, i.e. 99.10 ± 1.20 %. The formulation has excellent quality and is stable, cost effective and processs simplified for formulation development. The stable orodispersible tablet composition that was created is an alternative to the standard tablet formulation available in the market.

Other class of drugs with a high solubility/permeability profile could benefit from this formulation strategy. The newly developed orodispersible tablet formulation of Levocetirizine HCl is superior to the marketed formulations. The benefits are quick action, avoiding first-pass metabolism, patient acceptance and low production cost. Orodispersible formulation is dominating the market over traditional tablet dosage forms. In turn, it gains attention among patients all around the world. Strong consumer demand and widespread patient acceptance uplift for the orodispersible tablet business acceptance as shown in graphical abstract **Figure 2.**

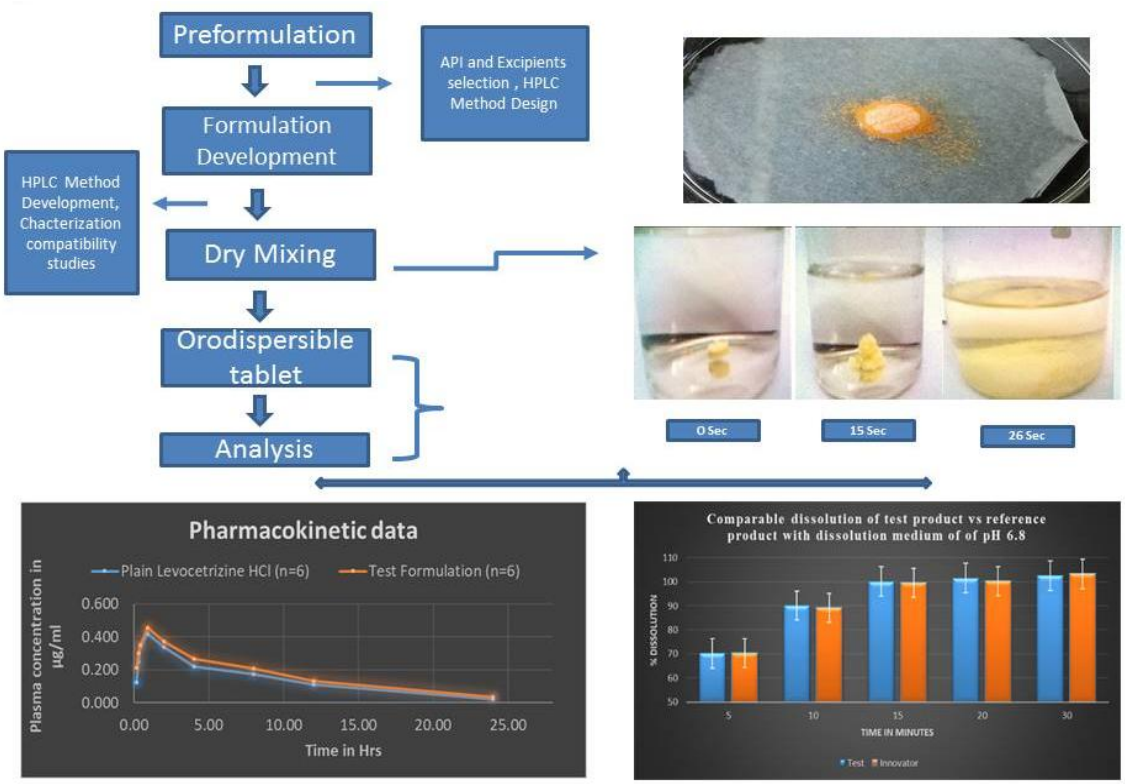

Figure 2: Graphical abstract of orodispersible tablet of Levocetirizine HCl

CHAPTER 1

Introduction

Drugs that have beneficial effects on the whole body are given orally which provides local and systemic effects. It is possible to provide drugs via the respiratory, nasal, ocular, buccal, and transdermal channels in addition to the parenteral, oral, buccal, and transdermal routes. The oral route of administration is ideally suited for the absorption of drugs because it fulfils all pharmacological requirements. However, the oral route has comparatively favourable for absorption due to its surface area, decreased metabolic activity, prolonged contact duration, abundant blood supply, ease of access, predictability, and lack of permeability (Cheng *et al.*,2020). Patients typically have a positive experience with non-invasive drug administration routes, such as oral medicines. An estimated 85 % or more of all medications used today in the market are taken orally. Dosage forms such as tablets, capsules, sprinkles, and granules are highly recommended. That's why research into methods of administering drugs through the digestive system is always being refined in the name of enhancing purity, potency, and safety. Uniform drug availability at the site of absorption is achieved through controlled drug delivery systems, which also keep post-absorption plasma drug concentrations within a therapeutic index, reduce the occurrence of adverse effects, and shorten the time between dosing. By delivering the medication at a steady and predetermined rate, controlled drug delivery system can produce long-lasting effects in a specific location of the digestive tract (Bhowmik *et al.*,2018).

Particularly for long-term use or limited therapeutic indices, controlled-release technologies that allow programmable delivery rates other than rapid input are becoming increasingly relevant to meet the growing requirement for therapeutic optimization. Therefore, it is crucial for the success of formulation research and development of oral delivery products to comprehend and employ the foundations of controlled release technology. Patients can take once or twice daily sustained-release tablets, which release their contents slowly in the digestive system over the course of 24 h. Some companies are changing their attention to medication delivery systems to improve efficiency and patient comfort as a result of the substantial cost and time

commitment necessary for drug development research (Charoo *et.al.*,2024). For this reason, patent protection enjoyed by the pharmaceutical industry. There are primarily two categories of elements that contribute to this thriving industry i.e those associated with patients and those generated by the market. Lower dose frequency, decreased incidence, severity of adverse effects, enhanced selectivity of pharmacological action, prolonged or durable therapeutic effect and reduced cost are some of the main benefits of patient-related factors. Companies in the drug delivery industry are now working on a variety of platform technologies, including those for slow release, rapid release, oral quick dispersing dosage forms and for delivering insoluble drugs (Laffleur *et al*.,2020).

The platform technology is a shared framework made up of various polymer systems that act as release modulators. There are wide variety of agents and platform technologies that can be utilized together or separately (Fang *et al.*, 2022). In-house knowledge and expertise gained in this manner can facilitate faster development and scaling, tighter quality management, and more efficient utilization of production resources. The intricacy of a system has a direct correlation with its practicality. Many clinical trials are needed for new drug development research, which is extremely expensive and time-consuming in today's synergistic environment. Thus, organizations are seeking for cutting-edge drug delivery technologies to boost efficacy, reduce costs, and increase patient access. Since this activity also benefited from patent protection, it increased after patenting the underlying product (the drivers of this booming business can be broken down into two categories: patient-based and market-based variables) (Greffier *et al.*, 2021).

The advanced platform technology should have below following properties:

Drug suitability: When developing drug delivery systems, scientists consider the drug's solubility, compressibility, flowability, half-life, bioavailability, and other pharmacokinetic factors (Savla *et al*., 2021).

Release design: The efficacy of a delivery system is determined when it meets the desired medication release patterns. The release profile of the finished dosage form may be modified significantly by even small alterations to the formulation. Release profiles for BCS class I medicines over 12-24 h are among the most demanding, and

hence provide realistic standards for measuring the performance of delivery systems (Homayun *et al.*,2019).

Targeting: Development of systems suitable for delivering drugs to the stomach (gastrointestinal) and colon (colonic formulations).

Dosing frequency: Dosing frequency should be reduced by creating a once-a-day dose.

Improved drug plasma profile: Plasma drug release profiles must be maintained within the therapeutic index to reduce side effects and also its toxicity.

Cost-effectiveness: The API and excipients utilized in this system are consumables that are produced in large quantities and are thus readily available at low prices. Direct tablet costs can be lowered by using this platform's cutting-edge technology, which integrates excipients in addition to conventional tableting.

Ease in manufacturing: The most up-to-date technology should be utilized by such an advanced platform system. requiring few or no extra components or steps to produce. The degree to which this ideal condition is met is indicative of the system's design, and the complexity of a system and the value it provides are frequently inversely related.

Less risk inactive excipients: The platform advanced technology consists of known high-density polymers based on literature. This minimizes risks and formulation design hurdles.

Intellectual property rights: Use of advanced platform technology to be able to contribute know-how, including proprietary intellectual property, flexible technology, drug delivery and development expertise. Platform technology intellectual property ensures no delays in regulatory approval to bring products to market (Mermelstein *et al.*,2021)

Life-cycle controlling of products: Technology built into the platform is used to solve numerous problems in the pharmaceutical industry and product lifecycle management. Cost-effective medicine for the public is made possible by the creating platform technology that can be applied to a broad variety of products, such as switching API and excipients suppliers, expanding batch sizes, adjusting manufacturing processes etc.

Limitation with existing conventional tablets

S (-) Metoprolol succinate half-life is only 2-7 h. For this reason, it is recommended to be administered twice it daily. When a single dose is administered the peak plasma concentration of metoprolol occurs between 2-4 h after dosing. Dosing intervals must be modified to maximise patient compliance, drug product quality, safety, efficacy and cost-effectiveness. It has always been difficult for pharmaceutical technologists to create oral sustained-release platform technology for freely water-soluble drugs with first-pass metabolism (Gangurde *et.al.*,2024).

Traditional dose forms, such as tablet, might be difficult to swallow in situations of motion sickness (kinetosis) and quick bouts of coughing due to the common cold, allergy condition, or bronchitis, especially in the absence of water. This is why there is so much focus on developing orally disintegrating tablets (ODT) that dissolve or disintegrate rapidly in the mouth (Mahapatra *et.al*.,2013).

Challenges associated with the Platform technology

The challenges associated with the MUPS tablets is to maintain uniform distribution of pellets, optimization of compaction force to avoid pellets rupture and tooling selection criteria. These challenge in the MUPS tablets affects the assay and dissolution of the drug product. (Shekhar *et al.,* 2021).

Challenges associated with the selection of orodispersible tablets were disintegration time, friability and hardness of tablets.

The present research work is divided into two parts.

Part A) MUPS tablet of S (-) Metoprolol Succinate study aims to design and developed novel MUPS tablets comprising of enteric coated pellets of S (-) Metoprolol Succinate. These pellets tend to retard drug release thereby providing extended release profile.

Part B) Orodisperible tablet of Levocetrizine HCl study aims to develop orodispersible system that can not only mask unpalatable taste of Levocetrizine HCl but also improve the dissolution thereby enhancing its therapeutic efficacy.

CHAPTER 2

Literature Review

2.1 Platform Technology

According to common usage, a "Platform" is a set of interoperable technologies that serves as a basis for the creation of new systems, procedures, and software. A platform is a basis upon which more complex infrastructure, layers, and procedures can be created to support novel ideas, cutting-edge approaches, and refined routines. In order to enhance production, platform technologies provide a set of standard resources. Using this scenario as a guide, establishing a universal protocol that facilitates the creation of additional methods that ultimately lead to the enhancement of our products. Effective and high-quality pharmaceutical products owe a great deal to the advancements in platform technology. The development of a platform technology idea combines a risk-based strategy with the extraction of historical data on targeted new compounds. The bioprocessing sector is rapidly adopting platform technology. Drug development can be made more productive and reliable with the help of platform technology. The most methodical technique to use existing information for a specific novel molecule is the platform in conjunction with a risk-based approach. In addition, the platform's reliability would increase with the inclusion of data for each new molecule generated using this method (Litvinova *et.al.*,2024)

Platform technologies lay the groundwork for the development of new applications, making it simple for users to adapt to changing circumstances. Platform technologies include, but are not limited to, computing, database, storage, application, mobile, and web platforms. All of these systems, and many of the associated apps and technologies, are put to use in the pharmaceutical sector. We first develop commercial batches by performing a number of validation stages and optimization approaches on pilot batches. Platforms for drug research and development rely heavily on technological advancements and are crucial to the process of constant progress and development (Lyytikainem *et.al.*,2024).

2.2: Pathway for development of new platform drug delivery technology

Below are the key steps in the improvement of drug delivery.

2.2.1: Selection of drug candidate

One or more of the criteria of pharmacokinetics and pharmacodynamics suggest that a benefit must be supplied, making sustained-release drugs preferable over immediate-release formulations. Drug delivery platform technologies should be developed and implemented such that they may be used across a wide range of medicines in the same BCS class (Based on solubility and permeability) or therapeutic class with only minor adjustments to the formulation (Bhalerao *et al.,* 2021). For every active moiety, determining its compatibility with the drug delivery system is the first and most crucial step in producing a controlled drug-release product. Long-term oral administration of an active moiety, however, is often limited by factors like its physiological, biological, pharmacological and effective therapeutic qualities and limits. The following are some of the most important things to think about when developing a platform medication delivery-based product which could affect the quality of product.

2.2.2: Solubility

In controlled-release formulations, the drug release rate is matched to the absorption rate. Drug solubility and dissolution are rate limiting factor for absorbtion. Drugs with weak basicity may dissolve at a stomach. Drug solubility is an additional aspect in the selection of control release systems since it affects the rate of product release for many control release technologies (Bergstrom *et al.,* 2019).

2.2.3: Stability

Product stability in the digestive tract can be evaluated with the help of pH and enzyme stability profiles (GIT). Preformulation research is conducted before a product is created. API excipient compatibility studies aim to predict drug stability in the presence of excipients used in formulation development (Jamrogiewicz *et al.,* 2019).

2.2.4: Permeability

Dosage position within the gastrointestinal tract is crucial for assessing and forecasting drug absorption in the body. Colon absorption and bioavailability can be decreased by a number of causes (Klein *et al.,* 2020). Solubility and permeability barriers, colonic dehydration, and bacterial multiplication all play a role.

2.2.5: Elimination half-life ($t_{1/2}$)

Drugs with a short half-life need to be dosed often to keep their blood levels stable. Adherence declines with increasing dosage frequency among individuals. Controlled drug release dosage forms are optimal for drugs having biological half-lives between 2 and 6 h, as they prevent accumulation *in vivo* (Nakamura *et al*., 2020).

2.2.6: Therapeutic drug window

Eliminating dosing fluctuations and keeping plasma concentrations of the drug within the therapeutic range are two of the most important benefits of oral controlled-release drug administration. Keeping the least effective concentration (IVIVC) as low as possible for medications with relatively short half-lives increases the likelihood that the controlled-release system will be able to provide prolonged drug exposure. However, this causes a significant decrease in plasma level variability, which is often unfavourable for API with limited therapeutic windows (Mehrotra *et.al.,*2024).

2.2.7: First-Pass metabolism

Low bioavailability and restricted controlled release potential are the results of controlled release systems for drugs whose first-pass metabolism (liver or gut) is saturated (Wang *et.al*.,2024).

2.3: Delivery system developed using platform technology

2.3.1: Sustained release formulation

The term "sustained-release technology" refers to methods used to keep a desired concentration of an active component in a system by delaying the release of that ingredient over a prolonged time. (Chapagain *et.al.,*2023). Only one tablet, with a special slow-release formula, needs to be taken by him each day. This cutting-edge technique employs targeted medication delivery across many therapeutic domains by virtue of a variety of design considerations. This could result in a lower risk of side effects, more stable pharmacological effectiveness, and fewer doses needed to achieve the desired effect. The vast majority of MUPS systems are oral dosage forms, with

each component consisting of a number of tiny, detachable parts that each have their own unique qualities, such as release profile and bioavailability. These administration methods included sprinkles, granules, micro pellets, microspheres, microcapsules and minitablets. The MUPS system is a break through in dose delivery that combines the best features of pellet-containing tablets and pellet-containing capsules.

2.3.2: Microspheres

Distinct formulations for precise administration are created with the use of microsphere technology. This method is useful for site-specific interventions to lessen the effects of external toxicity and it saves patients to the trouble of frequent injections. Microsphere technology is distinct from microencapsulation and liposome technology (Ahmad *et.al.*,2022). During microencapsulation, a drug is sealed inside a tiny capsule that, if opened, releases all of the medicine inside. Liposomes, in contrast to microspheres, have a lower entrapment efficiency (about 30%). Liposome technology guarantees microbiological stability, whereas microsphere technology eliminates the need for preservatives (Martinez *et.al,* 2023).

2.3.3: Hot melt extrusion

Solid molecular dispersions can be made by hot-melt extrusion techniques, which can be used in nearly solvent-based procedures like spray drying and co-precipitation. Drugs can be delivered in a controlled, sustained, and in specific manner. This modern tech may be used in tablet implants, transdermal patches, and topical liposomal formulations (Patil *et.al,* 2024).

As a promising manufacturing method, hot melt extrusion (HME) has the potential to facilitate the creation of chemicals now in the R&D stage and the enhancement of existing goods. Some estimates have the % age of BCS class II APIs now in use in drug discovery and development process. For increasing the bioavailability, the pharmaceutical industry must create new formulations that increase the chemicals' solubility. Furthermore, intellectual property can be acquired with HME technology. The increasing number of patents and publications describing HME technology as a unique drug formulation technique over the past few decades are evidence of this.

2.3.4: Oral disintegrating tablets

Dissolving tablets have become a popular substitute for traditional pill forms such granules, tablets, sprinkles, and capsules. Oral dispersible tablets are a type of solid dosage form that can be dissolved in the mouth without the need for water. Unlike the more common sublingual, lozenge, or buccal tablets, these dissolve quickly in the mouth. Dispersible, orally disintegrating, rapid dissolving, fast melting, fast disintegrating tablets, and freeze-dried wafers are all names for ODT (Ajay *et.al.*,2023). Market research shows that more than half of patients prefer ODT over other conventional dose forms, with the majority of customers either inquiring about ODT from their doctor (70%) or making ODT purchases (70%). These responses could be explained in part by ODT's well-documented advantages, such as its low glycemic index, small size, pleasant taste, and wide range of flavour options. The clinical benefits of ODT include increased safety, the potential for increased efficacy and new and expanded applications. Multiple business needs are driving innovation in ODT and the introduction of new items to the marketplace.

2.3.5: Sprinkles

For easy dosing, medicinal pellets or granules are available in sprinkles formulations, which may be added to yoghurt, custard, and other soft foods. These formulations provide approximately the same dosing flexibility and ease of administration as liquid formulations when sprinkled on liquid or semi-solid vehicles including applesauce, custard, and yoghurt. Patients are more likely to take their medication as prescribed if they are able to hide its bad taste and odour with food. Crushing or opening it up makes it convenient for sprinkling. In comparison to liquid formulations, the loaded medicinal product is more stable in litter formulations due to the solid agglomerated in it. Dysphagia patients' adherence can be enhanced by sprinkle formulations. In fact, the sprinkle-on dosage form was chosen by more than 75% of kids. The selection of products, nevertheless, remains limited. Fewer options in litter reduce management convenience and adaptability. Dispersed and other dosage forms can add complexity to dosing schedules, which can be problematic for patients. It is anticipated that more and more sprinkler products will be introduced in the future in response to this unmet need and shifting market trends. Unfortunately, this intriguing dose form lacks industry-wide guidelines. The development of sprinkler formulations can be sped up,

even more, leading to better therapeutic benefits for patients, by consolidating and expanding knowledge concerning sprinkler formulations found in numerous regulatory papers (Kaye *et.al.*, 2024).

2.4. Multiple unit pellets system (MUPS)

An innovative method of altering or controlling medication distribution is the multiparticulate drug delivery system (MUPS). But when compared to conventional distribution networks, MUPS offers numerous benefits. Multiparticulate systems have been shown to have more consistent pharmacokinetic behaviour and less inter- and intra-subject variability compared to conventional oral formulations. To improve stability and decrease oesophagal mean residence time, pellets can be added to tablets. This is an improvement over traditional granules, liquid suspensions, and capsules (Abdul *et al*., 2010). Patients of all ages, from infants to the elderly, can benefit from the extended-release, taste masking, modified release, controlled release, and orodispersible formulations made possible by the MUPS tablet.

Formulation development can make use of several different sustained-release technologies. Common oral systems involve tablets with both hydrophilic and lipophilic matrices. Osmotic systems include, but are not limited to, asymmetric membrane technology (AMT) and swelling technology (SCT) (including those produced by fluid bed or melt spray solidification processes). Drug release from hydrophilic matrix tablets is regulated largely by matrix diffusion. Drug delivery companies focus on a wide variety of technologies, including multiparticulate controlled drug release via diffusion over barrier membranes (Simancas *et al*., 2020).

2.4.1: Functional-coated multiparticulate as oral drug delivery systems

Research and development efforts are disproportionately focused on CR drug delivery systems because to their therapeutic advantages. Maximum coverage is attained, which is especially important for APIs with a narrow therapeutic index; fewer dosing events occur; efficacy is increased with fewer side effects; patient compliance is improved; efficacy is more consistent; gastrointestinal symptoms are reduced; plasma concentrations are more stable; etc. In addition, product similarity resulting from clinically better sustained release drug products and increased therapeutic efficacy can significantly increase drug potential, market development, and cost-effectiveness. In addition to their pharmacological value and ease of use in formulation creation,

multiparticulate systems have attracted a lot of attention in the business world during the past two decades. When compared to unit dosage forms, there are many advantages to using multiparticulate (Colombo *et al.,* 2022). Multiparticulates, when taken orally, are dispersed extensively throughout the digestive tract, where they allow for optimal absorption, minimal side effects, decreased inter- and intra-patient variability and no local discomfort. A less variable stomach emptying time is another benefit of avoiding the all-or-nothing impact. Pellets are defined as geometric aggregates made from a variety of beginning materials like sugar, starch, microcrystalline cellulose, etc. and processed in a variety of ways. Pellets containing multiple medications can be combined to make a customised dosage. Whether or not the treatments are chemically compatible, this opens the door to the possibility of administering many drugs at once or in different locations inside the digestive system. Pellets of the same drug with different release rates may be combined to make a unit dosage form. This morphology is ideal for film coating because of the low surface area to volume ratio, which results in a tight particle size distribution, excellent flow, minimal friability, and uniform, repeatable batches. Coated pellets may be compressed into tablets or hard gelatin capsules to create finished dosage forms (Hirjau *et al*., 2020).

2.4.1.1 Matrix-coated systems

Matrix-coated systems achieve regulated drug release by spraying a polymer/drug solution into the pellets. An API that has been dispersed throughout the polymer can now be dissolved. There are a number of benefits to using matrix-coated devices, including reduced dosage disruption and the possibility of increased water solubility of the drug. There are benefits to this. Polymer-drug interactions can also occur, which has the added benefit of modifying the drug's physical and chemical properties for the better.

One major problem is that the initial release occurs too quickly, and subsequent releases are never fully completed within the allotted time frame. Embodying the sugar centres with different polymer: drug ratios may prevent the latter. Here, the medication tends to accumulate in the matrix's lower layers, where it is less likely to

permeate upward. It has also been shown that matrix coating techniques are effective for the controlled release of extremely soluble medicines (Cardinal *et al*., 2019).

2.4.1.2 Reservoir drug-coated systems

There is an API coated core surrounded by a polymer in the reservoir drug coated system. Reservoir systems have the advantage of being able to use highly accurate medication (Reddy *et al.,* 2017).

2.4.1.3: Aqueous and Non aqueous drug coating

When coating pellets for controlled medication release, aqueous or non-aqueous polymer dispersions can be used. Non-aqueous coatings have a number of limitations, including a dependence on the molecular weight and concentration of the polymer used in order to achieve the desired viscosity. The coating process can be completed more quickly using water-based polymer dispersions because of their low viscosity despite their high solids content. The film-forming characteristics of the coated product can be altered and environmental pollution can occur when organic solutions are used. As a result, pharmaceutical coatings benefit from polymer dispersions that are soluble in water. Water-based and water-free coatings have significantly distinct film-forming mechanisms. Organic polymer solutions are very thick because the macromolecules of the polymer dissolve in the solvent. In the process of solvent evaporation, a gel-like mesophase is produced (Hamman *et al*., 2007). Once the solvent has evaporated, the polymer layers can be seen. Film layering from water-based dispersions, is more challenging to achieve. Functional polymer particles suspended in water get attached to one another when the solution dries. A layer of water-filled polymer beads forms due to the high interfacial tension between air and water.

2.4.2: Advantages of MUPS tablet

Several advantages of MUPS tablet formulations are mentioned below:

Pharmacokinetic and pharmacodynamic advantages

When swallowed, MUPS tablets (pellets) are easily absorbed and swiftly eliminated from the body, (Stomach to intestine) which help to prevent localised irritations. Because pellets are released from the stomach into the small intestine more uniformly

and the coated pellets break down more rapidly, maximum plasma concentration is reached in enteric-coated formulations. There is less regularity in drug release and less dose dumping with MUPS sustained release tablets, but there is less inter-individual variability as well (Moutaharrik *et.al.*,2024).

Greater surface area are characteristics of microparticles. Smooth medication release in the GIT from uniformly dissolving MUPS pellets facilitates uniform drug absorption and maintains the drug's therapeutic efficacy over time. Each pellet in a MUPS tablet is its discrete unit, thus there is less room for error in the dosing process and more uniform absorption.

- The MUPS system is unaffected by the splitting of tablets.
- Pellets in tablet form have less of a tendency to stick to the stomach (GIT) after being swallowed. Patients are more likely to take MUPS tablets because of their smaller size (Majeed *et al.,* 2020).

2.4.3: Challenges in designing MUPS tablets

It is more difficult to produce MUPS tablets than encapsulated pellets or conventional tablets. Althrough talc can alleviate the flow issues caused by the greater static charge of drug and functionally coated pellets during compression.

There will always be variances in physical characteristics when mixing pellets and additives. Pellets in the shape of spheres are denser than inert substances. The pellets became separated as the lubricated mixture was sent to the compression machine's hopper. Additives with similar physical characteristics and a proper mixing pattern were found to be the solution to this issue.

- For consistent mixing, get the pellet-to-adjuvant ratio just right. When the granule concentration is more than 60%, separation occurs.
- The pellet shell of a tablet breaks down when it contains too many pellets.
- Modifying the drug's % age release profile is possible through compression, pellet shell shattering, or structural modifications. This is the single most crucial aspect of pellets in tablet compression that needs to be throught through and optimized. A combination of plasticizers, buffer coatings, and buffering agents applied to the film's extragranular section at just the right concentrations can prevent it from tearing.

- MUPS tablets are inconsistent in weight, soft and easily broken (Shekhar *et al.,* 2021).

2.4.4: Method of preparation using pelletization techniques

Using an agglomeration process called pelleting, powders like drugs and excipients are transformed into tiny, easily dispensed pellets. Different types of wurster coating have significant effects on the drug and polymer layering structure and drug release profile. Numerous formulation methods exist now for the production of round pellets. Production methods and machinery are what make up the technology category. Wurster coating is a more recent method of pelletization; it entails doing the steps of pellet preparation, uniform drying, and pelletization all in one batch (fluid bed equipment). Drug and excipients powders are compressed into pellets during the pelleting process. To facilitate drug discharge and release kinetics, wurster coating presents polymer-layered pellets as a starting point. Different methods of manufacturing and forms of machinery make up the technological category. Wurster coating is a common pelletization method wherein the pellet preparation, uniform drying, and pellet coating operations all occur in one batch (closed system). The rate of success is much greater than any alternative approach now offered. The pelletizing procedure is time-consuming and costly. A single batch could take anywhere from several hr to several days to finish. Melt-spheronization, freeze-pelletization, drying, and spheronization are four further pelletizing techniques that have limited use in commercial settings. When using powder coating technique, the medicament is added to the pellets as a powder while the binder is constantly sprayed, with the powder addition rate, binder spray pattern, spray pressure, and process variables all being controllable (Muley *et al.*, 2016).

2.4.4.1: Extrusion-spheronization

Spheronization of the extrudate to generate spherical pellets, drying of the pellets, and step involving sieving pellets at the necessary particle size are all part of this technology's multi-step process. Water absorption, extruder speed, opening aperture, spheronizer plate speed, manufacturer, type, and processing duration are all crucial process characteristics (Xia *et al*., 2018).

2.4.4.2: Solution/suspension layering

This method necessitates the sequential deposition of a polymeric solution containing the drug moiety and binder into starting inert pellets. Flow wurster granulators, which are similar to vintage coating pans were used for this purpose. Starter cores can be made from a variety of substances, including sugar spheres (made from sucrose and starch) or microcrystalline cellulose pellets (excellent strength and low brittleness). Wurster systems are commonly used to apply coatings to the bottom of vehicles. In order to achieve a tangential spray, Huettlin technology is used (Yadav *et al*., 2016).

2.4.4.3: Wurster fluid bed coating process

Wurster fluid bed coating is frequently used in the pharmaceutical industry for pelletization. Batch sizes from 100 to 500 g all the way up to 800 Kg are no problem for the range of available wurster fluid bed containers. Particles smaller than 120 micron can be coated successfully using the wurster fluid bed coating technique on the pellets. The coating chamber of a wurster fluid bed is typically fairly conical, with a cylindrical partition that is about half the diameter of the coating pan's end separating the two parts. The floor space still contains a plate for air circulation. More air volume and air velocity, analogous to the airflow, can be transported through the exposed portion of the plate underneath the wurster fluid bed column. This higher bed accelerates the intake midair upwards, and the particles then flow through a spray nozzle located in the middle of the device. The nozzle is of the dualistic kind, with one port for liquid and another for compressed air. The spray conFigureuration, also known as the coating zone, is a solid cone of droplets with a spray angle of around 35-55 °C. The space beneath the bed, beyond the screen. It is the size and density of the substance that determines which Air distribution plate (ADP) is selected. This is achieved by airflow in the lower bed region, which keeps the material in suspension and drags it horizontally into the space at the bottom of the partition. The coating zone's horizontal substrate flow rate is governed by the height of the column. As the coating process progressed and the mass increase, the column had to be raised higher and higher to maintain a constant pellet flux (Maremanda *et.al.*,2024).

In **Figure 3**, a large, cylindric space is placed above the product container to slow the flow of air and dust particles (Podrekar *et al*., 2018).

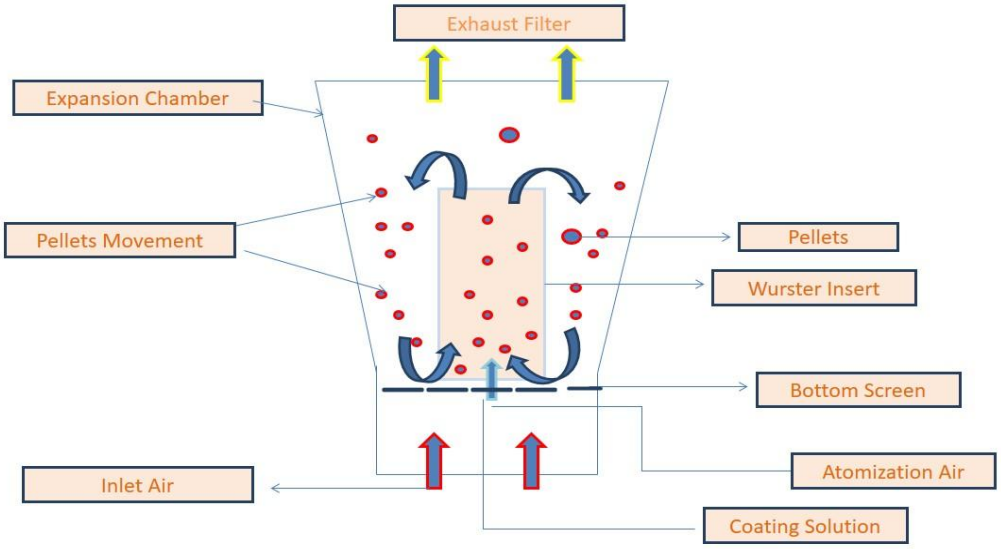

Figure 3 Wurster coating of S (-) Metoprolol succinate pellets

Critical process parameters (CPP) plays an important role in the wurster coating of Pantaprazole enteric coated pellets. Risk assessment performed and different variables were optimization such as spray rate, automization air pressure, air volume and impact of CPP on critical quality attributes were evaluated i.e assay, dissolution amnd LOD (Sonar *et.al.*, 2015).

2.4.4.4: Powder layering:

In powder layering, a binder is used to deposit a dry-formed layer of drug and excipients onto a core. The spray of medication and polymeric solution tangentially in a wurster coater is the equipment that has revolutionized powder coating, also known as pelletizing technique. If the polymeric solution or dispersion is too thick or lacks strength, powder coating methods can be used instead of solution/suspension coating methods; if there are too many medications, however, pellet potency must be increased, and the process must be sped up. Pellet densities that are unstable or relatively low are preferred (Foppoli *et al.*, 2020).

2.4.4.5: Direct pelletization

Direct pelletization creates pellets that are structurally uniform and have no visible centre. The incorporation of a viscous binder solution and appropriate agitation of the wet powder facilitates drug and polymer coating of powder starting materials.

Typically, high-shear granulators and fluidized bed processors are used for the direct pelletization process (Politis *et al*., 2017).

2.4.5: Process variables in formulating MUPS tablets

Separation of functional coated pellets and lubricated blends can be avoided with a tableting blend that has superior flowability and restricted particle size arrangements. External phase scaling is an option for big coated particles (Majeed *et al.*, 2020). For consistent, reliable drug release and film integrity following tableting, many variables must be taken into account.

2.4.5.1: Pellet shape

For optimal medication and polymeric coating, a spherical pellet form is required. Due to flaws and cracks during pressing, irregularly shaped compacts do not reach to desired results in terms of release (Moutaharrik *et.al.*,2024).

2.4.5.2: Pellet size

In order to endure compression pressure, coated pellets can be as large as 2 mm in diameter. Due to the pellets' separation from the tableting excipients, the pellet coating splits when large pellets act on the force transmitted from the top-shaped punch to the lower-shaped punch. This compromises the stability of the tablets physical properties (Moutaharrik *et.al.*,2024).

2.4.5.3: Pellet concentration

Gastric pouring is accelerated for pellets with a density of about 1.6 g/cm^3, compared to pellets with a density of more than 2.5 g/cm^3. In both the empty and fed stages, the pyloric sphincter will allow passage of objects with a thickness or density of less than 2 mm and 2 g/cm^3, respectively (Kallai-Szabo *et.al.*,2024).

2.4.5.4: Pellet core structure and core material composition

The pellet's surface area to volume ratio should be minimised. Which aid in minimising particle-to-particle contact as the mixture solidifies. Thus, pellet cores must have some pliability so that they can deform during compression without damaging the coated film. Microcrystalline cellulose (MCC) powders and granules have been the subject of much scientific investigation, and it has been determined that MCC exhibits plastic deformation when squeezed, making it a perfect material for coating particles and providing protection against damage. Compression with MCC and starch reduces compact strength, however rising concentrations of MCC produces

stronger compacts, according to studies utilising varying concentrations of microcrystalline cellulose and pregelatinised starch. The core material should not be too brittle, like DCP pellets, so that pellets may easily flow around it. Compressive pressures in this scenario act on the surface, deforming the surface and altering the release properties (Xu *et al.*, 2016).

2.4.5.5: Porosity

The degree to which pellets are porous affects how they compress and deform. Densification of minimum, medium, and maximum porosity pellets with granulating excipients including microcrystalline cellulose (MCC), lactose, talc, and dicalcium phosphate resulted in structural alteration. Pellets of medium and high porosity were given preference. It has been discovered that very porous structures become denser under compression and form aggregated units distorted by non-interfering excipients (Maremanda *et.al.*,2024). The drug release pattern is unaffected by the increased distortion seen when using compression forces to densify highly porous reservoir pellets. The drug release rate is greatly improved because minimally porous pellets are densified and deformed to a low degree. The trapped air is forced out by the compression pressure applied to the porous pellet, which causes the air to expand and surround the pellet. The resulting bond shuffling causes more substantial structural alterations in the pellet. It is the polymer covering and extra-particle substances that initiate the development of coherent units. It is important that the preparation ingredients do not change the pellet's form or the drug's release profile. Instead of grains, the non-granular material should compress into deformed pellets (Elsergany *et al.*, 2020).

2.4.5.6: Polymer coating and film flexibility

To tailor release profiles, several manufacturers turn to polymers like cellulose derivatives and polyacrylics. Cellulose and its derivatives like HPMC and HPMCP have an elongation of less than 5% and break sheets when squeezed, but polyacrylic and acrylic co-polymers generate flexible films that readily deform when compressed. As before, triethyl citrate (TEC) was successful. The polymer coating cannot be torn because of the highly elastic layer, which confirms its elasticity under pressure. Incorporating a polymer like Eudragit and the plasticizer triethyl citrate in enough

quantities increases the film's adaptability. There is a rise in the prevalence of delayed qualities (Osei-Yeboah *et al.,* 2017).

2.4.5.7: Aqueous and non-aqueous solvents used

It is required to apply coatings using both water and solvent. Water-based coatings have some advantages, but they also have some disadvantages, such as the degradation of the drug as a result of moisture being trapped; temperature also contributes to degradation because it takes longer for pellets to harden in order to remove moisture, therefore modifying the pellets' and spray solution's microenvironment's pH and glueyness. The presence of electrolytes, the pH of the spray polymeric dispersion, and the combination of polymer conFigureurations all have a role in the solution's viscosity. Instead, the thixotropy changes from sol to gel in solvent-based coatings. Non aqueous solutions evaporate significantly more quickly than water-based solutions, making them excellent for coating polymer solutions. Polymer films are susceptible to coagulation when exposed to water-based solvents (Patel *et al.,* 2018).

2.4.5.8: Mechanical resistance

Because of the film's pliability, the pellets mechanical stability is increased as they are compressed. Pellets don't get squashed and the film doesn't get distorted in high mechanical resistance experienced during compression. High mechanical stability is achieved through the use of dense structures like minitablets, extruded pellets, and roller-compacted granules. Increased mechanical stability and reduced film degradation are two additional benefits of bigger grains (Thio *et.al.,*2024).

2.4.5.9: Film thickness

The mechanical conflict between the pellet and the compressing apparatus correlates with the film thickness of the polymeric layer. However, even highly elastic films fail below a critical film thickness. Changes in precompression and compression can deform functional coated pellets. When the coating swelled due to distortion of the substrate pellet, it became less layered and more porous, resulting in faster drug release. However, the coating may become thicker or less permeable as a result of matrix pellet densification, hence delaying drug absorption (Brunmayr *et.al*.,2024).

2.4.5.10: Lubrication and cushioning excipients used

The compression-stage ultra-particulate matter affects the stability of functional polymeric-coated pellets. Coatings are vulnerable to wear when subjected to the increased compression stresses caused by sharp and abrasive crystalline minerals. The drug's release profile will be altered the next time it's compressed into a tablet. Coating, additives including plasticizers, auxiliary buffering agents, and release rates need to be carefully managed to achieve subunit drug release properties that aid in film protection. Film integrity can be preserved by using soft, plastic and elastic ingredients like MCC, lactose, or traditional powder adjuvants. 35-75 % w/w of additional lubricant granules are compressed into the pellet as it is being formed. Additional blend particles at least 35 % (w/w) should be added to ensure pellet integrity and padding. For this reason, MUPS tablets are formed without segregation of the enteric layered subunits, which are abundantly integrated into the blend (Kállai-Szabó *et.al.*,2024). Mixtures of filler grades with varying particle sizes, such as MCC PH 200 and MCC PH 101, are commonly advised as adjuvants. Polyethylene-glycol is used as an attenuation agent (PEG). Cushion-coated granules are made from common fillers and are more absorbent and flexible than regular-coated medication pellets. To protect the coating film from being harmed, it is crucial to use a blend ratio of dampening functional coated pellets (Hasnain *et al*., 2019).

2.4.5.11: Electrostatic charges

Pellet flow during the tablet compression cycle can be disrupted by a static charge on the pellet surface. Addition of talc, which functions as a lubricant, is the typical solution used for this issue. Dissolution studies comparing the MUPS tablets to the noncompressed blend mixture should be conducted throughout the development of multiparticulate tablets. Not more than a 15 % variation between the two dissolution drug release rates is acceptable for confirming recurrent drug release. (Steiner *et.al.*,2024)

2.4.5.12: Compression force

In a wider sense, this causes variations in the dissolution release pattern determined during the controlled, ideal trial and damage to the macromolecular polymeric covering. Drug release and subsequent drug degradation in acidic environments occur

in sustained drug-release MUPS tablets due to damage to the functional coating (Thio *et.al.,*2024).

2.4.5.13: Compression speed

At high speeds, die-filling errors are more likely to occur. Preventing capping and lamination requires a greater degree of contact between the stamp head and the pressure roller. In order to achieve the best results, compression rates must be maximised (Thio *et.al.,*2024).

2.4.5.14: Batch size

When the septum is resting on the bottom dutch mess, the working volume of a wurster insert is the space outside the septum. In order to maintain the spray gun clean before coating begins, it is best to avoid adding anything to the bulkhead. This is especially crucial when covering small particles like granules or pellets.

About 15-30 % of production capacity is the minimum batch size. The grains on top of the bowl must be large enough to hold all of the medicine and functional solution that will be ingested. In that case, efficiency (the ratio of actual yield to potential yield) would be reduced (Wilkins *et.al.,*2024).

2.4.5.15: Fluidization-pattern

The fluidization-pattern is well-ordered in base plate arrangement, baffle location, and amount of fluidizing bed air, regardless of the quantity of inert pellets in the wurster insert. The intended outcomes can only be attained by establishing a bed that is both fast and relatively smooth. This is best if the product being sprayed is visually appealing, but it is not always achievable because it depends on the particle size (Tiny particles fluidized). When heated, or just left to their own devices, some coating materials will attach to whatever they're applied to. Rather than attempting to achieve uniform flow, it is essential in such a situation to maintain the entire bed involved in slight turbulence. To accomplish this, the walls could be raised somewhat more permeable floor panels could be installed so that air may flow freely over the tumbling goods. The spray rate on the FBE bowl could be too low in some spots, preventing you from attaining the optimal functional coating for various experiments.

Ventilation is especially important for pellets, which require a great deal of airflow. In addition, selected plates with panel areas that allow for sufficient airflow to shorten

the distance functional pellets must travel from the panel and reduce abrasion. Perforated panels for coating with functional granules might also vary widely in appearance. There are porous panels within the screen, and the under bed area is punctured only to the point where the product runs downwards virtually weightlessly. Coating a tablet only needs to cover about a fourth of its surface area, on average, hence this condition may be achieved with relatively little effort. Finally, the lower bed area of powder-specific plates is even more impenetrable. Changing where the baffle is placed in relation to where the spray plate is located is another significant methodological variable in the fluidization pattern used in sausage processing. Tablets, which are relatively big substrates, need a large partition position so that a sufficient number of tablets can pass through the gap simultaneously to absorb the excessive coating that is being placed onto the separation zone. Microsized granules and pellets only needed a very little area to obtain a homogeneous fluidization pattern, hence particles/pellets do not require separation elevation. Type of material and partition height as shown in **Table 1** (Reddy *et al.,* 2018).

Table 1. Type of material and partition-height

Type of material	Partition-Height
Small Tablets	20-45 mm in small wursters machines
	55-105 mm in 20" wursters or more
Pellets	10-30 mm in small wursters machines
	40-55 mm in 20"wursters or more
Powders	20-55 mm in wursters machines

2.4.5.16: Atomization air-pressure and volume

Coatings should be applied to particles that are relatively small compared to the globule size. It may only need 2.5 bar of pressure to stack drugs and polymers in tiny tablets (35 psi). As the air pressure and volume are raised, the atomizing air speed is increased, leading to more kinetic energy at the spray pattern's interface with the substrate. Tablet wear is further exacerbated by acceleration to mechanical parts. Finally, fluidization patterns may be distorted by high atomizing air velocities (Patel *et al.,* 2019).

2.4.5.17: Port size of nozzle used

Nozzle port size is mainly insensitive to orifice. If the fluid spray pattern velocity is held constant, the rate of polymeric dispersion into the atomizing air can be calculated from the nozzle's pore size. When moving at a slower speed, the liquid is atomized over a larger area, resulting in smaller droplets on average. Additionally, liquid viscosity and surface tension affect this behaviour; hence, it is ideal that both be low to prevent the need for high atomization air pressures regardless of substrate size. The aperture size of the nozzle should be adjusted (to reduce spray pump back pressure) if the viscosity is high (Pansare *et al.,* 2021).

2.4.5.18: Solvent evaporation capacity

The temperature of the fluidizing air bed is often adjusted to achieve and sustain thermal homogeneity. The spray pattern and air CFM entering the bed affect the temperature. To keep product temperatures from lowering due to increased evaporative cooling, the incoming temperature must be amplified as the spray rate within a particular batch increases. Second, we can't verify the consistency of our method if you limit the amount of air coming in. It's important to note that dew points change with the seasons, often staying below zero at the year's end and above 18°C in the middle of the year (particularly in northern regions). Processing times can increase or decrease significantly due to even mild changes in these environmental conditions (Aliev et.al., 2024).

Static electricity might cause issues during fluidization in the winter. Spray rates, particularly for water-based coatings, can be dramatically slowed in high % age humidity situations during the heat season. Obviously, this phenomenon is magnified when product bed temperatures need to be kept below 35°C (heat sensitive substrates API and excipients). Depending on the relative humidity, the glass transition temperature of finished goods may shift by as much as 100° F.

Due to the obvious intrinsic moisture in rubber-type excipients, their drug release effectiveness deteriorates over time, a phenomenon known as "ageing" (product instability). Most products are recommended to be stored in a constant temperature and humidity environment of 15-25 °C to reduce the so-called "weather effect." If the

drug molecule is extremely delicate and easily damaged by even min amounts of moisture in the process air, or if the molecule is sensitive to changes in temperature, it is recommended that you use an adsorption dryer with a dew point far below 0 °C (Elsergany *et al.,* 2020).

2.4.5.19. Product temperature

A high capacity for heat and mass transmission is a feature shared by all air suspension processes. As a result, it has a wide range of possible product temperatures. Temperature-sensitive materials can be stored at temperatures lower than 25 °C. Practically, temperatures above 45 °C can be used with minimal spray dehydration of the applied polymeric and drug solution. Bed temperatures should be kept high for aqueous-based dispersions. In most instances, the applied solution's physical and chemical characteristics will be connected to the development phase known as the rate-proportional phase.Psychometrics is useful for pinpointing the exact level of surface wetness at which a substrate becomes preferable for use.

The aggregation process begins at the tipping point (Voytkov *et al.,* 2018). Tackiness on the surface facilitates adhesion between the substrate's particles. The product temperature determines the relative humidity limit for the exhaust air. When starting with a moisture theshold of 65 %, for instance, the rate of moisture removal increases by nearly 100 % when the bed temperature is increased from 35 to 40°C. Increased humidity is a common problem in man-made environments. The rate of water evaporation from the bed increases substantially, and clumping is not an issue, at higher temperatures (Broumand *et al.,* 2020). **Literature review Summary of various oral solid dosage forms and Metoprolol succinate in Table 2.**

Table 2 Literature review Summary of various oral solid dosage forms and Metoprolol succinate.

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
1	International Journal of Pharmatech Research **(Deshmukh *et al.*, 2009)**	The formulation and assessment of a metoprolol succinate sustained-release tablet using hydrophilic gums as release modifiers	The weight addition per tablet was comparative to the amount of hydration gain upto 6 h, hence the swelling index increased with time, but after that, the outermost gelled layer of the tablet dissolved in the dissolution medium. concluded that it decreased gradually
2	Journal of Pharmacy Research **(Sandeep *et al*., 2009)**	Metoprolol succinate extended-release matrix tablet: formulation and optimization	Direct compression yields a 20 h acting formulation of matrix tablets made from hydrophilic polymers such hydroxypropyl methylcellulose, hydroxypropyl cellulose, ethyl cellulose, and Carbopol 934. Finally, the medicine can be released. This phenomenon is also indicative of abnormal diffusion or non-labile transport, as it controls drug release by diffusion through inflated matrices and matrix erosion
3	Journal of Pharmacy Research **(Mahaparale *et al.*, 2006)**	Metoprolol Sucinate Extended-Release Matrixes with Compritol 888 ATO and Precirol ATO	Preparation and evaluation of a sustained release matrix of metoprolol succinate employing Compritol 888 ATO and Precipol ATO 05 were studied. Melt granulation was utilized to create the matrix. In comparison to using either Compritol or Precipol alone, matrices built with both waxes resulted in a longer delay in drug release
4	Journal of Controlled Release **(Rekhi, *et al.*, 1999)**	Metoprolol tartrate ER matrix tablet formulation and processing essential formulation and processing factors identification	For sustained-release matrix tablets of metoprolol tartrate, the impact of important formulation and processing variables were studied. These tablets used the hydrophilic polymer hydroxypropyl methylcellulose. Analyses of variance revealed that variations in polymer composition had the greatest impact on drug release
5	Dissolution Technologies **(Reddy *et al.*, 2011)**	Biopharmaceutics classification system- a regulatory approach	Biopharmaceutical categorization system (BCS) for biowaivers was established with the aid of NDA and abbreviated new drug application (ANDA) submissions and statistical analysis.Consistent work has led to this result

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
6	Journal of Pharmacy and Pharmacology **(Lennernas *et al*., 2005)**	The use of BCS of drugs in drug discovery and development: current status and future extension	BCS classification system, a methodical way of categorising medicinal compounds according to their solubility and intestinal permeability. BCS is a straightforward method for evaluating potential new drugs
7	European Journal of Pharmaceutics and Biopharmaceutics **(Lindenberg *et al*., 2004)**	Orally given drugs on the WHO model list of essential medicines and their BCS classification	He elaborated on how BCS systems are rapidly developing into a crucial instrument for global pharmaceutical regulation. The WHO model list of essential medicines was organised using the BCS system
8	Current Drug Metobolism **(Varma *et al*., 2004)**	A scientific framework for optimising drug development based on pharmacokinetics: the biopharmaceutics classification system	Since drug absorption and pharmacokinetics are dependent on these two characteristics, understanding their importance in biopharmaceutical new drug discovery is crucial
9	Asian Journal of Pharmaceutics **(Sarvankumar *et al*., 2010)**	Stavudine extended-release matrix tablet development and in vitro experiments	Hydrophilic matrix materials like hydroxypropyl methylcellulose (HPMC) K4M and carbopol 974P are being used in the creation of once-daily, sustained-release stavudine matrix tablets. Different physical tests were then performed on the finished extended-release pills
10	International Journal of Pharmacy and Pharmaceutical Sciences **(Ragavendra, *et al*., 2009)**	Formulation and evaluation of sustained release matrix tablet of tramadol hydrochloride	Scientists have been experimenting with various polymers to develop sustained-release matrix tablets of tramadol hydrochloride so that it might be more widely used. Hydroxypropyl methylcellulose (HPMC) is a synthetic gum that is used in place of natural gums like karaya gum (KG) and carrageenan (CG). The drug-to-polymer ratios used in this investigation ranged from 1:10 to 1:20
11	Pharmceutical Research **(Goyal *et al*., 2009)**	Evaluation of a once-daily hydrophilic matrix sustained-release tablet formulation of venlafaxine hydrochloride	An oral sustained-release drug delivery system for venlafaxine hydrochloride was developed and tested using hydrophilic gums and polymers such xanthan gum, guar gum, and HPMC. Pills containing venlafaxine hydrochloride matrix were made using direct compression technology.
12	Iranian Journal of Pharmaceutical Sciences (**Maghsoodia *et al*., 2008)**	Phenobarbital release from HPMC matrices: the influence of formulation factors	The effect of formulation variables on phenobarbital release from HPMC matrices. His research showed that formulations with low HPMC/lactose ratios and low HPMC viscosity grades had the highest drug release rates.

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
13	The Indian Pharmacist **(Sasidhara *et al.*, 2007)**	Controlled-release pills of verapamil hydrochloride were developed at Polyox. (ethylene oxide)	Drug release experiments in vitro were compared to drug release studies of commercially available products. According to the study's findings, formulations containing verapamil HCl at a drug-to-polymer ratio of 1:5 for Polyox WSR 303 and 1:1 for Polyox WSR 301 were linear with the drug release kinetics of the commercial product
14	Acta Pharmaceutica Turcica **(Misha *et al.*, 2005)**	Diltiazem hydrochloride hydrophilic matrix tablet development and in vitro assessment	The research was conducted to create hydrophilic matrix tablets of diltiazem hydrochloride and test them in vitro. Based on his observations, he concluded that the CMC matrix tablet had undergone greater hydration and degradation than the others. When compared to other hydrophilic polymers, HPMC K15M-containing tablets had a more prolonged sustained release
15	Indian Journal of Pharmaceutical Sciences **(Vidyadhara *et al.*, 2004)**	Oral controlled release matrix tablets of propranolol HCl: formulation and efficacy assessment.	A propranolol HCl oral tablet with a controlled release matrix was created using HPMC K-4M with electrolytes.According to in vitro data, variations in matrix swelling rate and hardening resulted in regulated drug release
17	Journal of Pharmacy and Pharmacology (**Reza *et al*., 2003)**	Controlled drug delivery: a comparison of plastic, hydrophobic, and hydrophilic polymers	The effect of plastic, hydrophilic, and hydrophobic polymer inclusion levels and types on the release profile of drugs from matrix systems is analyzed. Kollidon SR, high molecular weight polyethylene (HPMC), and carnauba wax were among the polymers used. By raising the matrix tortuosity and lowering the porosity with an increase in polymer content, the drug release rate may be delayed. Drug release is significantly slowed by carnauba wax, research shows
18	Pharmaceutical Research (**Peppas *et al.*, 2002)**	Swelling and equilibrium network structure of pharmaceutically relevant cellulose ethers	Clarifying the network structure of the swollen matrix under dynamic and equilibrium conditions and examining the swelling behaviour of four cellulose ethers (HPMC K4M, HPMC K15M, HEC, and HPC)
19	Drug Development and Industrial Pharmacy **(Dhopeshwarkar *et al.*, 1993)**	Evaluation of xanthan gum in the preparation of sustained release matrix tablets	Studying how well xanthan gum works as a matrix additive for extended release formulations. The tablets with low quantities of xanthan gum release both soluble (chlorpheniramine maleate) and insoluble (theophylline) medicines predominantly through diffusion and erosion, respectively

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
20	International Journal of Pharmaceutics **(Sadeghi *et al*., 2003)**	Release profiles of drugs from surelease-coated pellets and the role of drug type	The release of metoclopramide HCl and diclofenac sodium from pellets was studied at varying doses of an aqueous ethylcellulose dispersion (Surelease®). Medication release slowed down when Surelease® coating density increased.
21	European Journal of Pharmaceutics and Biopharmaceutics **(Frohoff-Hulsmann *et al*., 1999)**	Coating material for diffusion pellets using aqueous ethyl cellulose dispersion with plasticizers of varying water solubility and hydroxypropyl methyl-cellulose II: film characteristics	We have characterised spray films made from aqueous ethyl cellulose (ECD) dispersions, including HPMC and many water-soluble plasticizers, to better understand the drug release mechanism of pellets coated with different materials.
23	Int Journal of Pharmaceutics **(Hyppolo *et al*., 1996)**	Part I: Analyzing the Physical Properties of Films Cast from an Ethanol Solution Containing Plasticized Ethyl Cellulose	Five different plasticizers (at concentrations of 10 % and 20 %) were used to make ethyl cellulose films. The ethanol solutions were used to cast the films in teflon moulds. Diethyl phthalate, triethyl citrate, triacetin, Myvacet® (acetylated monoglyceride) and dibutyl sebacate were all employed as plasticizers. Thermal analysis, tensile testing, porosimetry, scanning electron microscopy, and hot stage microscopy were used to assess the films' physical qualities
24	European Journal of Pharmaceutical Sciences **(Gunder *et al*., 1995)**	The use of pore formers and pore fusion to facilitate medication release from ethyl cellulose microcapsules (diffusion pellets)	An aqueous ethylcellulose (EC) dispersion of hydroxypropyl methylcellulose (HPMC) mixed with 20 percent dibutyl sebacate (DBS) as a plasticizer produces diffusion pellets with water-filled holes in the controlled release membrane after extraction.However, if the release happens at a temperature above the minimum temperature of membrane formation while utilising 25 % HPMC and acidic media at the outset, these pores become irreversible after 2 h due to melting. successfully ends
25	Journal of Controlled Release **(Dressman *et al*., 1995)**	Ethylcellulose-coated pellets' pH-dependent release is prevented.	This research examined the pH-dependent release mechanism by coating phenylpropanolamine HCl pellets with ethylcellulose. All dibutyl sebecate-plasticized batches showed a release that varied with pH

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
26	Scholars Research Library **(Albhar *et al.*, 2012)**	Drug release and swelling in sustained-release matrices of ambroxol hydrochloride: the role of gums and inert ingredients	Researchers looked into how different gums and excipients affected the swelling and drug release of sustained-release ambroxol hydrochloride matrices. Xanthan gum and carrageenan gum was more effective than guar gum in delaying medication release. Dissolution rate was enhanced by Avicel 102 and lactose, and drug release was slowed by dicalcium phosphate
27	International Journal of Pharmaceutics **(Jannin *et al.*, 2006)**	Dissolution performance and stability of a controlled-release formulation containing precirol ATO 05 were studied in relation to the introduction of poloxamer.	Addition of poloxamers alters the stability and solubility of controlled-release drugs. Precirol ATO 05 claims that the addition of these hydrophilic polymers to the lipid matrix causes the lipids to expand, creating a porous network that enhances theophylline release. concluded to heighten the inactive lipid matrix
28	International Journal of Pharmaceutics **(Killen *et al.*, 2006)**	Effect of soluble filler on drug release from stearic acid-based compacts	The influence of lactose concentration was studied during the production of a sustained-release wax matrix tablet. Higher lactose concentration resulted in a greater amount of medication being released
29	Journal of Pharmaceutical sciences **(Levina *et al.*, 2004)**	Drug release from hydroxypropyl methylcellulose matrices and the impact of excipients	Drug release from HPMC matrix systems was studied to determine the impact of regularly used excipients such spray-dried lactose, microcrystalline cellulose and starch 1500. When compared to MCC or spray dried lactose, decreased drug release observed
30	Indian Drugs Journal **(Paradkar *et al.*, 2004)**	Glyceryl behenate and metformin hydrochloride sustained-release matrices	The use of direct compression, melt granulation, and excipients should be studied for their effects. It was investigated how adding release enhancers such lactose and MCC affected the release of the medication. This study demonstrated that the matrix-forming chemical glyceryl behenate (which has a viscosity similar to wax) may be used to control the release of water-soluble drugs.
31	Journal of Pharmaceutical Sciences **(Bravo *et al.*, 2002)**	Controlled release of diclofenac sodium from biopolymer matrices: in vitro investigations	MCC, starch, and lactose influence drug release from HPMC matrix tablets. It was found that these excipients affected how the drugs were absorbed and digested.
32	European Journal of Drug Metabolism and Pharmacokinetics	Tramadol hydrochloride matrix formulated with glyceryl behenate for	Different polymers and fillers both hydrophilic and lipophilic, affected the rate of release of atenolol from HPMC matrices. Matrices with

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
	(Obaidat *et al.*, 2001)	sustained release	HPMC or EC make it very hard to achieve zero-order release
33	AAPS Pharm Sci Tech **(Amaral *et al.*, 2001)**	Naproxen sustained-release tablet release affected by hydroxypropyl methylcellulose and hydrogenated castor oil	HPMC, hydrogenated castor oil, lactose and dicalcium phosphate affected the rate at which naproxen was released. HPMC and hydrogenated castor oil matrix tablets have a dose-dependent decrease in drug release rate
34	Drug Development and Industrial Pharmacy **(Dashevsky *et al.*, 2010)**	Effect of water-soluble polymers on the physical stability of aqueous polymeric dispersions and their implications on the drug release from coated pellets	Kollicoat® SR 30 D was more resistant to agglomeration than Aquacoat® ECD when water-soluble polymers were added. Hydrogenated castor oil and hydroxypropyl methylcellulose's impact on naproxen release from extended-release tablets
35	European Journal of Pharmaceutics and Biopharmaceutics **(Frohoff-Hulsmann *et al.*, 1999a)**	Coating material for diffusion pellets using aqueous ethyl cellulose dispersion with plasticizers of varying water solubility and hydroxypropyl methyl-cellulose II: film properties	To investigate the mechanism of drug release from pellets coated with HPMC and ECD, we prepared aqueous dispersions of both materials, which included a variety of water-soluble plasticizers. Examine the spray film's composition in detail.High ionic strength separation media keep most of the water-insoluble plasticizer in the film and slow down the migration rate of HPMC
36	International Journal of Pharmaceutics **(Frohoff-Hulsmann *et al.*, 1999b)**	Coating material for diffusion pellets is aqueous dispersions of ethyl cellulose incorporating plasticizers of varying water solubility, such as HPMC.	The release mechanism of theophylline pellets was investigated after they were coated with an aqueous ethyl cellulose (EC) dispersion containing a plasticizer and hydroxypropyl methyl cellulose (HPMC) as a water-soluble pore builder.
37	International Journal of Pharmaceutics **(Bodmeier *et al.*, 1997)**	Coating solid dosage forms with aqueous colloidal polymer dispersions that uptake plasticizers	Aqueous phase and polymer in colloidal polymer dispersions may be used to disperse both water-soluble (triethyl citrate, triacetin) and water-insoluble plasticizers (acetyl triethyl citrate, acetyl tributyl citrate, tributyl citrate, diethyl phthalate, dibutyl phthalate) Using binding kinetics and affinity constants, the rate and extent of phase separation were determined.
38	International Journal of Pharmaceutics (**Hyppola *et .al.*, 1996)**	Films made of plasticized ethyl cellulose from an ethanol solution were analyzed for their	Dibutyl sebacate and Myvacet® proved to be the two most efficient plasticizers for ethyl cellulose films cast from ethanol solutions

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
		physical properties.	
39	Multiparticulate Oral Drug Delivery **(Digenis *et al*., 1994)**	*in vivo* behaviour of multiparticulate versus single-unit dose formulations	Sodium alginate (high viscosity) and Carbopol 974P, two swellable hydrophilic polymers were used to examine the systems' swelling and erosion behaviour. Experiments on swelling and erosion showed that the carbopol preparation swelled more and eroded less than the sodium alginate formulation
40	International Journal of Pharmaceutics **(Bodmeier *et al.*, 1994a)**	Aqueous colloidal polymer dispersions' plasticizer distribution in the aqueous and polymer phases.	The quantity of plasticizer dissolved in the aqueous phase, and in the case of water-insoluble plasticizers, emulsified and dissolved in colloidal polymer particles, was determined using a separation method.
41	Materials and Design **(Cao *et al*,2023)**	The structural diversity of ibuprofen sustained-release pellets on the same goal of bioequivalence consistency	Synchrotron radiation-FTIR mapping was used to evaluate the material distribution and composition of IBU pellets. Internal structure characterization, material design, and dosage form development might all benefit greatly from the use of micro-CT.
42	Journal of Food Hygiene and Safety **(Yang *et al*,2023)**	Dissolution Properties of Immediate-Release and Controlled-Release Vitamin C Tablets: A Comparative Study	Both the controlled-release tablet and the immediate-release tablet had their disintegration profiles compared. According to the data, the controlled-release vitamin C tablet was completely dissolved after 480 minutes, whereas the immediate-release vitamin C tablet was dissolved at 100 percent after 45 minutes.
43	International Journal of Pharmaceutics **(Saliha *et al*,2024)**	Cushion-coated pellets for tableting without external excipients	Adhesion problems associated with the use of PEG1500 were overcome by applying an outer Kollicoat® IR film. The tableted cushion-coated pellet systems manufactured would allow a relatively high load of modified-release units to be conveyed, thus setting out a versatile and scalable approach to oral administration of multiple-unit dosage forms.
44	International Journal of Pharmaceutics **(Daniel *et.al*, 2024)**	Tableting of coated multiparticulates: Influences of punch face configurations	Increased rearrangement energy of the compacted material due to the high punch concavity, which sequestered compaction stress exerted on pellet coats. Although the deep concave punch reduced the stress, the resultant tablets containing pellets coated with acrylic were weaker ($p = 0.01$). Overall, the punch face configuration significantly affected the quality of MUPS tablets.

S.No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
PATENTS GRANTED			
43	Patent ***CN116687881A*** **(Guilin Huaxin Pharmaceutical Co ltd) 2023**	Metoprolol succinate sustained-release capsule and preparation method	The sustain release capsule contain pellets of Metoprolol succinate and exciepients such as MCC and polyethylene glycol.
44	United States Patent 2010/0323010 A1 **(Sriwongjanya *et al.*, 2010)**	Formulation and process for drug loaded cores	The issues with using water-soluble and/or water-swellable cores for controlled release metoprolol pellets are addressed by the present invention. To create controlled-release pellets, a medication layer is applied to a polymer-coated, water-soluble or water-swellable substance
45	WIPO WO2007/097770 A1 **(TEVA Pharmaceutical Industries Ltd, 2007)**	Metoprolol succinate ER tablet and method of their preparation	This research details beta-blockers, including but not limited to metoprolol succinate, and their techniques of preparation in sustained-release pharmaceutical formulations
45	United States Patent 5395626 **(Kotwal *et al.*, 1995)**\	Multilayered controlled release pharmaceutical dosage form	Specifically, a dosage form that comprises of coated particles, each of which has a drug-containing core surrounding by multiple layers of coating, is used to account for the drug's water solubility.
46	United States Patent 5,260,068 **(Chih-Ming Chen, 1993)**	Multiparticulate pulsatile drug delivery System	Several pellets from two or more populations make constitute a capsule, pill, or other unit dose form. A medicinal drug and a penetrant that dissolves in water are contained in the centre of each pellet
47	United States Patent 5110597 **(Wong, *et al.*, 1992)**	Multi-unit delivery system	The present growth is centred on the methodical administration of medicines. In particular, the current invention concerns the patterning administration of numerous tablets or other drug delivery units

2.5: Orodispersible formulations

Secretion, digesting, absorption, and excretion in the gastrointestinal tract (GIT) is a highly specialised system in the body. All food consumed must be absorbed into the digestive system before entering the body's main blood supply. The GIT also protects against the irritant and poisonous effects of potentially hazardous chemicals (Deng *et al*., 2021). For this reason, there are many roadblocks produced for medication

molecules to reach the bloodstream via the only gastrointestinal route. Many hydrophilic and lipophilic barriers, as well as the presence and high pH conditions of degrading enzymes during digestion, absorption, and excretion (including first pass metabolism in the liver), represent significant challenges. Oral dispersible formulations have been developed using API and excipients alone and in combination to eliminate all obstacles while increasing patient acceptability (delivery systems) (Gaikwad *et.al*.,2024). The drug's physicochemical and pharmacokinetic features inform the development of an oral delivery system optimized for efficiency in administration and dosing, aesthetics in packaging, and gastrointestinal tract stability. Moreover, it enhances the distribution and local absorption of the medication. Despite great strides in intravenous, respiratory, and other delivery methods. Human suffering and pharmaceutical corporations alike continue to give oral administration the most preference. Invasive-free and risk-free oral medication delivery are common, despite its association with adverse effects. However, oral administration systems are less expensive to produce since they don't require rigorous aseptic settings and may handle medications with varying physical, chemical, and pharmacological properties. (Wilkins *et.al,* 2024). Therefore, improving the efficacy of medications and lowering human suffering may be greatly influenced by optimising their administration in their conventional dose forms. Many innovative methods of oral dosing have emerged in recent decades. Dosage forms, site-specific drug administration, and innovative controlled-release dosage forms are all examples of what are known as "fast disintegrating formulations." Sales of oral dosage forms (tablets, etc.) are projected to reach $110 billion in 2019, an annual growth rate of 15%, thanks to the advent of cutting-edge technologies that have substantially expanded this market. The quick-melting tablets and its over-the-counter market are what keep this restaurant bustling. As of the end of 2018, the worldwide market for fast-acting formulation was estimated to be worth around US$ 10.6 billion. Rapidly dissolving tablets can be taken orally and released in the buccal cavity without the need for a liquid vehicle. The basic idea behind ODT is to combine the best features of several types of solid (stable, easy to handle), easily administered oral dosage forms. Many people who have trouble swallowing can benefit from ODT (dysphagia) (Tazi A *et.al.*,2024). Patients of all ages and conditions (from infants to the elderly) are included here. It is

predicted that almost 55 % of the population is impacted by this issue, which could result in extremely high rates of non-compliance and ineffective treatment for a large portion of the population. Normal users also place a premium on ODT's adaptability and convenience. Since oral disintegrating tablets (ODT) allow for easy administration even when water is scarce, they are a practical and simple option. In addition to enhancing patient convenience, ODT offers a speedy onset of action by enhancing the drug's dissolving profile, eliminating the need for stomach degradation, and enhancing gastric absorption, are being tested to see if they can improve the bioavailability of medications in the BCS class III and class IV. In addition, pharmaceutical companies due to financial interests are aligned with the widespread use of ODT. To maintain market dominance after a product's patent has expired, pharmaceutical firms often resort to developing and formulating new dosage forms of the medicine in question.

2.5.1: Recent trends in development of orodispersible tablets

As each patent must include some form of novelty, patent files are among the most authoritative and up-to-date sources of technical evidence. The patent documents were examined by searching free Int online patent databases for issued patents in oromucosal tablets and related topics. Each patent's manufacturing method, as well as any additional or active substances, are presented in tables, and the textual summary emphasises the rationale, primary claims, innovative step, and consequences that are relevant to the manufacturing strategy. Compression-based processes, freeze-drying, moulding, tablet loading, and milling were all identified through quantitative analysis of these patents as being used in the production of ODT. Up to 80 % of pending patents during this time used dry mix followed by compression to create his ODT, making it the most popular technique at the time. Comparatively, moulding technology accounted for 11 % of ODT production, 4 % of lyophilization, and 2 % of consumers who used filling and crushing technology. Submissions were received from a wide range of countries, including Bangladesh, India, United States, United Kingdom, France, Belgium, the Netherland, Italy, Denmark, Ireland, South Korea, and Portugal. The United States and Canada accounted for the largest share (up to 38 %) of respondents, followed by Asia (40 %) and Europe (14%) (Sallam *et.al*.,2024).

2.5.2: Selection of technology

Reduced production costs:

The total cost of producing ODT is highly technology dependent. Producing ODT via lyophilization is a high-priced process. Lyophilization operations take a long time and require many different types of industrial machinery, tools, and workers.

Measurement of ingredient dosage:

By using typical compression and moulding procedures, manufacturers of tablets can pack in as much as 1.00 mg of active substance each tablet. Lyophillization presents challenges when attempting to include high quantities of water-soluble pharmaceuticals, with average doses having up to 60 mg of water-soluble medication per tablet.

Physicochemical properties of API and excipients:

A mixture of excipients with high water solubility and high moldability is often used to assure the manufacture of stable tablets with a predictable dissolving and release pattern.Product performance and characteristics of the orodispersible tablet formulation: The technology used to create orodispersible formulations has a major impact on the ODT's final qualities. The very absorbent tablets produced by lyophilization technology, for instance, dissolve in the buccal cavity quickly and painlessly, but they lack physical qualities like tablet hardness and friability.

Fluidized bed granulation

In the pharmaceutical and other industries, the fluidization of bed process of wet matter is known as a closed process. This approach lowers material handling and process times compared to traditional aqueous and non-aqueous granulation processes since the API and excipients can be uniformly combined, wet granulated and dried in the same fluid bed equipment. Wet granulation is used in tablet production, but the drying and spraying process creates even more homogeneous granules with a more absorbent structure, improving both solubility and wetting (Korniyenko *et.al.*,2018). Lactose products, food, and medicines all benefit from using fluidized bed grains. Spraying and powder coating both make extensive use of fluidized bed techniques. FBE (Fluid bed equipment) is often utilized in the pharmaceutical sector for API stacking and drug release modification or control coatings due to its superior film

quality compared to other coating processes. Granulation and pelletization were accomplished using a tangential spray (rotational) technique (Svetič *et.al.*, 2023).

2.5.3: Orodispersible formulation by granulation

There are a number of advantages to using granular or agglomerated particles rather than fine powders. Pharmaceuticals are often granular.

• To improve compressibility during tableting.

• Reduce dust for operator and environmental safety.

• Improves dispersion.

• Homogeneity is enhanced by dissolving and spraying active component solutions, which mixes all chemicals together or distributes low amounts of active ingredient uniformly.

When it comes to wet binding, top spray and tangential spray are the two most common techniques. Lowest-cost spraying technology's process variables can be used to make consistent granules (Vishali *et.al.*,2020).

2.5.3.1: Top spraying fluidized bed granulation

For more than three decades, numerous pharmaceutical businesses have relied on top-spraying fluidized bed granulation to produce their wet granules. The following components make up a top-spraying FBE.

- FBE bowl and product area.
- Outlet area

2.5.3.2: Fluidized bed spraying and drying

Fluidized bed spraying and drying and more traditional methods of spraying and drying because of the similarities between the two processes. Dehydration can be sped up in both methods by applying a spray dispersion solution to a heated air product region. The volume of air to be treated can be varied with the top spray approach. Spray drying liquids at significantly lower in air temperatures in the product area is made possible by operating at high airflow. For best results in fluidized bed spray

drying, the initial liquid spray rate should be low while the drying rate should be high. Because of the combined impacts of the particle mass production and drying process, the liquid addition can be maintained at a high rate after spray-drying has taken place. When compared to the lyophillization technique, fluid bed spraying and drying saves time and money. Literature review Summary of Various Oral Solid dosage form and Levocetrizine HCl mentioned in Table 3.

Table 3. Literature review Summary of Various Oral Solid dosage form and Levocetrizine HCl

S. No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
1	Journal of Pharmaceutical Research Int (Rupalben *et al.,* 2021)	Development of tropisetron hydrochloride orodispersible tablet using natural superdisintegrants	Orodispersible tablets with banana powder and cassiatra powder are super-disintegrants with excellent appearance and faster disintegration time
2	Saudi Pharmaceutical Journal (Hadyah *et al.,* 2019)	Design of taste masked enteric orodispersible tablets of diclofenac sodium by applying fluid bed coating technology	Sugar bead cores were coated with DS to create diclofenac sodium pellets, which were then coated with Eudragit L100 for enteric coating and Eudragit E100 for flavour masking.
3	Journal of Pharmaceutics (Niraj *et al.,* 2019)	Fast disintegrating combination tablets of taste masked Levocetirizine HCl and montelukast sodium: formulation design, development, and characterization	This article's focus is on the function of superdisintegrants in tablet disintegration and drug release, including both natural and manufactured varieties. These super-disintegrants are included into formulations for improved medication administration that is more physician.
4	Saudi Pharmaceutical Journal (Aleksandra *et al.,* 2017)	Microparticle cetirizine dihydrochloride for use in orally disintegrating tablets and lyophilisates: evaluation of taste masking.	Microparticles containing Eudragit were shown to be efficient taste-masking carriers for cetirizine dihydrochloride in three separate taste-masking assessments (E-tongue evaluation, human test panel, and in vitro drug release).

5	Journal of Pharmacy Research (Pathan *et al.,* 2013)	Novel venlafaxine hydrochloride sublimation formulation development and optimization	This study aims to develop a new process for preparing rapidly dissolving highly porous venlafaxine hydrochloride compressed tablets in the mouth using camphor as a sublimation agent. A new process developed to produce venlafaxine hydrochloride compressed tablets with high porosity that melts quickly in the mouth may be industrially feasible
6	European Journal of Pharmaceutics and Biopharmaceutics (Shoukri *et al.,* 2009)	In vitro and in vivo evaluation of nimesulide lyophilized orally disintegrating Tablets	ODT was prepared by freeze-drying an aqueous nimesulide dispersion containing a matrix-forming agent, a sugar alcohol and an anti-disintegrant. Various disintegration accelerators were also tested. ODT was prepared by lyophilisation
7	US patent 0155360 (Venkatesh *et al.,* 2009d)	Orally disintegrating tablets comprising diphenhydramine	The diphenhydramine particles produced were coated with taste-masking cellulose acetate and exhibited significant taste-masking
8	US patent 0292701 (Shimizu *et al.,* 2008b)	Orally disintegrable tablets	The average particle diameter of the current invention's tablet is small enough that it does not cause any pain during administration and does not leave any overpowering scent in the mouth.
9	US patent 0240101. (Chungi *et al.,* 2006)	Orally disintegrating pharmaceutical tablet formulations of olanzapine	The present invention also provides methods of treating patients in need of treatment with olanzapine
10	European Journals of Pharmaceutics and Biopharmaceutics. (Bayrak *et al.,* 2011)	Formulation of zolmitriptan sublingual tablets prepared by direct compression with different polymers: in vitro and in vivo evaluation	Precise amounts of active ingredients and optional additives were passed through a 500 mesh screen and then uniformly mixed using geometric dilution. PEG3350 was then added to the mixture. Zolmitriptan is absorbed sublingually and bioavailability by this route is greatly enhanced by the addition of chitosan at a 5 ratio
11	Carbohydrate Polymers (Abdelbary *et al.,* 2009)	Effects of several cellulosic-based directly comparative. compressed orodispersible tablets for oral administration. bioavailability of famotidine	A 3^2 full factorial design remained used to assess the properties of famotidine-ODT and the effects of various excipients on in vitro dissolution. Increased relative bioavailability compared to conventional tablets on the market

S. No	Name of Journal/ Year of Publication/ Name of Author	Title of Article	Type of work done
12	US Patent 0202163. (Rawas-Qalaji *et al.*, 2007.)	Epinephrine sublingual and buccal fast-dissolving tablets	Tablets may be made by dry mixing all the formulation material in a suitable blender, then adding lubricants to the powder combination, and lastly utilising direct compression. Sublingual or buccal delivery is suggested for tablets.
13	US Patent 0196475. (Withiam *et al.*, 2007a.)	Tablets made of silica components that dissolve quickly and have a low tendency to collapse	The prepared tablets are dimensionally stable (low friability) prior to use and disintegrate within approximately 60 seconds when immersed in water
14	US Patent 0196476 (Withiam *et al.*, 2007b)	Fast-dissolving pills. comprising low surface. titanium dioxide in the area	Titanium dioxide materials have a sufficiently small surface area to enhance disintegration time.
15	US Patent 0196474. (Withiam *et al.*, 2007c)	Rapidly disintegrating low friability tablets comprising Calciumcarbonate	The calcium carbonate material have a surface area small enough to reinforce the disintegration time.
16	US Patent 0269599. (Ohashi *et al.*, 2006)	Fast-dissolving pharmaceutical composition	Involves; mix ingredients with meloxicam for 30 min, then add lubricant. Mix again for 5 min and compress to form tablets. Other excipients such as lubricants, sweeteners and flavors added
17	US patent 0165781 (Ferran 2006)	Tablets that dissolve in the mouth. and the strategy utilizes to get them	Spray dried mannitol is utilized because it is highly water soluble, highly compressible, highly dilutable and chemically stable
18	US Patent 0244493. (Withiam *et al.*, 2005)	Rapidly disintegrating tablets comprising calcium carbonate	Involves; Mix the drug with excipients. It is then directly compressed to prepare tablets. It is smaller than about 3 % brittle and rapidly disintegrates in less than about 55 sec when submerged in purified water
19	International Journal of Pharmaceutics (Zheng *et al.*,2024)	Selection of lubricant type and concentration for orodispersible tablets	As the lubricant concentration increased, powder flow and tablet ejection improved. The lubrication efficiency generally decreased as follows: MgSt (Magnesium Stearate > HCO (Hydrogenated castor oil > SA (Stearic acid) > SLS (Sodium Lauryl Sulphate). Despite its superior lubrication efficacy, MgSt is the only lubricant of four evaluated that reduced tablet tensile strength.
20	World Journal of Pharmaceutical Research	Formulation and Evaluation of Clopidogrel	Clopidogrel orodispersible tablet shows better results than PLAVIX depending on the dissolution test. The formulation shows 92.34 % at 5 minutes and assay of

	(Alburyhi *et.al.*, 2024)	orodispersible tablet	Clopidogrel was within acceptance limit.

2.6: Marketed products under platform technology

Losec MUPS, a tablet containing microencapsulated medication granules and excipients, ranked second in sales in Sweden in 2008. AstraZeneca's Nexium and Lossec's patented method of compressing internal proton pump inhibitors are two more examples (PPIs). Launch a MUPS tablet to the market (Majeed *et al*., 2020). **Table 4** enlist various marketed products developed using MUPS technique.

Table 4: Marketed formulation of MUPS

Product	Company	Drug	Category	Formulation type
Losec MUPS	Astra-Zeneca	Omeprazole-Magnesim	Anti-ulcer	Tablet
Esomeprazole	Astra-Zeneca	Esomeprazole magnesium	Anti-ulcer	Tablet
Toprol XL	Astra-Zeneca	Metoprolol Tartrate	Anti-hypertensive	Tablet
Pravacid SoluTab.	Takedda	Lansoprazole	Anti-ulcer	Tablet

Unlike traditional dosage forms, ODT doesn't require the use of water because it rapidly degrades and/or dissolves and releases the medication upon contact with saliva. Direct compression, freeze drying, spray drying, moulding, phase change processes, melt granulation, sublimation, bulk extrusion, and a number of patented technologies including Zydis, Lyoc, Quicksolv, Orasolv, Durasolv, Flashtab, Oraquick, Wowtab, and Ziplet have all been used to create ODTs (Majeed *et.al.*,2020) **(Table 5)**

Table 5. Orodispersible tablets technological patents

Sr. No	ODT Technologies	Technological basis	Patent owners
1	Zydis	Lyophillization	R.P. Scherer Inc
2	Quicksolv	Lyophillization	Janseen Pharmaceutica
3	Flashtab	Multiparticulate compressed tablets	Prographarm
4	Lyoc	Lyophillization	Cephalon Corporation
5	Orasolv	Compressed tablets	Cima Labs Inc.
6	Durasolv	Compressed tablets	Cima Labs Inc.
7	Wowtab	Compressed molded tablets	Yamanouchi Pharma Technologies, Inc
8	Flashdose	Cotton candy process	Fuisz Technologies, Ltd.
9	AdvaTab	Microencapsulation	Eurand
10	Multiflash	Multi-unit tablet composed of coated micro granules	Prographarm

2.7: Selection of drugs:

2.7.1: Drug profile: Metoprolol succinate (MS)

Structure shown in Figure 4 illustrates the chemical structure of Metoprolol Succinate

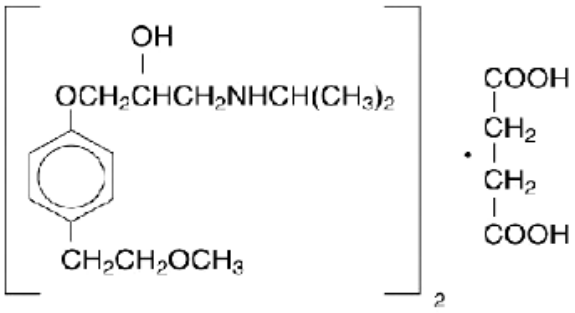

Figure.4: Chemical structure of S (-) Metoprolol succinate

Table 6: Drug profile of Metoprolol succinate (PubChem, 2024)

Chemical Name	Butanedioic acid;1-[4-(2-methoxyethyl)phenoxy]-3-(propan-2-ylamino)propan-2-ol
Molecular formula	$C_{34}H_{56}N_2O_{10}$
Molecular weight	652.8 g/mol
Synonyms	Metoprolol succinate
Solubility	Freely soluble in water
PKa	9.64
Melting point	136 ℃
Dose	25, 50, 100 and 200 mg

- **Pharmacodynamics**

The drug is by nature a beta1-adrenergic (beta-blocker). It is hostile, with average lipid levels. solvent properties, no intrinsic sympathomimetic action (ISA), and a permeable Membrane Stabilising Activity (MSA) (Thomas *et al.,* 2020).

- **Pharmacokinetics**

Absorption of S (-) Metoprolol approaches 95%, whereas systemic bioavailability of IR metoprolol was approximately 50% due to broad first-pass metabolism. First-pass metabolism takes an even bigger impact on S (-) Metoprolol succinate and the systemic bioavailability of this formulation is 20-35 % lower than his immediate release product. This is probably due to the slow release rate leading to maximal first-pass metabolism of drug results (Yang *et.al*.,2023).

Metoprolol is weakly absorbed in the stomach and is instead absorbed in the small and large intestines (S). As the pill is eliminated from the body, some of the ER medicine may be lost before it is entirely removed (Rüdesheim *et al.,* 2020).

- **Metabolism**

The drug is widely metabolized via multiple oxidative paths, primarily a or α-hydroxylation. S (-) Drugs that inhibit the metabolism of the isoenzyme cytochrome P450 2D6 may alter the plasma concentrations of other medications, including metoprolol (Brocker *et al.,* 2020).

2.7.2: Drug Profile- Levocetirizine HCl:

Structure shown in Figure 5 illustrates the chemical structure of Levocetirizine HCl

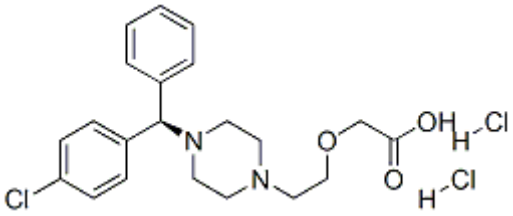

Figure.5: Chemical structure of Levocetirizine HCl

Table 7. Drug Profile of Levocetirizine HCl (PubChem,2024)

S.No	Parameter(s)	Details
1	Chemical Name	(R)-[2-[4-[(4-chlorophenyl).Phenylmethyl.]-1-piperazinyl] ethoxy] acetic acid Dihydrochloride
2	Molecular Formula	$C_{21}H_{25}ClN_2O_3.2HCl$
3	Molecular weight	461.82 g/mol
4	Synonym	Levocetirizine HCl
5	Solubility	Freely soluble in water
6	pKa	3.6 (pKa1) and 7.79 (pKa2)
7	Melting point	215 - 220 ^{0} C
8	Dose	2.5 and 5 mg
9	IUPAC name	2-(2-{4-[(R)-(4 -chlorophenyl)(phenyl)methyl]piperazin-1- yl}ethoxy)acetic acid

- **Pharmacodynamics**

Levocetirizine suppresses wheal and flare reactions in children and adults for up to 24 h. Symptoms of seasonal and permanent allergic rhinitis, as well as symptoms of chonic idiopathic urticaria, can be alleviated by levocetirizine (Jacob *et.al.*,2024).

Seasonal allergic rhinitis

Levocetirizine hydrochloride is approved for the treatment of symptoms in people 6 years of age and older who suffer from seasonal allergic rhinitis.

Perennial allergic rhinitis

Levocetirizine hydrochloride is indicated for the respite of indications associated with perennial allergic rhinitis in old age persons and children aged 6 years and older (Bernstein *et.al.*,2024).

Chronic idiopathic urticaria

Levocetirizine hydrochloride is approved for use in adults and children older than 6 years to treat the skin cases of chronic idiopathic urticaria.

Pharmacokinetics

Upon oral administration, Levocetirizine is swiftly and completely absorbed. In 0.9 h after consumption, peak plasma concentrations are obtained. After two days' conditions have stabilized. Single and repeated measurements of 5 mg OD generally yield peak concentrations of 270 ng/mL and 308 ng/mL, respectively. Food has no effect on the rate of absorption or on the total amount absorbed, althrough it does slow down the rise to peak concentration. 90 % of Levocetirizine is linked to plasma proteins. Levocetirizine's low distribution volume of 0.4 L/kg makes it difficult to administer. Plasma half-life in adults is 7.9 h. Apparent systemic clearance averages 0.63 mL/min/kg (Kim *et.al.*,2018).

Mechanism of action

Antihistamines, including Levocetirizine (the active enantiomer of cetirizine), work by blocking H1 receptors. Levocetirizine's antihistamine effects have been observed in a number of animal and human studies. Levocetirizine was shown to have a binding affinity for human H1 receptors that was two times *in vitro* tests than cetirizine (Ki=3 and 6 nmol/L, respectively) (Adnani *et.al*.,2024).

Overdose

Overdosing on Levocetirizine causes side effects that point to its anticholinergic properties or effects on the central nervous system. Confusion, diarrhea, weariness, headache, malaise, mydriasis, itching, restlessness, sedation, somnolence,

lightheadedness, and tachycardia were all recorded in those who took at least 5 times the recommended daily amount (Xiang *et.al.*,2024).

Side effects: Drowsiness, fatigue, dry mouth, dizziness, headache, nausea, vomiting, abdominal pain and diarrhea.

Drug interactions:

Based on the pharmacokinetics, pharmacodynamics and tolerability profile of Levocetirizine interactions with this antihistamine are not expected. Pseudoephedrine and theophylline, in particular, have not been documented to have any significant pharmacokinetic or pharmacodynamic interactions in drug-drug interaction studies. (400 mg/day) (Lin *et.al.*,2024).

2.8. Polymers and excipients profile

2.8.1: Hydroxypropyl methylcellulose (HPMC)

HPMC is an o-(2-hydroxypropylated) cellulose that is partially o-methylated, as described by the European Pharmacopoeia. Hypromellose is a slow, odourless, and bright nonionic water-soluble polymer (Pitpisutkul *et.al.*,2024). Made from renewable resources including cotton linters and wood pulp. Reacting cellulose with an alkali like sodium hydroxide produces soluble alkali cellulose. To make methylhydroxypropyl ether of cellulose, alkali cellulose is treated with chloromethane and propylene oxide. The final product is before washed and ground into blend (Ghadermazi *et al.*, 2019).

Non-proprietary names

BP: Hypromellose JP: Hydroxypropylmethylcellulose.

Substitutes

Benecel MHPC, Hydroxypropyl methyl cellulose (HPMC)

Molecular weight: - Approximately 12000–1400000 g/mol

Functional category

Coating agents, film formers, slow release rate-limiting polymers, stabilizers, suspending agents, tablet binders and thickeners.

Pharmaceutical use:

Hydroxypropyl methylcellulose is a versatile material that serves as a tablet binder, a polymer film coating, and a formulation environment for elongated pills.

Concentration from 2.5 to 5 %w/w. It can be used as a binding agent in wet or dry granulation formulation. At concentrations between 10 and 80 percent w/w % in tablets and capsules, very viscous locations can be used to postpone the drug dissolution profile from the matrix. Used in the preparation of topical formulations as a viscosity agent and suspending agent (Guarve *et.al.*,2021).

Melting point: Brown at 195-205 °C and Char at 230-235 °C.

Dissolution:

- Almost intractable in hot water, acetone, ether, and toluene. Also hardly dissolves in pure ethanol. Mixes into a cloudy liquid when put into cold water. Hypromellose is the most often utilized hydrophilic polymer in the production of CR dosage forms. This is because of its many advantages: non-toxicity, easy compaction, ability to hold large % concentration of drug, and low sensitivity to process variables. The release of drugs from the matrix. **Table 8** lists the many mechanisms, such as polymer wetting, polymer hydration, gelation, swelling, and polymer dissolution, by which drugs are released from hydrophilic matrix CR systems.

  Table 8. Viscosity values for 2% (w/v) aqueous solutions of methocel at 25°C

Methocel Product	Nominal viscosity (mPa s)
Methocel K100 Premium LVEP	105
Methocel K4M Premium	5000
Methocel K15M Premium	20000
Methocel K100M Premium	150000
Methocel E4M Premium	5000
Methocel F50 Premium	5000
Methocel E10M Premium CR	120000
Methocel E3. Premium LV	30
Methocel E5. Premium LV	50
Methocel E6 Premium LV	60
Methocel E15 Premium LV	150
Methocel E50 Premium LV	500

Stability of the excipient

Hypromellose is a hygroscopic material.

Incompatibility with other material

Hypromellose is not compatible with some oxidizing excipients. Hypromellose neither form complexes using metal salts.

2.8.2: Ethylcellulose

- **Non-proprietary names*:*** BP.: Ethylcellulose.
- **Synonyms :** Aquacoat ECM, Aqualon, E465, Ethocel.
- **Empirical formula and molecular weight:** -Ethylcellulose with complete ethoxyl substitution (DS=3) is $C_{12}H_{23}O_6$ ($C_{12}H_{22}O_5$) n-$C_{12}H_{23}O_5$

Category of excipients:

Film formation agents, flavor fixatives, binders, fillers and thickeners.

Uses in pharmaceutical companies:

Forms of this drug with timed release are used. In tablet oral formulations, ethylcellulose is most often used for its water-repellent coating qualities for tablets and granules. Drug release can be controlled by covering the pills with ethyl cellulose. It can be used alone or in conjunction with other solvents to make films that are insoluble in water (Qosim *et.al.*,2024). Cellulose derivatives with higher viscosity grades are typically used to make a more robust and long-lasting polymeric coating. Dispersing the drug through a polymeric film coating allows for controlled drug release from the polymer. Layered pellets and granules of ethylcellulose, which have the properties to absorb pressure and have strong tensile strength, are ideal for making MUPS tablets. Different grades of ethyl cellulose with a high viscosity are employed for microencapsulation of medicines. Microcapsule surface area and thickness affect the rate of API release from a cellulose-based substance. Concentration usage shown in **Table 9** (Wasilewska *et al.*, 2019).

Representation:

Ethylcellulose is having no taste, free flowing and white to brown powder.

Table 9. Concentration usage of Ethylcellulose

Dosage form	**% age of Ethylcellulose**
Micro-encapsulation	15 – 35
Extended release formulation	5 – 25
Film and enteric coating	2 – 5
Wet and Dry granulation formulation	2 – 5

Concentration: 0.50 g/cm^3

Solubility of Ethyl cellulose: Ethyl cellulose is not soluble in glycerin, propylene glycol and purified water.

Viscous Nature: Ethylcellulose viscous nature is typically measured at 30°C using 7 % w/v. Measured quantity of material dissolved in a solvent mixture of 70 % toluene: 30 % ethanol (w/w).

Material intactness

Ethyl cellulose physical and chemically stable, slightly moisture absorbent property. Chemically unaffected to base material, but more sensitive to acid based substances.

Not compatible: - Ethyl cellulose is not compatible with waxy based material.

2.8.3: Polymethacrylate

Chemical Term: (Poly-ethyl acrylate, methyl methacrylate) 2 :1

Chemical formulary and molecular mass: - *(*$C_6H_{10}O_5$)n. ≈36000

A methacrylic acid-ethyl acrylate copolymer (1:1) as a copolymer of methacrylic acid and ethyl acrylate having an average molecular weight of about 250,000

Functional category:

Film-forming, tablet viscosity agent, release rate modifier

- **Applications in pharmaceutical formulation or technology**

As a film former, Eudragit E can be used to create either a simple film or an insulating film. Easily dissolved in stomach acid. On the other hand, enteric coating agents of the Eudragit L, S, and FS widespread application. Some enteric compounds are only soluble at acidic physiological pH levels, while others dissolve at alkaline pH levels. Both Eudragit D and Eudragit H are soluble above pH 6.5 and above pH 7.5, respectively. Tablet film creation often employs Grade S, while particle layering can

benefit from the flexibility of dispersant FS 35 D. In order to create the insoluble film coatings utilized in extended release products, Eudragit grade ingredients are used. Combining two films with varied permeabilities yields the more permeable Eudragit RL film. There are no ionic functional formulation groups in Eudragit ND/NM kinds. In the presence of water, Eudragit D remains stable and does not dissolve or swell, regardless of the pH of the liquid. Eudragit L 30 D-55, when taken orally, produces a film in the intestines. However, with a pH of 5.5 or above, the coating dissolves quickly and easily, making it suitable for oral administration. You can now substitute Eudragit L 100-55 for Eudragit L 30 D-55. Water-based eudragit copolymer dispersions include Eastacryl 35 D and Kollicoat MAE 20 DH. It's also utilized to coat sustained-release pills with an enteric coating (Robota *et.al.*,2022).

Description

Eudragit NE 20 D is a water based dispersion of a unbiased copolymer of polymethacrylates. The dispersion is a thin, milky white liquid with a very subtle floral aroma. Films made from paint swell with water and become permeable. Films produced by this method are insoluble in water, but the active substance is released in a pH-independent manner.

Solubility

Aqueous dispersions can be mixed with water in any ratio while retaining a milky appearance. Mixing 1 part Eudragit NP 20 with 6 parts acetone produces a transparent to slightly hazy, viscous liquid. When mixed with ethanol or IPA, the eudragit first precipitates and then dissolves in excess organic solvent. This dispersion does not dissolve when mixed with 0.1 N sodium hydroxide solution into 1:4 ratios. It retains its milky appearance.

2.8.4: Cellulose, silicified microcrystalline

Synonym: - Prosolv

Chemical name: Silicified MCC contains 3 % w/w colloidal silicon dioxide.

Functional category: Tablets and capsule formulation.

Use in pharmaceutical formulation or technology

Silica-modified MCC is a common filler in capsule and tablet production. It exhibits improved compression assets in both wet and dry compression in comparison to

traditional MCC. It is specifically designed to talk the compression damage that occurs with MCC after water based granulation.

Depiction

Silicified MCC is a synergistic near corporeal blend of two materials: MCC and colloidal silica dioxide. MCC contains 3 % by weight of colloidal silicon dioxide.

Solubility:

It really doesn't dissolve in clean water, weak acid solutions, or many other organic or inorganic solvents. The MCC fraction that has been silicified dissolves easily in a NaOH solution of 5% by weight.

Physical and chemical Stability

When maintained in an airtight container, silicified MCC maintains its integrity.

2.8.5: Talcum

Synonym:

Calcium silica, Silica magnesia, white talc powder.

Chemical Name: - Talc

Empirical formula and molecular weight:

Talc is a refined form of magnesium silicate with a chemical formula of Mg6 (Si2O5)4(OH)4. Small levels of aluminium silicate and iron can be found in talc.

Functional category: - Glidant (Improve flow property)

Applications in pharmaceutical formulation or technology

Talcum is widely used as a lubricant and glident in tablet and capsule preparations, a new type of fine particles coating for slow-release profile granules, and as an absorbent. Talc was commonly used as a lubricant, glident, and diluent in oral solid dose forms. In contrast, controlled release products frequently employ talcum to reduce the effectiveness of their dissolution profile. (Ozkan, C *et al*., 2021).

Physical characteristics

Talc does have the crystalline form and is extremely fine, white to off-mint white, and slightly greasy in nature. Talcum easy to get familiar with the human skin and has a lax texture without roughness.

Soluble

Talcum is not soluble in water, weak acidic solution, alkaline and volatile organic solute and solvents.

Stability conditions

Talcum is a stable excipients and can be purified by heating at 150°C for at least 2 h. Heating to ethylene oxide or alpha and gamma radiation can also be used to sterilize talc. Keep talcum in a dark, cold, and airtight container.

2.8.6: Microcrystalline cellulose (MCC)

Common names:

Ethispheres, Ceolus KG, crystalline cellulose E460, Emcocel, and Ethicel; Avicel PH 102, Celex, cellulose gel, Celphere

Chemical name: Cellulose

Molecular mass and formula: - ($C_6H_{11}O_5)_n \approx 35000$ g/mol.

Common names:

Adsorbents, suspending excipients, tablets and diluents and disintegrants.

Pharmaceutical Application:

In the pharmaceutical industry, MCC is employed as a viscosity-enhancing ingredient, a filler in oral tablet and capsule preparations, and in direct compression operations. Microcrystalline cellulose has certain lubricating and dissolving qualities that make it useful for tableting in addition to its usage as a binder/diluent. Cosmetics and food aren't the only places you may find microcrystalline cellulose its concentration usage are in **Table 10**.

Table 10: Concentration usage of Microcrystalline cellulose

Use	Concentration (%)
Adsorbent	20-95
Antiadherent	10-25
Capsule binder/diluents	25-95
Tablet disintegrants	10-20
Tablet binder/diluents	10-80

Description

A white, colourless, and tasteless crystalline powder made up of porous particles, microcrystalline cellulose is a refined, partially depolymerized form of cellulose. Particle size and moisture content may be tailored to specific qualities and applications, and it is commercially available in a wide range. (Chaerunisaa, A. Y. *et.al*.,2019)

Soluble characteristics:

MCC is readily dissolved in 7 % w/v NaOH solution. It is not soluble in water, weak acids and most inorganic and organic solvents.

2.8.7: Mannitol

Nonproprietary names: B.P. Mannitol, USP- Mannitol

Chemical formation: $C_6H_{14}O_6$

Molecular mass: 183.17

Mannitol is in form D and S-mannitol. Alcohol bound to sucrose is hexahydric and, in solution, isomeric. Mannitol can be found in the form of a white to off-white, odourless, crystalline, or fluid substance. Its sweet flavour, which is almost as sweet as sucrose and half as sweet as fructose, leaves a refreshing feeling in the mouth. (Ohrem H *et.al*., 2014).

Typical properties

Bulk density	:	0.44 g/cm^3 for powder
Tapped density	:	0.72 g/cm^3 for powder
Density (true)	:	1.51 g/cm^3
Flow	:	Powder is cohesive, granules are free flowing
Heat of Combustion	:	17.17 kJ/g
Melting point	:	165-170 ^{0}C
Solubility	:	0.50 in 7.50 parts

- **Stability characteristics:**

Either dry mannitol and mannitol dissolved in water have a long shelf life. Filtration and moist heat sterilization are two methods that can be used on solutions. Mannitol not able to undergo the Maillard reaction. Mannitol materials can be kept cool and silica get added well-sealed containers.

Pharmaceutical applications:

In pharmaceuticals, it is mainly utilized as a diluent for tablet formulations (concentration 15-85 % w/w). It can be utilized directly for preparing granules (Both Dry mixing and wet granulation).

2.8.8. Low -substituted hydroxypropylcellulose

Common names:

Cellulose, 2-hydroxypropyl ether; 2-hydroxypropyl ether (low substituted) cellulose ; hyprolose, low-substituted; L-HPC, hydoxypropylated cellulose.

Chemical name: Cellulose, 2-HPE (low-substituted HPC)

Empirical formula and molecular weight:

Low-substituted HPC is a Hydroxypropyl ether of cellulose derivative, according to USP 32-NF28. Only one of the three free hydroxyl groups per glucose subunit is transformed to a hydroxypropyl ether in the production of low-substituted hydroxypropyl cellulose, which is a consequence of HPC.Contains 5 to 16 % hydroxypropyl when dried at 105°C for 1 h (Erkoc *et.al.,* 2022).

Pharmaceutical use: Binder and disintegrants

Depiction:

L-Hydroxyl propyl cellulose material appears as a white to off white powder with granular nature.

Soluble characteristics:

L-HPC not soluble in ethanol (90 %) acetone and in ester. L-HPC liquefies in a solution of 0.10 N NaOH. It is practically not soluble but get swelled in water.

Stability characteristics:

L-HPC is a hygroscopic yet remarkably time- and temperature-stable substance. Keep the powder in an airtight container at all times.

Incompatibilities:

L-HPC is alkaline substances. Potential excipient interactions include. Disintegration period may be increased after storage if a tablet formulation includes such a substance.

Applications in pharmaceutical formulation or technology:

L-HPC is successfully utilized as disintegrants, diluents with viscosity enhancing binder for tablet and dry mix blend in wet or dry granulation process.

2.8.9: Crospovidone

Synonyms:

Crospovidone, Crospsopharm, cross-linked povidone, Kollidon CL; Kollidon CL-M; Poly-plasdone XL, Poly-plasdone XL-10, poly-vinylpolypyrrolidone.

IUPAC name: 1-Ethenyl-2-pyrrolidinone homopolymer

Formula and molecular name: ($(C_6H_{10}NO)_n$ >1000000

Crospovidone is not water soluble semi-synthetic cross-linked photopolymer of N-vinyl-2-pyrrolidiinone. Precise grit of molecular weight has not been well-known because substance is insoluble. (Chaudhari, S.P et.al.,2012).

Use: Disintegrants

Apperance:

Crospovidone is an exciepient that appears white to off-white, is wonderfully separated, is free flowing, has no flavour, and is odourless or virtually colorless.

Solubility:

Crospovidone is a white to off-white, finely divided, free-flowing, virtually tasteless, odorless, or almost odorless hygroscopic powder.

Compatibility:

Crospovidone is not compatible with most organic and inorganic pharmaceutical solvents.

Applications in pharmaceutical formulation or technology:

Crospovidone is a water-insoluble disintegrants used in concentrations of 2-5 % in tablets manufacturing by direct compression by wet and dry granulation processes.

CHAPTER 3

Research hypothesis, aim and objectives

3.1: Hypothesis

Part A: Development and evaluation of wurster processed platform technology for modified release formulations.

S (-) Metoprolol is used to treat hypertension, angina, and as a migraine prophylaxis. Metoprolol acts by inhibiting the beta-adrenergic system. The half-life of metoprolol is 2-7 h. This means tablets to take twice a day. A white crystalline powder, having a bioavailability of 50 % and a protein binding of 12 %. Metoprolol has a pKa of 9.68, making it a strong base; it is hydrophilic and highly soluble in water (BCS class I). Absorption is rapid and complete throughout the intestines. Metoprolol reaches its peak plasma concentrations between 1 and 2 h following a single dose. About 3-4 h later, the S (-) Metoprolol will have been excreted in the urine. Therefore, the medicine can be used as often as four times daily. There are multiple dosage levels of metoprolol to choose from, including 25, 50, 100, and 200 mg. Compliance, as well as the quality, safety, efficacy, and cost-effectiveness of the drug, should all be taken into account when determining the dosing interval. Research engineers face a difficult task in creating sustained-release oral platform technologies for free hydrophilic medicines with extensive first-pass metabolism. Extremely hydrophilic active pharmaceutical ingredients (APIs), if not correctly prepared, can dissolve rapidly in the stomach, resulting in dangerous amounts if taken orally. This method of emancipation is rather prevalent. S(-) Metoprolol succinate pellets and powdered lubricants are compacted together to make multiple unit pellet systems (MUPS). A drug-containing or drug-coated spherical core is at the heart of a multilayer controlled-release drug delivery system (MUPS) (cellulose and acrylic polymers). In the pharmaceutical sector, MUPS technology has replaced immediate and modified release tablets. Protection from stomach acid can be achieved by encasing APIs in enteric-coated pellets, which can then be administered orally. The potential for local irritation and toxicity is lessened with MUPS formulations, and dosage dumping and fluctuations in plasma concentration are minimized.

Part B: Development and evaluation of spray dried fluid bed processed orodispersible platform technology.

The hydrochloride form of levocetirizine, or Levoxyl®, is exceptionally soluble in water. The investigation of already medicinal compounds is of tremendous interest. Numerous standard pharmaceuticals can be purchased today. This conventional approach is flawed in several ways. An emerging field is the use of novel drug delivery methods. Significant gains in convenience, security, and effectiveness for the patient. In order to maintain a competitive edge, get more patents, and capture a larger share of the drug delivery business, several companies are diversifying their research and development efforts by creating new platforms. Tablets that rapidly dissolve or disintegrate in the mouth into a liquid suspension are called orodispersible. Normal dosage forms, such as pills, can be difficult for those with motion sickness (motion sickness), sudden coughing due to a cold or allergies, or bronchitis if they are taken without water. So, people are interested in tablets that disintegrate and dissolve rapidly in the mouth. Orodispersible tablets (ODT) are convenient for those who have trouble swallowing or are on the go. Tablets that dissolve instantaneously when placed on the tongue are called orodispersible. The drug they contain is then able to dissolve or disperse in the saliva in your mouth. The quicker the medicine reaches its target; the sooner its pharmacological effects can be felt there. The oral cavity (mouth) and throat can be used to absorb some active pharmaceutical ingredients as saliva travels down the oesophagus and into the stomach. In this study, researchers used dry mixing, direct compression, and a super disintegrants to create a mouth dissolving formulation of Levocetirizine HCl. Several characteristics of the finished tablets were evaluated, including their density, thickness, hardness, friability, disintegration time, wetting time, and In-vitro and In-vivo dissolving times.

3.2: Aim: The focus of the study is on developing a novel formulation by means of the platform technology.

3.3: Objectives:

The objectives of present study are:

1. To develop solid dosage forms of existing drug molecules using platform technology.
2. To reduce the manufacturing and process cost and provide accuracy in the dosing.
3. To expand market potential of drug manufacturers of India through introduction of generic version utilizing novel and non-infringing platform systems.

CHAPTER 4

Material and method

4.1. Materials and method

4.1.1: List of materials used in the study

The basic details like manufacturers/ suppliers names with or without model numbers of various chemicals and different instruments that had been used in the experiments are displayed in Table 11 **(**Maryadele *et al.*,1996).

Table 11. Chemical lists along with manufacturers names

Table: 11.1 MUPS tablets of S(-) Metoprolol succinate

S.No	Material /Chemical	Manufacturer
1	Acetonitrile	LOBA Chemie Private Limited, India
2	Aerosil	Evonik, India
3	Ammonium acetate	LOBA Chemie Private Limited, India
4	Crosspovidone	Jungbunzlauer, China
5	Ethanol	LOBA Chemie Private Limited, India
6	Glacial acetic acid	LOBA Chemie Private Limited, India
7	Hydrochloric acid	LOBA Chemie Private Limited, India
8	Hypromellose	Wanbury, India
9	Hypromellose, K4-M	Spansules Formulation, India
10	Magnesium stearate	BASF, Germany
11	MCC PH 102	Colourcon , India
12	MCC PH 200	Asland, India
13	Methanol	LOBA Chemie Private Limited, India
14	Methocel K-100 M	Spansules Formulation Limited, India
15	Metoprolol succinate	Emcure Pharmaceutical Limited, India
16	Millipore water	Bio-age Equipment Limited, India
17	Orthophosphoric acid	LOBA Chemie Private Limited, India
18	Phosphoric acid	LOBA Chemie Private Limited, India
19	Potassium bromide	LOBA Chemie Private Limited, India
20	Sodium hydroxide pellets	Central Drug House Private Limited, India
21	Sodium steryl fumarate	Lubrizol, India
22	Talc IP	Alembic Limited, India
23	Triethylamine	LOBA Chemie Private Limited, India
24	Tween (20 and 80)	LOBA Chemie Private Limited, India

Table 11.2: Orodispersible tablets of Levocetirizine HCl

S.No	Material /Chemical	Manufacturer
1	Acetonitrile	LOBA Chemie Private Limited, India
2	Ammonium acetate	LOBA Chemie Private Limited, India
3	Aspartame	Nutrasweet, USA
4	Citric acid	Amijal Chemicals, India
5	Colloidal silicon dioxide	Cabot Sanmar, India
6	Croscarmellose sodium	DFE Pharma, India
7	Crospovidone (Polyplasdone XL)	ISP , UK
8	Ethanol	LOBA Chemie Private Limited, India
9	Flavour orange	IFF, India
10	Glacial acetic acid	LOBA Chemie Private Limited, India
11	Hydrochloric acid	LOBA Chemie Private Limited, India
12	Lactose monohydrate, DCL-11	Scheiber Dynamix Dairies, India
13	Lactose monohydrate, DCL-11	Scheiber Dynamix Dairies, India
14	Levocetirizine HCl	Apex Chemical, India
15	Low substituted hydroxypropyl cellulose	ShinEstu, Japan
16	Magnesium stearate	Sunshine Organic, India
17	Mannitol, Perlitol SD 200	Roquette, India
18	Methanol	LOBA Chemie Private Limited, India
19	Microcrystalline cellulose PH101, PH102	DFE pharma, India
20	Millipore water	Bio-Age Equipment Limited, India
21	Orthophosphoric acid	LOBA Chemie Private Limited, India
22	Phosphoric acid.	LOBA Chemie Private Limited, India
23	Polyvinyl pyrrolidone K-30 (PVP K 30)	BASF, India
24	Potassium bromide	LOBA Chemie Private Limited, India
25	Propylene glycol	Central Drug House Private Limited, India
26	Sodium hydroxide pellets	LOBA Chemie Private Limited, India
27	Sodium saccharin	Amijal Chemicals, India
28	Sucralose	JK Sucralose Inc, China
29	Triethylamine	LOBA Chemie Private Limited, India
30	Tween (80, 20)	LOBA Chemie Private Limited, India

4.2.2: List of equipment used in the study

Table 12. List of equipment along with make and Model Number

S.No.	Equipments	Make	Model Number
1	Digital top pan balance	Sartorius, Germany	BSA224S-CW
2	Bulk density apparatus	Electrolab, India	ETD-1020X 0320600
3	Centrifuge	REMI RM-12C, India	PR-23
4	Differential scanning Calorimeter	PerkinElmer, USA	DSC 6000
5	Disintegration apparatus	Electrolab, India	EDI-2I
6	Dissolution apparatus	Electrolab, India	EDT08LX
7	Fluidized bed processor	Umang Pharmaceuticals Limited, India	UFBD – 15
8	Friability test apparatus	Electrolab, India	EGF-1
9	FTIR spectrophotometer	JASCO, Japan	FT/IR 4000
10	Hot air oven	Biotechnics, India	BTI-21
11	HPLC	Dionex, India	Ultimate 3000
12	Melting point apparatus	Lab India, India	MR-VIS+
13	Moisture analyzer	Mettler Toledo, Switzerland	HX204
14	Autotester	Scalenger, India	560-97
15	pH meter	Lab India, India	PICO pH
16	Compression Machine	Cadmach, India	CTX-26D
17	Stability chamber	Newtronic, India	NLHC26SI
18	UV spectrophotometer	Shimadzu Co. Limited, Japan	UV-2600i
19	Vernier calipers	Mitutoyo, Japan	500-196-20

4.2. Methodology

4.2.1. Development and evaluation of wurster processed extended-release platform technology for MUPS tablet of S (-) Metoprolol Succinate. (Part A)

4.2.1.1 Preformulation studies of S (-) Metoprolol succinate

Preformulation studies look into the therapeutic ingredient's physical and chemical characteristics, both on their own and in conjunction with excipients. Formulation design, pharmacokinetic biopharmaceutical characteristics, and manufacturing strategy may all be impacted by preformulation research. Before incorporating any chemicals into the formulation, whether as active pharmaceutical ingredients (APIs) or as excipients, it is important to conduct tests on their physico-chemical properties in order to obtain accurate, first-hand information on them. Preformulation study is a catchall word for all of these kinds of research. Method of formulation creation, drug

entrapment efficiency, compatibility testing between APIs and excipients or excipients and excipients and pharmacokinetic response of APIs-loaded formulation are all heavily influenced by the API or excipients critical material attributes (CMA). As a result, only by strictly adhering to all of the preformulation studies for active pharmaceutical ingredients and excipients can a satisfactory final product be attained. (Rockville *et al*., 2012)

4.2.1.1.1. Organoleptic evaluation

Examining appearances by naked eye observation was used to take note of the selected API initial and final visual appearances upon delivery from suppliers and after proper storage.

4.2.1.1.2. Solubility

Solubility studies are performed to identify the solubility characteristics of drug and selection of the best diluent in which drug suspended or dissolved and to achieve a solution saturation at constant temperature. It is measured in term of part of solute dissolved in volume of solvent. As per IP solubility to be refered.

4.2.1.1.3. Determination of bulk density and tap density

The granulated cylinder was filled to a known volume (V_o) with a powder of known weight (W). There were to be 500 taps on the density instrument. After that, the volume (V_f) was measured, and the process was repeated until the two subsequent readings were the same. Using **Equation 1** and **Equation 2**, we were able to determine the bulk density and the tapped density (Akseli *et al.*, 2019).

$$Bulk\ Density\ = \frac{W}{Vi} \times 100 \qquad \textbf{Equation :1}$$

$$Tapped\ Density\ = \frac{W}{Vf} \times 100 \qquad \textbf{Equation :2}$$

Where W= Weight of the powder, Vi = Initial Volume and Vf = Final Volume

4.2.1.1.4. Compressibility index and Hausner's ratio:

For predicting powder flow characteristics, compressibility index and Hausner's ratio have become the simple and most popular methods. Both the compressibility index and the Hausner's ratio were determined by using bulk density and the tapped density of a powder given in **Equation 3.**

$$\%\ compressibility\ = \frac{P_t - P_o}{P_t} \times 100 \qquad \textbf{Equation:3}$$

Where, P_t = Tapped density, P_O = Bulk density and Hausner ratio = Tapped density/Bulk density.

4.2.1.1.5. Drug identification

a) By FTIR

Weigh about 2 mg of sample in 200.0 mg of Potassium bromide previously dried at 105°C for 1 h. Carefully grind the mixture and fill in sample cell and measure the spectra between 4000 cm^{-1} to 450 cm^{-1}. Maintain a constant method of working. Absorption maximum positions and intensities in the spectra obtained with the sample under investigation are consistent with those in the spectra obtained with the reference material (Jain *et al*.,2012).

b) By HPLC

Inject 20 µl each of Blank, Standard Preparation and Sample Preparation on HPLC, using HPLC condition of assay and record the retention time of principal peak in HPLC chromatograph.

4.2.1.1.6. UV: Spectroscopy determination of λ max of S (-) Metoprolol succinate

Stock solution: S (-) Metoprolol succinate in distilled water (100 mg in 100 mL)

Scanning: From the stock solution, a suitable concentration of S(-) Metoprolol Succinate (10 µg/ mL) was prepared in distilled water and UV scan was taken for the above stock solutions between the wavelengths of 200- 400 nm.

4.2.1.1.7. pH

Weigh about 2 g of sample in a 100 mL beaker, add to it 100 mL of distilled water. Stir well to dissolve and check the pH at 25 °C (Ghanbarzadeh *et al*,2021).

4.2.1.1.8. Melting point

A solid change into liquid matter at some temperature, that temperature is melting point of particular compound. This is determined in a simple manner using an apparatus known as capillary melting point apparatus. If there are any impurities mixed with compound, then, it will produce a depression or an elevation in the melting point range. So to assess the presence of purity in compound and to identify

the compound itself, the melting point determination of a compound plays a crucial role at preformulation stage. Using a melting point apparatus, a minimum quantity of medication was placed in a very tiny capillary tube, and the tube was then attached to the stem of a thermometer placed in the contraption's centre. Then, the temperature in the equipment was gradually increased. It was repeated three times to record the melting point of the medication molecules (Vaghela *et al*.,2014).

4.2.1.1.9. Loss on drying

Weigh a glass LOD bottle which is dried and cooled (W_1). Transfer to it about 1.0g of sample. Distribute the sample evenly. Cover the LOD bottle with stopper and weigh (W_2). Place the LOD bottle in vacuum oven. Remove the stopper and leave it in vacuum oven. Apply the vacuum to oven. After drying is completed, Remove the vacuum and open the vacuum oven. Close the bottle. Allow it to cool in desiccators and weigh (W_3). Again heat the sample for half an h then cool it in a desiccators and weigh. (W_4). LOD measured by using **Equation 4.** Continue this procedure until the difference between two consecutive weights should not be more than 0.50 mg (Sunil *et al*., 2012).

Calculations:

$$\% LOD = \frac{(W_2 - W_4)}{(W_2 - W_1)} \times 100 \qquad \textbf{Equation. 4.}$$

4.2.1.1.10. Related substance (By HPLC)

i) Mobile Phase: Buffer: Glacial acetic acid: triethylamine: phosphoric acid: acetonitrile (810: 10: 2: 3: 146)

Buffer : Weigh about 3.90 g of ammonium acetate in 810 mL water.

ii) Chromatographic conditions:

Column : Inertsil ODS - 3, 250 mm x 4.60 mm, 5 micron or equivalent.

Flow Rate : 1.50 mL/min.

Wavelength : 280 nm.

Run Time : 60 min.

Injection Volume: 20 µL.

Approximate retention time: S (-) Metoprolol succinate: 14.50 min.

Standard preparation: Weigh about 20 mg of S (-) Metoprolol succinate working standard in 10 mL volumetric flask. Incorporate and dilute to the suitable concentration with mobile phase. Pipette out 1 mL of diluted solution in 100 mL volumetric flask and dilute upto the mark with mobile phase (Phadke, R., *et al*,2018).

Test preparation: Weigh about 20 mg of sample in 10 mL volumetric flask. Dissolve and dilute upto the mark with mobile phase.

System suitability preparation: Inject standard preparation as system suitability.

Proceure: Inject separately each of blank followed by system suitability preparation. Record the chromatogram and measure the system suitability parameters. Limits are as below:

The relative standard deviation for thee replicate injections should not be more than 2 %.

If system suitability passes, then inject of test preparation and calculate the individual impurity and total impurity by using **Equation 5** and **Equation 6**.

$$\text{Highest individual impurity} = \frac{\text{AH x WS x DT x P}}{\text{AS x WT x DS x 100}} \times 100 \qquad \textbf{Equation 5}$$

Where,

AH = Area of highest individual impurity, AS = Area of standard, WS = Weight of standard, WT = Weight of test, DS = Dilution of standard, DT = Dilution of test, P = Potency of standard

Total impurity:

$$\text{Total impurity} = \frac{\text{AH x WS x DT x P}}{\text{AS x WT x DS x 100}} \times 100 \qquad \textbf{Equation: 6}$$

Where,

AT = Total area of impurity, AS = Area of standard, WS = Weight of standard, WT = Weight of test, DS = Dilution of standard, DT = Dilution of test, P = Potency of standard.

4.2.1.1.11. Drug assay (By HPLC)

i) Mobile Phase: Buffer: Glacial acetic acid: triethylamine: phosphoric acid: acetonitrile (810: 10: 2: 3: 146)

Buffer : Weigh about 3.90 g of Ammonium acetate in 810 mL water

ii) Chromatographic conditions:

Column : Inertsil ODS - 3, 250 mm x 4.60 mm, 5 micron or equivalent

Flow Rate : 1.5 mL/min

Wavelength : 280 nm

Run Time : 30 min

Injection Volume: 20 µL

Approximate retention time: S (-) Metoprolol Succinate: About 14.5 min.

Standard preparation: Fill a 100 mL volumetric flask with water and weigh in 50 mg of S (-) Metoprolol Succinate as a working standard. Incorporate and dilute to the proper concentration with mobile phase.

Test preparation: Weigh about 50 mg of Sample in 100 mL volumetric flask. Integrate and dilute to the proper concentration with mobile phase.

System suitability preparation: Inject standard preparation as system suitability preparation.

Procedure: Inject separately Blank followed by five replicates of System suitability preparation. Record the chromatogram and measure the system suitability parameters: Limits are as below:

The relative standard deviation for five replicate injection should be not more than 2 %

If system suitability passes, then make duplicate injection of test preparation and calculate the assay by using **Equation 7.**

Calculation:

$$\% \text{ Assay } = \frac{\text{AT x WS x DT x P}}{\text{AS x WT x DS x } (100 - \text{LOD})} \times 100 \quad \textbf{Equation: 7}$$

Where,

AT = Total area of impurity, AS = Area of standard, WS = Weight of standard, WT = Weight of test, DS = Dilution of standard, DT = Dilution of test, P = Potency of standard.

4.2.1.1.12. Sieve analysis

The primary goal of screening analysis was to quantify the range of medication particle sizes. The standard sieves were arranged in a stack with the bigger pore sieves on top and the smaller pore sieves at the bottom (Dhwani *et al.*,2016).

Procedure

A number of sieves were arranged in order of decreasing pore diameter (increasing number of sieves), i.e. 20 #, 30 #, 40 #, 60 #, 80 # and 100 #. 50 g of the preparation was carefully weighed and transferred to a sieve no. ie 20 # carried out above (**Equation 8).** The sieves were shaken for about 5-10 min, then the drug remaining in each sieve was taken, weighed separately and expressed in percentage. Weigh the remaining quantity in the sieve as X.

Calculation:

$$\% \text{ of material passed} = \frac{\text{Weight of sample in g} - \text{X}}{\text{Weight of sample in g}} \times 100 \qquad \textbf{Equation: 8}$$

4.2.1.2. Selection of manufacturing process

Sustained-release medication formulations can be made using a number of different methods. Previously dormant processes such as dry mix, wet granulation, compaction, melt extrusion, etc., have been brought back to life. When combining an API with additional excipients, granulation using Wursters processing technology is frequently utilized to ameliorate the undesired powder properties of the API. The raw ingredients in a fluidized bed granulation are typically heated and liquefied by hot intake air. The granulation solution is sprayed onto the material until the desired degree of wetness or granule size is reached. While the binder solution is most often employed as a liquid for granulating, it can also be applied to the powder bed in dry form. The fluid bed technique results in granules that are more uniform, less thick, and easier to handle. Althrough top spray granules are less dense than those formed by other granulation techniques, they still require a significant amount of pressure to compress into tablets. This renders them inappropriate for use in coating spheres and fine particles for controlled release products. Since the coating solution is sprayed from the bottom, where the coating efficiency is generally significantly greater than top spraying, they showed that bottom spraying provided a far smoother coating than top spraying,

especially when an organic solvent based solution was sprayed. A rough surface is produced when a solvent-based solution is sprayed from above because of the quick evaporation and increased spray drying that occurs. Due to its many benefits, including consistent dosing, reduced risk of overdosing, easy replication, and a time-released pharmacological action, wurster processing technology was a primary focus of this research. To begin, a nozzle is attached to the base of the product container, above the air distribution plate. Second, the plate used to disperse air has wider pores in the middle than on the perimeter. Increased airflow is enabled in the board's centre. Finally, the insert (partition) is laid down over the tabletop. Particles are buoyed into the air, fluidized upwards in the liner, fall out of the liner, pass beneath the liner, and are subsequently hoisted back into the liner. The interior of the liner is called the upper bed area, while the outside is called the lower bed area. After being sprayed in the top bed, the particles are dried once again in the bottom bed before achieving the desired film thickness.

Wurster technology to create a universal platform for controlled-release oral formulations, one that can be applied to a wide variety of products and which can achieve a variety of dissolution profiles. This polymer composition could be hydrophilic, hydrophobic, or a combination of the two. Microcrystalline cellulose pellets, hypromellose, ethyl cellulose (5 cps), ethyl cellulose (10 cps), eudragit, Methocel (K-100 M), and Methocel (K-100 M) were all chosen as carriers for this investigation (K4M). Several pellets and tablet properties were investigated, including the effects of binders *i.e.* povidone and disintegrants *i.e.* crosspovidone, as well as fillers *i.e.* mannitol, ceolus, microcrystalline cellulose glident, and lubricants like aerocil, sodium starch fumarate and magnesium stearate (Naveen *et al*.,2014)

4.2.1.2.1. Selection of polymer

The Wurster method can be used to coat or encapsulate particles uniformly. Fluidized beds of solid particles are the hallmark of this technique, and the spray nozzle is located at the bed's base. An air stream with fluidizing properties is used to propel the particles upward in a cyclical motion around the spray nozzle. At the same time that the stream of particles is being sprayed through the nozzle, atomized droplets of the

coating solution or suspension are being sprayed. As droplets are deposited on the surface of passing particles, these particles rise into the expansion chamber. The expansion chamber slows the airflow, allowing the particles to recirculate into the coating chamber. Further, it permits particles to momentarily separate from one another, reducing the likelihood of agglomeration and accretion. As particles pass through the expansion chamber, the organic solvent or aqueous coating vehicle evaporates, leaving only the non-volatile components of the coating formulation on the particle's surface. This batch procedure keeps on until all of the particles have been coated with the specified amount of coating material. The wurster coating method has been selected as the optimal method for developing the platform. Multiple pilot projects were prepared to help choose an ideal polymer for the platform. Because it is a low-cost, easily available polymer that is soluble in organic solvents and aids in the diffusional release of pharmaceuticals, ethylcellulose was chosen for the platform's construction (Srinivasa *et al.*,2015)**.**

4.2.1.2.2. Loading of the carrier pellets in the fluid bed equipment chamber

The substrate upon which the drugs were layered and other release modification kinds were placed is mostly located in the central component. These coatings often consist of spheres made of a variety of substances, such as lactose, sugar, or microcrystalline cellulose (MCC). Precisely measured quantities of pellets of the desired size were fed into the fluidized bed coater's processing chamber. The bed temperature was reached by fluidizing the pellets at an intake temperature of 60 ± 5°C (Govindaraj *et al.*,2015)

4.2.1.2.3. Preparation of drug layer solution and drug coating of pellets

Methocel ES water solution was used to dissolve the drug (MS), and then the mixture was continuously vortexed at 30 °C. Preheated MCC spheres were sifted through 25 # before being sprayed with the drug solution in FBE utilising the bottom spray technique. The pellets were coated, then dried for 30 min before being sifted through a 16 # sieve. The spray rate was optimized between 8 and 20 g/min, inlet temperature was 40 to 50 °C and the output temperature was 35 to 45 °C as shown in **Table 13.** Constant attention to the bed temperature is required to prevent recrystallization during layering. Bulk density, compressibility index, angle of repose and drug content were tested on these pellets to evaluate their processing potential (Jasti *et al*., 2013).

Table: 13. Drug coating of S (-) Metoprolol succinate on inert pellets

Drug loading (in mg)								
Trial No	**PT1**	**PT2**	**PT3**	**PT4**	**PT5**	**PT6**	**PT7**	**PT8**
MCC pellets (50-100#)	50	50	50	50	50	50	50	50
Metoprolol succinate	25	25	25	25	25	25	25	25
Povidone (PVP K-30)	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Talc IP	-	-	-	-	2.5	3.5	2.5	3.5
Hypromellose	-	-	2.5	3.5	-	-	3.0	3.5
Purified water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.

Parameters	**Specification and Observation**
Inlet air temperature	**40 -50 ºC**
Exhaust temperature	**35 -45 ºC**
Bed temperature	**35 -45 ºC**
Spray rate	**0-120 min: 8 ±1 g per min** **121-180 min: 13 ±1 g per min** **181-onwards : 20 ±1 g per min**

4.2.1.2.4 Preparation of polymer layer suspension and functional coating of pellets

For the coating of the control release polymer, we employed methocel K4M and methocel K100 M. After researching numerous additional polymers, including ethylcellulose (5 cps), ethyl cellulose (10 cps), and eudragit, these were deemed to be the most promising. Under vortex condition, methocel K4M and methocel K100M (1:1) were dissolved in purified water, talc was then added, and the mixture was stirred until a clear solution was created. This slurry was sifted through 60 # and stored until it was sprayed over drug-loaded pellets that had been prepared to the correct temperature in FBE by the bottom spray procedure. Over-wetting of pellets can be avoided with the right spray rate and temperature. The pellets were sprayed with the seal coating solution and dry for 60 min, then sifted through a 14 # screen and tested for various chemical and physical properties. (24,25). Several trials were conducted to determine the optimal values for the process variables as shown in **Table 14** and MUPS tablets shown in **Table 15**. Air inlet at 1800-3000 cfm, product

bed at 30-40 °C, spray rate at 8-20 g/min, and inlet air temperature at 40-50 °C (Varma *et al.*,2012).

4.2.1.3 Physical characterization of pellets

4.2.1.3.1 Powder flow properties (bulk and tap density)

10 g of pellets sample was weighed and poured into a graduated 100 mL measuring cylinder. The granules' bulk density was calculated to be in g per mL by reading the volume in the cylinder. The cylinder was tapped 100 times on a tapped density apparatus and the tapped density was determined in g per mL (Boyka *et al.*,2012)

4.2.1.3.2. Angle of repose

A device designed to measure angles of repose was used to get the final result.10 g of pellets sample was allowed to flow through a 4.6 cm orifice. The granules formed a pile on a 5 cm circular platform. The height of the pile was measured. An individual's angle of repose was computed by taking the arc tangent of their height and the platform's radius.

Table 14. Functional coating on S (-) Metoprolol succinate coated pellets

Trial no	PT9	PT10	PT11	PT12	PT13	PT14	PT15	P16	P17
Drug loading MCC Pellets (50-100#) 50 mg									
Metoprolol succinate	25	25	25	25	25	25	25	25	25
Talc IP	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50	3.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Functional coating									
Ethyl cellulose (5 Cps)	15	30	-	-	-	-	-	-	-
Ethyl cellulose 10 Cps	-		15	30	-	-	-	-	-
Eudragit	-	-	-	-	15	30	-	-	-
Methocel K-100 M	-	-	-	-	-	-	15	-	30
Hypromellose , K4-M	-	-	-	-	-	-	-	15	30
Talc IP	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50	2.50
Isopropyl Alcohol	-	-	-	-	q.s.	q.s.	-	-	-
Methylene Chloride	-	-	-	-	q.s.	q.s.	-	-	-
Purified Water	q.s.	q.s.	q.s.	q.s.	-	-	q.s.	q.s.	q.s.

Parameters	**Specification and observation**	
Inlet air temperature	40-50 °C	
Exhaust temperature	30-40 °C	
Product bed temperature	30-40 °C	
Spray rate (g/min)	**Time (min)**	**g/min**
	0-120	8±1
	121-180	13±1
	181-onward	20±1

Table 15. MUPS tablets of S (-) Metoprolol succinate

Trial No	FT1	FT2	FT3	FT4	FT5
Drug loading					
S(-) Metoprolol succinate	25	25	25	25	25
Talc IP	2.50	2.50	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50	3.50	3.50
Water	q.s.	q.s.	q.s.	q.s.	q.s.
Functional coating					
Methocel K-100 M	30	30	30	30	30
Hypromellose, K4-M	30	30	30	30	30
Talc	2.50	2.50	2.50	2.50	2.50
Purified water	q.s	q.s	q.s	q.s	q.s
Lubrication					
Pregelatinized starch	25	---	25	25	-
Hydrogenated castor oil (Lubritab)	---	---	---	---	25
Mannitol	---	25	25	--	-
Crospovidone	---	---	---	--	8
Ceolus KG 802	---	---	---	50	-
Ceolus PH 200	---	---	---	q.s to 250	-
MCC PH 200	---	---	---	---	56
Aerosil	---	---	---	---	1.79
Sodium stearyl fumarate	---	---	---	---	5.91
Magnesium stearate	3.60	3.60	3.60	3.60	-
MCC 102	q.s	q.s	q.s	-	q.s
Total in mg	250	250	250	250	250

4.2.1.3.3. Loss on drying

Around 3 g sample of the granules was dried at 105°C for constant weight, immediately after drug and functional coating process. The loss in weight after constant weight gave the loss on drying (LOD) (%, w/w).

4.2.1.3.4. Drug content

The HPLC technique modified for this formulation was used to determine drug content. The conditions for chromatography were as follows; column for HPLC was C8 250 mm*4.60 mm, 5 µ, samples were tested over 280 nm wavelength with 1.0 mL/min flow rate, the samples were calculated using the following equation **Equation 9.**

$$Drug\ content = \frac{Area\ spl}{Area\ Std} \times \frac{Std\ wt(mg)}{100} \times \frac{5}{50} \times \frac{100}{spl.wt.} \times \frac{25}{5} \times \frac{P}{100} \times \frac{100}{23.75} \times 100 \quad \textbf{Equation 9}$$

Where, L.C: labeled claim; P: % Purity of S (-) Metoprolol succinate working standard.

4.2.1.4 Compression of MUPS tablets

4.2.1.4.1 Compaction study and Preparation of compacts

The compaction behaviour of both powders were evaluated for out-of-die analysis. Tablets weighing 250 mg were compressed alone at pressures ranging from 35–300 MPa on a single rotory compression machine using 8 mm flat-faced punches. These compacts were hold for 30 s at maximum compaction during the last stage of compression leading to detachment and ejection of the tablets. After ejection, the tablets were stored in a desiccator for 24 h to allow its complete elastic recovery. The tablet parameters of weight, thickness and crushing strength were measured for each tablet and the following calculation volume (V), apparent density (ρA), relative density (D), porosity (ε) and tensile strength (TS) respectively.

S (-) Metoprolol succinate compacts were prepared by using MCC PH 102, MCC PH 200, aerosil, sodium stearyl fumarate and lubritab. Compression force were applied between 3 Kg/cm^2 to 24 Kg/cm^2. Different compacts were prepared at the time of the compression of the trial batch. The punches which was to be used for the compression of batch were lubricated with magnesium stearate (8.0 mm (U: Plain, L: Plain). The prepared compacts kept in desiccant container containing silica gel to avoid moisture penetration in the tabl*et al*ong with the elastic recovery, hardening of the tablet for 36 hours. The stored tablets were analyzed for physical parameters such as weight variation, hardness, diameters. The relative density (ρr) measured as the ratio of

apparent density (ρA) of the tablets compact to the true density (ρT) of the lubricated blend of the MUPS tablets. Tablet ejected method was used to determine the Heckel plots. Linear regression performed for the compression force between 3.0 Kg/cm^2 to 24 Kg/cm^2. In process parameters were measured by using Heckel Plots.

Heckel-Plot

The powder compaction features of the powder were calculated by the use of the Heckel **Equation 10.**

$$ln\frac{1}{1-D} = KP + A \qquad \textbf{Equation. 10}$$

Where, D is relative density of powder (ρ_A/ ρ_B), Py is Yield pressure, A is original compact volume and K is slope of the linear portion

Direct compression was used to create MUPS tablets. Some cushioning agents were made by combining MCC PH 102, MCC PH 200, Aerosil, sodium stearyl fumarate, and Lubritab. Cushioning excipients were combined with pellets that were coated to perform specific functions. The distance between the turret and the feed frame was minimized to lessen the blend's mechanical stress during rotation. White to off-white tablets having standard weight with a 250 mg dose, 3.60 ± 0.40 mm thickness, hardness: NLT 3 kg/cm^2, turret speed: 12-30 rpm, force feeder: 12-20 rpm, and hydraulic pressure: NLT 15 pounds are the parameters for compressing a lubricated MUPS blend in a single rotary compression machine as shown in Table 16 (Raja *et al.*,2010).

4.2.1.5. Characterization of MUPS tablets

4.2.1.5.1. Weight uniformity

Using autotester, the individual weights of 10 chosen pills were calculated. (Sainath *et al.*, 2012)

4.2.1.5.2. Thickness

Thickness of tablets was measured using vernier caliper, Mitutoyo, Japan

4.2.1.5.3. Hardness

The tablets' hardness was determined with a Mansanto hardness tester from India.

4.2.1.5.4. Friability test:

The friability of the tablets was determined using automated tablets friabilator. India's Roche Friabilator. Using **Equation 11,** we were able to determine the tablet's level of friability.

$$\%\ Friability = \frac{Wa - Wb}{Wa} \times 100 \qquad \textbf{Equation 11}$$

Where W_a: Initial weight and W_b: Final weight

4.2.1.5.5. *In vitro* drug release studies

The cumulative % drug released was determined using the Paddle (USP type II) apparatus (Electrolab TDT 06P, USP XXIII) at 37 ± 0.50 °C. Samples were taken at various time intervals up to 20 hours and filtered through a 0.45-micron filter after being added to a dissolving media consisting of 6.80 phosphate buffer in 900 mL medium and containing accurately weighed MUPS tablets (N=6). During dissolutions studies, various factors were observed. The effect of these factors were studied on release rate such as RPM (50,60,70) of the pedal, dissolution medium (pH 1.20 HCl, pH 5, and 6.80 phosphate buffer (Mehul *et al.,* 2012)

4.2.1.6. Effect of process variable on dissolution

4.2.1.6.1. Effect of type of pellets

Different trials to be conducted using CR1: Non peril seeds (50 #-100 #) , CR2: MCC pellets (50 #-100#) and CR3: Starch pellets (50 #-100#) were carried as shown in **Table 16**. Effect of various types of pellets was studied after drug and functional coating (Hinge, *et al*.2015).

Batches were manufactured as per the process explained in section **Table 16**. Trial CR1, CR2 and CR3 was evaluated for blend and physicochemical parameter such as flow properties and hardness, friability and dissolution (Bindi *et al*.,2012).

4.2.1.6.2. Effect of pellets size:

MCC pellets shows the optimized results during the study further trials were planned by considering the CR2 formulation. To check the effect of pellets size on physical parameters and on dissolution. Trial no CR4, CR5 and CR6 were planned as shown in **Table 17.** The different particle size of pellets was selected as

CR4 = MCC pellets (20 #30)

CR5 = MCC pellets (30 #40)

CR6 = MCC pellets (50 # - 100 #) (Pagar, D *et al*.,2013)

Table 16. Effect of type of pellets on dissolution of S (-) Metoprolol succinate coated pellets

Ingredients	CR1	CR2	CR3
Non peril seeds (50 # 100 #)	50	---	---
MCC pellets (50 # 100)	---	50	---
Starch pellets (50 # 100)	---	---	50
Drug loading			
Metoprolol succinate	25	25	25
Talc IP	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50
Water	q.s	q.s	q.s
Functional coating			
Methocel K-100 M	30	30	30
Hypromellose, K4-M	30	30	30
Talc	2.50	2.50	2.50
Purified Water	q.s	q.s	q.s
Lubrication			
Hydrogeneted castor oil (Lubritab)	25	25	25
MCC PH 200	76	76	76
MCC PH 102	qs to 250	qs to 250	qs to 250
Crospovidone	8	8	8
Aerosil	1.79	1.79	1.79
Sodium stearyl fumarate	5.91	5.91	5.91
Total in mg	250	250	250

Table 17: Effect of pellets size on dissolution of S (-) Metoprolol succinate coated pellets

Ingredients	CR 4	CR5	CR6
MCC pellets (20 #30)	50	---	---
MCC pellets (30 #40)	---	50	---
MCC pellets (50 # - 100 #)	---	---	50
Drug loading			
S(-) Metoprolol succinate	25	25	25
Talc IP	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50
Water	Qs	Qs	qs
Functional coating			
Methocel K-100 M	30	30	30
Methocel, K4-M	30	30	30
Ingredients	**CR 4**	**CR5**	**CR6**
Talc	2.50	2.50	2.50
Purified Water	Qs	Qs	Qs
Lubrication			
Hydrogeneted castor oil (Lubritab)	25	25	25
MCC PH 200	76	76	76
MCC PH 102	qs to 250	qs to 250	qs to 250
Crosspovidone	8	8	8
Aerosil	1.79	1.79	1.79
Sodium stearyl fumarate	5.91	5.91	5.91
Total in mg	250	250	250

Trial CR4, CR5 and CR6 was evaluated for blend and physicochemical parameter, such as flow properties and hardness, friability and dissolution (Madhuri *et al.*,2015)

4.2.1.6.3. Effect of inlet temperature

The effect of inlet temperature on physical parameters and on dissolution was studied. The developed platform was studied on different inlet temperature such as CR7: 45 ^{0}C ± 5 ^{0}C, CR8: 60 ^{0}C ± 5 ^{0}C and CR9: 70 ^{0}C ± 5 ^{0}C as shown in Table 18 (Viral *et al.*,2015)

Table 18. Effect of inlet temperature on dissolution of S(-) Metoprolol succinate coated pellets

Ingredients	CR7	CR8	CR9
Inlet temperature	45 ^{0}C± 5 ^{0}C	60 ^{0}C±5 ^{0}C	70 ^{0}C ±5 ^{0}C
MCC pellets (50 #100)	50	50	50
Drug loading			
Metoprolol succinate	25	25	25
Talc IP	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50
Water	Qs	Qs	qs
Functional Coating			
Methocel K-100 M	30	30	30
Hypromellose, K4-M	30	30	30
Talc	2.50	2.50	2.50
Purified water	Qs	Qs	qs
Lubrication			
Hydrogeneted castor oil (Lubritab)	25	25	25
MCC PH 200	76	76	76
MCC PH 102	qs to 250	qs to 250	qs to 250
Crosspovidone	8	8	8
Aerosil	1.79	1.79	1.79
Sodium Steryl Fumarate	5.91	5.91	5.91
Total in mg	**250**	**250**	**250**

CR7, CR8 and CR9 were evaluated for blend and physicochemical parameters such as flow properties, hardness, friability and dissolution as discussed.

4.2.1.6.4. Effect of nozzle diameter

The effect of nozzle diameter on physical parameters and dissolution was studied in wurster coating, particle size and on dissolution profile on the Metoprolol pellets. In the development of platform coating was carried out with different nozzle diameters

such as CR10: 0.50 mm, CR11: 1.20 mm and CR12: 2 mm as shown in Table 19 (Shital *et al.*, 2013)

Table 19 Effect of nozzle diameter on dissolution profile of S (-) Metoprolol succinate coated pellets

Effect of nozzle diameter	**0.55 mm**	**1.20 mm**	**2 mm**
Ingredients	**CR10**	**CR11**	**CR12**
MCC pellets (50 #100)	50	50	50
Drug Loading			
Metoprolol succinate	25	25	25
Talc IP	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50
Water	Qs	Qs	qs
Functional Coating			
Methocel K-100 M	30	30	30
Hypromellose, K4-M	30	30	30
Talc	2.50	2.50	2.50
Purified Water	Qs	Qs	qs
Lubrication			
Effect of nozzle diameter	**0.55 mm**	**1.20 mm**	**2 mm**
Hydrogeneted castor oil (Lubritab)	25	25	25
MCC PH 200	76	76	76
MCC PH 102	qs to 250	qs to 250	qs to 250
Crosspovidone	8	8	8
Aerosil	1.79	1.79	1.79
Sodium steryl fumarate	5.91	5.91	5.91
Total in mg	**250**	**250**	**250**

The flow properties, hardness, friability, and dissolution of CR10, CR11, and CR12, as well as their mix and physicochemical parameters, were tested.

4.2.1.6.5. Effect of fluidization air pressure

The effect of fluidization air pressure on physical parameters and dissolution was studied. The developed platform was studied on different air pressure such as CR13: 2500 CFM, CR14: 3000 CFM and CR15: 3500 CFM as shown in Table 20 (Mayur *et al.*,2012)

Table 20. Effect of fluidization air pressure on dissolution of S(-) Metoprolol succinate coated pellets

Effect of fluidization air pressure (cfm)	**2500**	**3000**	**3500**
Ingredients in mg	**CR13**	**CR14**	**CR15**
MCC Pellets (50#- 100 #)	50	50	50
Drug loading			
Metoprolol succinate	25	25	25
Talc IP	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50
Water	Qs	Qs	qs
Functional coating			
Methocel K-100 M	30	30	30
Hypromellose, K4-M	30	30	30
Talc	2.50	2.50	2.50
Purified water	Qs	Qs	Qs
Lubrication			
Hydrogeneted castor oil (Lubritab)	25	25	25
MCC PH 200	76	76	76
Effect of fluidization air pressure (cfm)	**2500**	**3000**	**3500**
MCC PH 102	qs to 250	qs to 250	qs to 250
Crosspovidone	8	8	8
Aerosil	1.79	1.79	1.79
Sodium stearyl fumarate	5.91	5.91	5.91
Total in mg	250	250	250

CR13, CR14 and CR15 were evaluated for blend and physicochemical parameter, such as flow properties and hardness, friability and dissolution as discussed.

4.2.1.6.6. Effect of height (position) of wurster

The effect of wurster position/height was studied on physical parameters and on dissolution as shown in **Table 21**. The developed platform was prepared by putting the wurster at different position and height i.e CR16: 1.50 cm, CR17: 2.50 cm and CR18:3.50 cm (Seema *et al.*,2013)

Table 21. Effect of height of Wurster coloumn on dissolution of S (-) Metoprolol succinate coated pellets

Effect of height of Wurster	**1.50 cm**	**2.50 cm**	**3.50 cm**
Ingredients	**CR16**	**CR17**	**CR18**
MCC pellets (50# - 100#)	50	50	50
Drug loading			
Metoprolol succinate	25	25	25
Talc IP	2.50	2.50	2.50
Hypromellose	3.50	3.50	3.50
Water	q.s	q.s	q.s
Functional coating			
Methocel K-100 M	30	30	30
Hypromellose, K4-M	30	30	30
Talc	2.50	2.50	2.50
Purified water	q.s	q.s	q.s
Lubrication			
Hydrogenated castor oil (lubritab)	25	25	25
MCC PH 200	76	76	76
MCC PH 102	q.s to 250	q.s to 250	q.s to 250
Crosspovidone	8	8	8
Aerosil	1.79	1.79	1.79
Sodium steryl fumarate	5.91	5.91	5.91
Total in mg	250	250	250

CR16, CR17 and CR18 was evaluated for blend and physicochemical parameter, such as flow properties and hardness, friability and dissolution (Chaitali *et al.*,2014)

4.2.1.7. Comparative dissolution profiling (CDP) of S (-) Metoprolol succinate MUPS tablets

Purpose of study: The purpose of this CDP study is to demonstrate the dissolution profile similarity factor (F2) of MUPS tablets of S (-) Metoprolol succinate **(Test)** and marketed sample (Toprol-XL 25) AstraZeneca, Sweden

Scope: The reports defining the method(s) / procedure(s) of analysis, acceptance criteria, Sampling method, Sampling points, evaluation, results of F2 and conclusion

for the comparative dissolution profile study.

4.2.1.7.1. CDP- dissolution medium

Comparative dissolution profiling of test product and reference product is performed in following dissolution medium.

a) CDP 1: 900 mL of sodium phosphate buffer pH 6.80 with 50 RPM agitation speed.

b) CDP 2: 900 mL of 0.1N HCl with 50 RPM agitation speed

c) CDP 3: 900 mL of acetate buffer pH 4.50 with 50 RPM agitation speed (Gadireddy *et al*.,2014).

4.2.1.7.2. CDP No. 1: Dissolution medium: 900 mL, sodium phosphate buffer pH 6.8

Dissolution conditions and instrumental conditions shown in **Table 22** and **Table 23.**

Table 22. Dissolution condition in CDP No.1

Parameter	Test condition
Dissolution media	900 mL, sodium phosphate buffer pH 6.80
Apparatus and type	USP Type 2 (paddle)(with sinkers)
Agitation speed	50 RPM
Temperature	37 C °± 1 °C
Time Points	2, 4, 8, 20 h
Volume withdrawn	10 mL

Standard Preparation: Accurately weigh 25 mg of S(-) Metoprolol succinate working standard into a 50 mL volumetric flask, add about 30 mL medium, sonicate for about 10 min and make up the volume with buffer, Dilute 5 mL of solution to 100 mL with medium (Kalyan *et al.*,2013)

Sample Preparation: Pipette 10 mL of sample solution from each jar at above mentioned regular interval, filter through a 0.45-µm-nylon membrane filter paper.

Table 23. Instrumental conditions in CDP No 1

Chromatographic condition	
Parameter	**Test conditions**
Column	
a. Type	C_8 - 250 mm× 4.60 mm, 5 µ
c. Temperature	30 °C
d. Run time	15 min
HPLC set up	
a. Flow rate	1 mL/min.
b. Detector	UV at 280 nm
c. Injection volume	100 µl
d. Auto sampler temperature	5 °C

Chromatographic system should be set up under instrumental circumstances with dissolution media injected as a blank, as indicated. Measure the system's accuracy with five independent injections of a standard S(-) Metoprolol succinate formulation. NMT 2% jump in relative standard deviation. S (-) Metoprolol succinate has a peak retention duration of about 6 min.

For the S (-) Metoprolol succinate peak, the column efficiency, as calculated by the number of theoretical plates, must be more than 1000, and the tailing factor must be less than 2 (Vachhani *et al*.,2011).

4.2.1.7.3. Calculations for phosphate buffer pH 6.80 (QC media with 50 RPM agitation speed) : Calculate cumulative % of S (-) Metoprolol succinate) dissolved in 2, 4, 8, and 20 h. Inject samples and calculate the *%* age of the labeled amount of S (-) Metoprolol succinate) dissolved using **Equation 12.** (Venkatachalam*et al.*,2010).

$$\frac{\text{Area of sample}}{\text{Area of standard}} \times \frac{\text{Std wt (mg)}}{50} \times \frac{5}{100} \times \frac{900}{23.75} \times \frac{P}{100} \times 100 \quad \textbf{Equation: 12}$$

4.2.1.7.4. CDP No. 2 : 900 mL of 0.1 N HCL

Multimedia dissolution study specification, instrumental conditions, dissolution apparatus and dissolution temperature are remains unchanged as mentioned in CDP No.1 mentioned in **Table 24** and **Table 25** (Kovalenko *et al.*,2012).

Table 24. Dissolution media, reagent and method of preparation in CDP No.2

Multimedia	Reagents	Preparation of Dissolution Medium
0.10 N HCl	Sodium dihydrogen phosphate anhydrous Sodium hydroxide Orthophosphoric acid Acetonitrile Hydrochloric acid Water	Dissolve 8.50 mL of HCl in 1000 mL of water
pH 4.50 Acetate buffer	Sodium dihydrogen phosphate anhydrous Sodium hydroxide Orthophosphoric acid Acetonitrile Sodium acetate trihydrate Glacial acetic acid Water	**2 N acetic acid solution:** Transfer 120 mL of glacial acetic acid in 1000 mL volumetric (Containing about 500 mL of water) and dilute to volume with water, mix gently. Dissolve 2.99 g of Sodium acetate trihydrate and 14 mL of 2 N acetic acid solution in 1000 mL of water . Dissolve in and dilute to volume with water , mix well.

Table 25. Dissolution condition for two multimedia dissolution in CDP No.2.

Parameter	Test condition
Dissolution media	0.1 N HCl
Apparatus	USP Type 2 (Paddle)
Agitation speed	50 RPM
Volume of medium	900 mL
Temperature	37 ± 1 °C
Time points	2,4,8 and 20 h
Volume withdrawn	10 mL

Preparation of 6 M Sodium hydroxide solution: Dissolve 24 g sodium hydroxide in 100 mL water.

Preparation of Sodium phosphate buffer pH 6.8 (Medium): Dissolve 6 g of sodium dihydrogen phosphate anhydrous in 1000 mL water. Adjust the pH of resulting solution to 6.80 ± 0.10 with 6 N sodium hydroxide solution.

Buffer Solution: Dissolve 6 g of Sodium dihydrogen phosphate anhydrous in 1000 mL water.

Mobile Phase: Mix buffer solution and acetonitrile in ratio of 50:50 and adjust the pH of resulting solution to 3 ± 0.05 with orthophosphoric acid.

Standard Preparation: Transfer about 25 mg of WS, accurately weighed, to a 100 mL volumetric flask. Dissolve in 5 mL of methanol and dilute to volume with dissolution media, mix well.

Test preparation: Set dissolution apparatus as described above. Add specified volume of dissolution media in to each vessel. Start the apparatus while each vessel attains temperature 37°C ± 1 ºC. Weigh and place one tablet without sinkers into each vessel and withdraw about 10 mL of the sample at the end of specified time from each vessel and centrifuge at 2500 rpm for 10 mins to get clear supernatant. Replace same volume of dissolution medium at the same time (Buchhorn *et al*.,2017).

Calculate cumulative % of S (-) Metoprolol succinate (X) dissolved in 2, 4, 6, 8 and 20 h. Inject samples and calculate the % age of the labeled amount of S (-) Metoprolol succinate dissolved using **Equation 13**.

$$\frac{\text{Area of sample}}{\text{Area of standard}} \times \frac{\text{Std wt (mg)}}{50} \times \frac{5}{100} \times \frac{900}{23.75} \times \frac{P}{100} \times 100 \quad \textbf{Equation: 13}$$

4.2.1.7.5. Acceptance criteria

F2 value : The percentage (percent) mean dissolution between the two profiles is quantified by the similarity factor (F2), which is a logarithmic reciprocal square root transformation of the sum of squared error. F2 value calculated using **Equation 14** (Mashkovskiy *et al*.,2012).

$$\mathbf{F2 = 50 \bullet \log \{[\, 1 + (1/n)\Sigma_{t=1}^{\,n} (R_t - T_t)^2 \,]^{-0.5} \bullet 100\}} \qquad \textbf{Equation 14}$$

Where

n = Number of time points

$\sum$ = Summation of overall time points

R_t = Dissolution value of the reference batch at time t

T_t = Dissolution value of the test batch at time t

4.2.1.8. Bioanalytical method development

High-performance liquid Chromatography (HPLC) with UV or fluorescence detection has been described as an effective approach for quantifying S(-) Metoprolol succinate in plasma. Some of these techniques are difficult to replicate since they require a lengthy process of separation. The goal of this study was to provide a technique for the quantitative measurement of S(-) Metoprolol succinate in low-volume human plasma that was both straightforward and accurate. This technique is also expected to be useful in pharmacokinetic, bioavailability, and bioequivalence investigations of S(-) Metoprolol succinate.

The concentration of S(-) Metoprolol succinate in plasma has been determined using a simple, selective, quick, accurate, and cost-effective reverse phase HPLC approach (Nabil *et al*.,2015).

4.2.1.8.1. Selection of precipitating agent

The solubility of the medicine and the presence of good protein protein precipitation properties inform the choice of precipitation agent. Acetonitrile was chosen as the protein precipitating agent because it is soluble in S (-) metoprolol succinate and has strong protein precipitating ability, as demonstrated in Table 27. (Cesme *et al*.,2011).

4.2.1.8.2. Selection of mobile phase

Multiple mobile phase numbers and ratios were first tested to estimate S (-) Metoprolol succinate. Taking into consideration the system suitability parameter like retention time, tailing factor and theoretical plates, the mobile phase found to be most suitable for analysis was acetonitrile: methanol: 20 mM ammonium acetate buffer (pH 5) in the ratio of 25:55:20 v/v/v. After sonicating the mobile phase to eliminate air pockets, it was filtered through a 0.45-micron filter. Flow rate employed for analysis was 1 mL/min as shown in **Table 26** (Hussain *et al*.,2012).

Table 26. Mobile phase selection in bioanalytical method development.

Mobile phase	Flow rate	Ratio	Outcomes
Water: methanol	1 mL/min	50: 50 % v/v	No peak observed
Water: CAN	1 mL/min	50: 50 % v/v	No peak observed
ACN: methanol	1 mL/min	50: 50 % v/v	No peak observed
20 mM: acetonitrile (pH adjust with 3.50 with OPA)	1 mL/min	30:70 % v/v	No peak observed
Acetonitrile: methanol: 20 mM ammonium acetate buffer (pH 5.0)	1 mL/min	25: 55: 20 % v/v	No peak observed

4.2.1.8.2.1. Procedure for preparation of the mobile phase

Step1. Preparation of buffer

20 mM ammonium acetate Buffer in 100 mL of HPLC grade water, sonicated and pH adjusted to 5 with orthophosphoric acid.

Step2. Preparation of mobile phase

Mixed 55 volume of acetonitrile, 25 volume of methanol and 20 volume of buffer. Filtered through 0.45 nylon filter in Millipore unit and degassed by sonication.

Selection of diluent

The sample preparation diluents employed were fully compatible with the mobile phase, and there was no discernible impact on retention or resolution of the analyte. After various trials acetonitrile: methanol: 20 mM ammonium acetate buffer (pH 5) was used as diluents. (Tabrizi *et al*.,2017)

4.2.1.8.3. Selection of HPLC variable

HPLC variable are important for developing bioanalytical method. HPLC variable include type of column, mobile phase, flow rate, temperature and retention time mentioned in **Table 27**.

Table 27. Chromatographic conditions in bioanalytical method development.

S.No	Name	State
1	Column	C18, 250 mm ×4.60 mm, 5 micron
2.	Mobile phase	Acetonitrile: methanol: 20 mM ammonium acetate buffer (pH 5), 25:55:20 % v/v
3.	Flow rate	1 mL/min
4.	Temperature	30 ℃
5.	Sample	25 µl
6.	Detection wavelength	274 nm
7.	Retention time	9 min

Preparation of stock solution:

Separately, 10 mg of Metoprolol succinate was weighed and transferred to 50 mL volumetric flasks, where it was dissolved in 10 mL of plasma before the remaining volume was brought up to 50 mL with Acetonitrile and vortexed to precipitate all of the plasma protein. After letting it sit for a few minutes, the protein precipitate should have settled, at which point you may collect the supernatant layer. Centrifuge the collected supernatant layer at 6000 rpm for 7 min at 4 ^{o}C and then filtered by whatmann filter paper (no.41). Concentration of MT was 200 µg/mL (Aceves *et al.*,2000)

Preparation of Sub Stock Solution: 5 mL of solution was taken from stock-A and transferred into 100 mL volumetric flask separately and diluted up to 100 mL with diluent (Mobile phase) to give concentration of 10 µg/mL. (Banakar *et al*.,1992)

Linearity and calibration graph

To establish the linearity of analytical method, a series of dilution ranging from 20-100 ng/mL was prepared. 0.20 mL, 0.40 mL, 0.60 mL, 0.80 mL and 1 mL of Stock-B was taken separately in 10 mL volumetric flask and volume was made up to 100mL with (Acetonitrile: methanol: ammonium acetate buffer (pH 5). This gives the solutions of 20 ng/mL, 40 ng/mL, 60 ng/mL, 80 ng/mL, 100 ng/mL for drug. Chromatograms were taken at 274 nm after injecting the filtered solution through a 0.25-micron membrane filter six times. The regression equation was generated using a

calibration curve showing the relationship between the average peak area and the concentrations (Beter *et al.*,1992).

4.2.1.9. Biopharmaceutical evaluation of MUPS tablets of S(-) Metoprolol Succinate

The in vivo study was conducted in accordance with a protocol authorised by the Institutional ethics committee and the standards set out by the 'Committee of Purpose of Control and Supervision of Experiments on Animals (CPCSEA), Ministry of Social Justice and Empowerment, Government of India.As per Protocol no. GDGU/IAEC/2022/04. The in vivo study performed in GD Goenka University, Gurugram, Haryana.The in vivo studies will be conducted on 12 adult healthy male new zealand rabbits weighing 4–4.50 Kg. A normal food will be offered to the rabbits once they have acclimated to the animal house for 1 weeks. Fasting for 24 h before to the experiment, twelve rabbits were split into two groups. The group I will be administered with pure drug solution of S (-) Metoprolol succinate (MS) 25 mg in 5 mL purified water and group II will be administered with prepared Sustained release MUPS tablets equivalent to 25 mg of S(-) Metoprolol succinate tablets. Water to be allowed during fasting and throughout the experiment. Blood samples (1 mL) will be collected carefully from the marginal ear vein by inserting pediatric catheter in rabbits for 24 h and sample to be collected into heparinized centrifuge tubes at 0 h before dosing and then at 0.15, 0.30, 1, 2, 4, 8, 12, 24, 30 and 36 h after administration of the drug formulation/drug solution. The blood samples will be placed in a series of graded centrifuge tubes with 0.40 mL of a sodium citrate solution at a concentration of 2.50 percent by weight. Plasma will be extracted from the samples by centrifuging them at 2500 rpm for 5 minutes. The plasma will be moved to a different set of sample tubes, where it will be frozen until analysis (Sabahuddin *et.al.,* 2011).

One plasma sample (without dose of drug) was kept as blank. A 0.25-m membrane filter (Millipore) was used to filter the sample. Following the HPLC procedure, the MS concentration in the plasma samples was determined. A total 200 µL of plasma sample was mixed with 1 mL of acetonitrile, and then it was centrifuged. The supernatant was evaporated under nitrogen stream, and the residue was dissolved with 300 µL of the HPLC mobile phase, and then it was injected into the column (C-18 ,

250 ×4.6 in 5 micron of HPLC apparatus with UV detector. A mixture of phosphate buffer (pH 3.0, containing 0.50 % triethylamine): methanol: acetonitrile (90:1:9) was used as mobile phase at a flow rate of 1.40mL/min (Chen *et al*.,2014).

4.2.1.9.1. Pharmacokinetic study and statistical analysis

Maximum plasma concentration (C_{max}), duration to achieve maximum concentration (T_{max}), and area under the curve (AUC_0) were determined by applying pharmacokinetic analysis to in vivo study data on plasma concentrations of s (-) Metoprolol succinate at varying times. Cmax and Tmax were calculated by extrapolating the linear portion of the plasma concentration versus time curve for s (-) Metoprolol succinate. The $AUC_{0-\infty}$ was determined by means of trapezoidal rule. The relative bioavailability of S(-) Metoprolol succinate from MUPS tablets in comparison to plain s (-) Metoprolol succinate and marketed SR tablet was calculated by dividing its $AUC_{0-\infty}$ with that of Plain s (-) Metoprolol succinate and marketed formulation (Filippis *et al.*,1995)

4.2.1.10 Stability studies

The stability of optimized formulation was tested according to ICH guidelines Q1A (R2). The MUPS tablets of S(-) Metoprolol succinate was stored at accelerated (40 ± 2 ºC/75 ±5 % RH) condition) in stability chamber The stability studies were performed on 0 , 3 and 6 months. MUPS tablets were tested for physical appearance, hardness, friability, thickness, drug assay and dissolution. (Gohel *et al.*,2002).

4.2.2 Development of novel platform technology for orodispersible tablets of Levocetirizine HCl (Part B)

4.2.2.1: Preformulation studies of Levocetirizine HCl

The first stage in the scientifically sound creation of a medication's dosage form is preformulation research. Preformulation studies are conducted to collect data on medication substances that may be used later in the formulation process. Preformulation is the process of learning about the medicinal substance's physical and chemical qualities, both on its own and in conjunction with excipients. The goal of pre-formulation research is to identify the physical and chemical features and excipients that will have an effect on the final formulation's architecture,

manufacturing process, and pharmacokinetic biopharmaceutical properties. The physical form, solubility, bulk and tapped density, compressibility, melting temperature, pH, and particle size of the bulk medication must be evaluated before it may be formulated into a dosage form.

4.2.2.1.1: Organoleptic properties

Examining appearances by naked eye observation was used to take note of the selected API initial and final visual appearances upon delivery from suppliers and after proper storage (Lachman *et al*., 2009)

4.2.2.1.2: Solubility

Solubility studies are performed to identify the solubility characteristics of drug and selection of the best diluent in which drug suspended or dissolved and to achieve a solution saturation at constant temperature. It is measured in term of part of solute dissolved in volume of solvent. As per IP solubility to be refered.

4.2.2.1.3: Determination of bulk density and tap density

A measured volume (Vo) of powder (W) was put cautiously into the granulating cylinder. A cover was placed on the measuring cylinder. There were to be 500 taps on the densitometer.The bulk volume (Vf) then calculated and the testing rechecked until two consecutive readings were same. Volumetric mass, swept mass were calculated using the **Equation 15** and **Equation 16** (Batheja *et al*.,2019).

$$\text{Bulk Density} = \frac{\text{W}}{Vo} \qquad \textbf{Equation: 15}$$

$$\text{Tapped Density} = \frac{\text{W}}{Vf} \qquad \textbf{Equation: 16}$$

Where, W = weight of the powder V_O = initial volume VF = final volume.

4.2.2.1.4: Compressibility index and hausner's ratio

Powder flow properties may be predicted quickly and easily using the compressibility index or the closely related Hausner's ratio. Using the bulk density and the tapped density of a powder, as given in **Equation 17**.

$$\%\ \text{Compressibilty} = \frac{\text{Pt} - \text{Po}}{Pt} \times 100 \qquad \textbf{Equation: 17}$$

Where, P_t = Tapped density and P_O = Bulk density

Hausner ratio = Tapped density divided by Bulk density.

4.2.2.1.5: Drug identification

a) By FTIR: Weigh about 2 mg of sample in 200 mg of Potassium bromide previously dried at 105°C for 1 h. Carefully grind the mixture and fill in sample cell and measure the spectra between 4000 cm^{-1} to 450 cm^{-1}. Maintain a constant method of working. The peak absorbance value and relative intensity spectra produced with the material under investigation match those of the working standard. There is a relationship between the sample's IR spectrum and the reference spectrum.

b) By HPLC

Inject 20 µL each of Blank, Standard preparation and sample preparation on HPLC, using HPLC condition of Assay and record the retention time of principal peak in HPLC chomatograph.

4.2.2.1.6: UV Spectroscopy: determination of λ max Levocetirizine HCl

Stock: Levocetirizine HCl dissolved distilled water (100 mg in 100 mL)

Scanning: A suitable concentration of Levocetirizine HCL (10 µg/ mL) was prepared in distilled water and UV scan was taken for the above stock solutions between the wavelengths of 200- 400 nm.

4.2.2.1.7: pH

Weigh about 2 g of sample in a 100 mL beaker, add to it 100 mL of distilled water. Stir well to dissolve and check the pH at 25°C.

4.2.2.1.8: Melting point

A solid change into liquid matter at some temperature, that temperature is melting point of particular compound. This is determined in a simple manner using an apparatus known as capillary melting point apparatus. An organic compound which is pure, non-ionic, and crystalline generally has produced a sharp and characteristic melting point with a temperature variation of usually 0.50-1.0° C range. If there are any impurities mixed with compound, then, it will produce a depression or an elevation in the melting point range. So to assess the presence of purity in compound

and to identify the compound itself, the melting point determination of a compound plays a crucial role at preformulation stage. The melting point of the Levocetirizine HCl was determined by introducing a min quantity of it into a small but very narrow capillary tube and attaching the capillary tube to the stem of a thermometer which is center positioned in a melting point apparatus. The equipment temperature was then gradually increased. Triplicate experiments were conducted to record the temperatures at which drug molecules began to melt (Arif *et al.*,2019).

4.2.2.1.9 Loss on drying:

Weigh a glass LOD bottle which is dried and cooled (W1). Transfer to it about 1.0g of sample. Distribute the sample evenly. Cover the LOD bottle with stopper and weigh (W2). Put the LOD bottle in vacuum oven at 60°C under vacuum. Eliminate the stopper and consent it in vacuum oven. Apply the vacuum to oven. After drying is completed, Remove the vacuum and take the sample. Allow it to cool in desiccators and weigh (W3). Again heat the sample for half an h then cool it in a desiccators and weigh. (W4). Continue this procedure until the difference between two consecutive weights should not be more than 0.50 mg. % LOD calucated by using **Equation18.**

Calculations:

$$\% \text{ LOD } = \frac{\text{W2} - \text{W4}}{\text{Weight of Sample in g}} \qquad \textbf{Equation: 18}$$

4.2.2.1.10: Related Substance:

Test solution: Dissolve 20 mg of the substance under examination in 100 mL of mobile phase and filter.

Reference solution (a): A 0.02% w/v solution Levocetirizine HCl mobile phase.

Reference solution (b): Dilute 1 mL of reference solution (a)to 100 mL with mobile phase.

Chromatographic system:

- A stainless steel column 25 cm, 4.60 mm packed with silica gel (5µm).
- Mobile phase: a mixture of 0.40 volume of 5.50 % v/v solution of sulphuric acid, 6.60 volumes of water and 93 volumes of acetonitrile.

- Flow rate: 1 mL per min
- Spectrophotometer set at 230 nm
- Injection volume: 20 µL.

4.2.2.1.11: Drug Assay (By HPLC)

Mobile phase: Acetonitrile, water, and 1 M sulfuric acid.

Standard solution: 0.05 mg/mL of Levocetirizine HCl

RS Mobile phase.

Sample solution: 0.05 mg/mL of Levocetirizine HCl in Mobile phase.

Chromatographic system:

- Column: C-18, 4.60-mm × 25-cm; 5-µm packing L3
- Column temperature: 30 C°
- Flow rate: 1 mL/min
- Injection volume: 20 µL

Samples: Standard solution and Sample solution calculate the % age of Levocetirizine HCl in the portion of Levocetirizine HCl taken:

Result = (rU/rS) × (CS/CU) × 100

Where: rU = peak response of Levocetirizine from the sample Solution.

rS = peak response of Levocetirizine from the Standard Solution.

CS = concentration of USP Levocetirizine HCl releated substance in the Standard solution (mg/mL)

CU = concentration of USP Levocetirizine HCl releated substance in the Sample solution (mg/mL).

Acceptance criteria: 98%–102% on the dried basis.

4.2.2.1.12: Particle size analysis

The main objective of sieve analysis was to test the different size of API particles present. Series of standard sieve were kept one another, so that the mesh with larger mesh size subjugate up position followed by sieve of decreasing trend pore size towards the bottom (Shafer *et al.*,1956). Particle size calculated using **Equation 19.**

Calculation:

$$\% \text{ Passed through mesh} = \frac{\text{Weight of sample in g} - \text{X}}{\text{Weight of Sample in g}} \times 100 \quad \textbf{Equation: 19}$$

4.2.2.2: Development of novel platform technology for orodispersible tablets (ODT).

Levocetirizine hydrochloride fast dissolving tablets were formulated by dry mixing method followed by compression. The formulation contains disintegrants, binder and sweeteners. In all formulations spray dried Mannitol was used as diluents. The Levocetirizine hydrochloride was sifted through 60 #, followed by sifting of remaining excipients through 40 mesh sieve. Sifted material were mixed for 25 mins in octagonal blender followed by addition of magnesium stearate for 5 mins. Bulk and tapped density, angle of repose, compressibility index and hausner ratio, were evaluated for lubricated granules. 10 mm flat surface punches, upper plain and lower plain were used for compressing tablet. Then the compressed tablets were tested for both physical and chemical parameters. (Piplani M *et al*.,2018)

4.2.2.2.1: Effect of superdisintegrants

Disintegrants have an significant role in the preparation of orodispersible formulation. Different superdisintegrants in varying concentration such as crospovidone (5-15 %), Croscarmellose sodium (5-15 %) and L-HPC (2-6 %) were screened. Tablet wetting time and dispersion time were evaluated and based on results as shown in **Table 28** the selection of superintendent was done (Sajal *et al.*,2018).

Table 28. Effect of Superdisintegrants

Ingredients (Qty in mg)	PT1	PT2	PT3	PT4	PT5	PT6	PT7	PT8	PT9	PT10
Levocetirizine hydrochloride	10	10	10	10	10	10	10	10	10	10
Mannitol	Qs	Qs	Qs	Qs	qs	qs	Qs	qs	qs	Qs
Crospovidone (XL)	5	10	15	---	---	---	---	---	---	15
Croscarmellose Sodium	---	---	---	5	10	15	---	---	---	---
L-HPC (LH-11)	---	---	---	---	---		2	4	6	6
PVP K-30	1	1	1	1	1	1	1	1	1	1
Mg stearate	20	20	20	20	20	200	2	20	20	20
Total (mg)	100	100	100	100	100	100	100	100	100	100

4.2.2.2.2: Effect of binder

Binder helps in the preparation of the tablet. Binder prevents weight variation, segregation of powder particles during manufacturing and provides good compressibility with improved hardness. Different binder such as starch, HPMC and povidone are available in the market. Based on the extensive literature survey povidone was screened and used in formulation by varying concentration. Different trial was conducted as shown in **Table 29** by varying concentration of povidone (0.50-2%). The prepared formulation was tested for thickness, tensile strength, % friability and disintegration (in sec) and wetting time (Vegad *et al.*,2013).

Table 29. Effect of various concentration of binders

Ingredients (Qty in mg)	PT11	PT12	PT13	PT14
Levocetirizine hydrochloride	10	10	10	10
Mannitol (Perlitol SD 200) spray dried	qs to 100	qs to 100	qs to 100	qs to 100
Crospovidone (polyplasdone XL)	15	15	15	15
L- Hydroxypropyl cellulose (LH – 11)	6	6	6	6
Povidone (PVP K-30)	0.50	1	1.50	2
Magnesium stearate	2	2	2	2
Total weight of tablet (in mg)	100	100	100	100

4.2.2.2.3: Effect of sweeteners

Taste masking is very much required to hide the sour taste of orodispersible formulation. Taste masking can be achieved by using suitable sweeteners. Different sweeteners in varying concentration such as such as sucralose (3 %), sodium saccharin (3 %) and aspartame (3 %) were screened as shown in **Table 30** and tested for all physical and chemical parameter (Pankaj *et al.*,2010).

Table 30 Effect of various concentration of sweeteners

Ingredients (Qty in mg)	PT15	PT16	PT17
Levocetirizine HCL	10	10	10
Mannitol (Perlitol SD 200) spray dried	Qs	qs	qs
L Hydroxypropyl cellulose (LH -11)	6	6	6
Crospovidone (polyplasdone XL)	15	15	15
Sucralose	----	----	3
Ingredients (Qty in mg)	**PT15**	**PT16**	**PT17**
Sodium saccharin	3	---	---
Aspartame	---	3	---
Povidone (PVP K-30)	1	1	1
Color sunset yellow supra FCF	0.20	0.20	0.20
Orange flavour	4	4	4
Magnesium stearate	2	2	2
Total in mg	100	100	100

4.2.2.3: Characterization of Levocetirizine HCl

For any API to formulate into an oral dosage form, it is essential to study the physical and chemical properties of the bulk drug (Srikanth *et al*,2015).

4.2.2.3.1: Micrometrics

4.2.2.3.1.1: Angle of repose

Powder flow characteristics of the powder were evaluated using angle of repose test. The powder was added into the funnel and height of the funnel was adjusted so that the powder flow freely to the surface. Angle of repose measuring by taking height and diameter half value of the powder (Sreejan *et al.*,2017).

4.2.2.3.1.2: Determination of bulk density and tap density

Weigh accurately lubricated blend (L) and add it to the measuring cylinder. Visually measure the intial powder volume (VI). Measuring cylinder was kept on the bulk and tapped density equipment. Set the tapped value for 500 taps. Measure the last measured volume (VF) of the powder after 500 tapping.The determination was carried out in triplicate using **Equation 20** and **Equation 21.**

$$\text{Bulk density} = \frac{L}{V1} \qquad \textbf{Equation :20}$$

$$\text{Tapped. density} = \frac{L}{VF} \qquad \textbf{Equation :21}$$

L = Intial weight of the powder V_I = Initial volume V_F = Final measured volume.

4.2.2.3.1.3: Hausner ratio and Compressibility index

HI ratio and CI index are accurate and most popular method for determining flow properties. Bulk and tapped density determination required for the calculation. All the calculation to be done in triplicate to minimize calculation errors. (Suresh *et al*.,2010)

HI ratio = Tapped density divided by bulk density.

Compressibility Index= (Tapped Density – Bulk density / Tapped density) x 100.

Direct compression to be used to prepare MUPS tablets. Some cushioning agents were made by combining MCC PH 102, MCC PH 200, Aerosil, sodium stearyl fumarate, and lubritab. White to off-white tablets having standard weight with a 250 mg dose, 3.60 ± 0.40 mm thickness, hardness: NLT 3 kg/cm^2, turret speed: 12-30 rpm, force feeder: 12-20 rpm, and hydraulic pressure: NLT 15 pounds are the parameters for compressing a lubricated MUPS blend in a single rotary compression machine (Raja *et al.*,2010).

4.2.2.3.2: Post compression evaluation

4.2.2.3.2.1: Appearance

Physical appearance of the tablet is an important characteristics to evaluate cracks, depressions and pinholes. Tablets thickness was measured using autotester and was measured in mm.

4.2.2.3.2.2: Hardness

Tablets hardness is an important aspect in orodispersible tablets. A standard amount of hardness is required to withheld vibrations and mechanical disturbances. Autotester was used to measure the hardness and value expressed in Kg/cm^2.

4.2.2.3.2.3: Friability

Roche friabilator was used to determine the friability of the tablets. Weight 6.50 g of tablets (Initial) and transferred it into the apparatus. Set the friabilator at 25 RPM for 4 min . After completion of the operation reweight the tablets (Final). Caluate the % Friability by using the formula.

% Friability of the Tablets = Intial weight– Final weight/ Intial Weight x 100 %

4.2.2.3.2.4: Disintegration test

In vito disintegration time of the formulation calculated using disintegration test equipment. In each six tubes of the basket place individual tablet with disc. Run the apparatus at temperature 37 C°± 2 °C with purified water. Visually record the time with no mass remaining on the mesh.

4.2.2.3.2.5: Wetting time

Wetting time is closely related to the inner structure of the tablets and to the hydrophilicity of the excipient. According to the following equation proposed by Washburn E.W (1921), the water penetration rate into the powder bed is proportional to the pore radius and is affected by the hydrophilicity of the powders. $dl/dt = r\Upsilon \cos\theta/(4\eta)$. (Force Tanciometer)

Where l is the length of penetration, r is the capillary radius, Υ is the surface tension, η is the liquid viscosity, t is the time, and θ is the contact angle. It is obvious that pores size becomes smaller and wetting time increases with an increase in compression force or a decrease in porosity. A linear relationship exists between wetting time and disintegration time. Thus wetting is the important step for disintegration process to take place.

In perti plate place a piece of folded tissue paper. Add 10 mL of water in it. Place one tablet on the wetted tissue paper and record complete wetting of the tablet. Perform the activity thee times and standard deviation was also determined.

4.2.2.3.2.6: Estimation of drug content

Weight and powdered the 20 tablets. Take 10 mg equivalent powder and add it to 100 mL mobile phase, filter and analyze for Levocetirizine HCl content at 231 nm. The drug content lies between 90-110 % of the specification.

4.2.2.3.2.7: Dissolution test

a) The dissolution test of orodispersible tablets accomplished using USP type II dissolution testing apparatus. pH 6.80 and 900 mL buffer used. Temperature 37°C ±0.50°C maintained and sample was collected after 5 min. Drug concentration was measured at 231 nm (Andrei *et al*.,2010).

b) In-vitro release studies were carried out using IP apparatus type I (Paddle type) in 900ml 6.8pH simulated salivary fluid as dissolution media at speed of 75rpm and temperature 37±0.5°c. 5ml of the of samples were withdrawn at 5, 10, 15 and 30, minutes time interval and replaced with fresh dissolution media at same time. Samples were analyzed at 231 nm in triplicates using UV spectrophotometer against simulated salivary fluid as blank. The Simulated salivary fluid was prepared by dissolving 13.87 g of Potassium dihydrogen phosphate and 35.08 g of disodium hydrogen phosphate in a sufficient amount of water to produce a final volume of 1000ml with a final pH of 6.8 to mimic the salivary fluid (Girish *et.al.*,2018).

4.2.2.4: Comparative dissolution profile (CDP) of Levocetirizine HCl tablets

4.2.2.4.1: Comparison of dissolution profile

CDP was performed on thee different dissolution mediums on two different batches as shown in **Table 31.**

The result of dissolution profile should be presented as below :

A) Demonstration of similarity factor between marketed sample and test sample.

Table 31. Product information Market Sample and Test Sample

Sample	Product	Batch No.
Marketed sample	**Levocetirizine HCl (Liecet MD)**	SKU1373
Test Sample	**Levocetirizine HCl**	ADU0811

CDP:

Prerequisites:

CDP of test product (Trial) and reference product (Marketed Product) is tested in following dissolution medium.

a) 500 mL of 0.10 N HCl

b) 500 mL, pH 4.50 acetate buffer

c) 500 mL, pH 6.80 phosphate buffer

Dissolution:

Methodology:

Not less than 70 % (Q) of the labeled amount of Levocetirizine HCl is dissolved in 30 min.

For S1 level each unit is not less than 75 %.

For S2 level average of 12 units (S1+S2) is equal to or greater than 70 % and no unit is less than 55 %.

For S3 level average of 24 units (S1+S2+S3) is equal to or greater than 70 % not more than 2 units are less

than 55 % and no unit is less than 45 %.

4.2.2.4.2. Dissolution medium: 500 mL of 0.1 N HCl

Apparatus:

Dissolution apparatus, HPLC, pH meter, Balance

Reagents :

Hydrochloric acid, Water

Preparation of dissolution medium: Dissolve 8.60 mL of Hydrochloric acid in 1000 mL of HPLC grade water. Dissolution conditions mentioned in **Table 32.**

Table 32. CDP of Levocetrizine tablets (Test vs Marketed) in 0.1 N HCl

Use a suitable equipement with following conditions**:**

Parameter	Test conditions
Dissolution medium	0.1 N HCl
Type of apparatus	USP Grade Type-II (paddle)
Volume	500 mL
Speed of paddle	50 RPM
Temperature of the bowl	37 °C ± 1 °C
Interval	5, 10, 15, 20 and 30 min

Dissolution procedure: (Sample solutions) :

Set dissolution apparatus as described above. Add specified volume of dissolution media in to each vessel. Start the apparatus while each vessel attain temperature 37 ±

0.50 ºC. Weigh and place one tablet into each vessel and withdraw about 10 mL of the substrate at the end of mentioned time from each vessel and filter each solution through 0.45 µm filter (Not more then 1 µm porosity) [10 ppm] **(**Jayalakshmi *et al.*,2012).

Standard preparation:

Weigh accurately about 40 mg of Levocetirizine hydrochloride WS in 100 mL volumetric flask. Add 70 mL of methanol and sonicate it to dissolve. Cool and dilute to volume and mix. Dilute 5 mL of standard solution to 200 mL dissolution medium and mix it properly [10 ppm].

Procedure:

Check the absorbance of standard solution and each substrate (Sample subunit) solutions at 280 nm against dissolution media as blank using suitable HPLC.

4.2.2.4.3. Dissolution medium: 500 mL, pH 4.50 acetate buffer

Apparatus:

Dissolution apparatus, HPLC, pH meter, Balance

Reagents :

Sodium acetate trihydrate, GLA (Glacial Acetic acid), Water

Acetate buffer solution, pH 4.5:

Add 2.9 g of Sodium acetate trihydrate in 1000 mL of HPLC grade water. Adjust its pH of resulting media to 4.5 by the help of glacial acetic acid. Dissolution conditions mentioned in **Table 33.**

Table 33. CDP of Levocetrizine tablets (Test vs Marketed) in acetate buffer pH 4.5

Parameter	Test condition
Dissolution medium	Acetate buffer pH 4.5
Apparatus	USP Type-II (Paddle)
Volume	500 mL
Speed	50 rpm
Temperature	37 ± 0.5°C
Time interval	5, 10, 15, 20 and 30 min

Dissolution procedure: (Sample solutions)

Set dissolution apparatus as described above. Add specified volume of dissolution media in to each vessel. Start the apparatus while each vessel attain temperature 37 ± 0.5 ºC. Weigh and place one tablet into each vessel and withdraw about 10 mL of the sample kept at the end of mentioned time from each vessel and filter each solution through 0.45 µm filter (Not more than 1 µm porosity) **[10 ppm] (**Pothu *et al*.,2015)

Standard preparation:

Weigh accurately about 40 mg of Levocetirizine Hydrochloride working standard in a 100 mL volumetric glass. Add 70 mL of methanol and sonicatation to dissolve. Cool and diluted it to volume and mix it properly. Dilute 5 mL of this solution to 200 mL with dissolution medium and mix **[10 ppm].**

Procedure:

Measure results using HPLC method.

4.2.2.4.4. Dissolution medium: 500 mL pH 6.80 phosphate buffer

Apparatus:

HPLC, pH meter, Balance

Reagents:

Potassium dihydrogen phosphate, Potassium hydroxide

Potassium phosphate buffer pH 6.8 :

Dissolve 6.80 g of Potassium dihydrogen phosphate and 1.0 g of Sodium hydroxide in sufficient water to produce 1000 mL. Adjust the pH of resulting solution to 6.8 with dilute sodium hydroxide.Dissolution conditions mentioned in **Table 34.**

Table 34 CDP of Levocetrizine tablets (Test vs Marketed) in phosphate buffer pH 6.8

Parameter	**Test conditions**
Dissolution media	Phosphate buffer 6.8 pH
Type of apparatus	USP grade Type-II (paddle)
Media volume	500 mL
Speed	50 rpm
Temperature of the media	37°C ± 0.50°C
Interval	5, 10, 15, 20 and 30 min

Dissolution procedure: (Sample solutions) :

Set dissolution apparatus as described above. Add specified volume of dissolution media in to each vessel. Start the apparatus while each vessel attain temperature 37 ± 0.50 ºC. Weigh and place one tablet into each vessel and withdraw about 10 mL of the sample at the end of mentioned time from each vessel and filter each solution through 0.45 µm filter (Not more then 1 µm porosity)[10 ppm] (Hina *et al*.,2017).

Standard preparation:

Weigh accurately about 40 mg of Levocetirizine HCl WS in a 100 mL volumetric glass. Add about 70 mL of methanol and sonicate it to dissolve. Cool and dilute it to required volume and mix. Dilute 5 mL of this solution to 200 mL with dissolution medium and mix [10 ppm].

Procedure:

Check the absorbance of standard and each sample solutions 280 nm against dissolution media w.r.t blank using suitable UV spectrophotometer.

Calculations (common for all 3 medium) :

The amount of Levocetirizine Hydrochloride (X) dissolved in 5, 10, 15, 20, 30 and 45 min measured by formula mentioned in **Equation 22-26.**

1. At 5 min

$$X = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{5}{200} \times \frac{500}{1(\text{Unit})} \times \frac{P}{LC} \qquad \textbf{Equation: 22}$$

2. At 10 min

$$X = \frac{AT}{AS} \times \frac{WS}{100} \times \frac{5}{200} \times \frac{500}{1(\text{Unit})} \times \frac{P}{LC} + C1 \qquad \textbf{Equation: 23}$$

$$C1 = (R \times \frac{VW}{VM})$$

Where,

C1 = Correction factor for 10 min.

R = % drug release at the end of 5 min.

VW = Volume withdrawn at the end of 5 min.

VM = Volume of medium

3. At 15 min

$$\mathrm{X} = \frac{\mathrm{AT}}{\mathrm{AS}} \times \frac{\mathrm{WS}}{100} \times \frac{5}{200} \times \frac{500}{1(\ \mathrm{Unit})} \times \frac{\mathrm{P}}{\mathrm{LC}} + \mathrm{C2} \qquad \textbf{Equation: 24}$$

$$C2 = (R \times \frac{VW}{VM})$$

Where,

C2 = Correction factor for 15 min.

R = % drug release at the end of 10 min.

VW = Volume withdrawn at the end of 10 min.

VM = Volume of medium

4. At 20 min

$$\mathrm{X} = \frac{\mathrm{AT}}{\mathrm{AS}} \times \frac{\mathrm{WS}}{100} \times \frac{5}{200} \times \frac{500}{1(\ \mathrm{Unit})} \times \frac{\mathrm{P}}{\mathrm{LC}} + \mathrm{C3} \qquad \textbf{Equation: 25}$$

$$C3 = (R \times \frac{VW}{VM})$$

Where,

C3 = Correction factor for 20 min.

R = % drug release at the end of 15 min.

VW = Volume withdrawn at the end of 15 min.

VM = Volume of medium

5. At 30 min

$$\mathrm{X} = \frac{\mathrm{AT}}{\mathrm{AS}} \times \frac{\mathrm{WS}}{100} \times \frac{5}{200} \times \frac{500}{1(\ \mathrm{Unit})} \times \frac{\mathrm{P}}{\mathrm{LC}} + \mathrm{C4} \qquad \textbf{Equation: 26}$$

$$C4 = (R \times \frac{VW}{VM})$$

Where,

C4 = Correction factor for 30 min.

R = % drug release at the end of 20 min.

VW = Volume withdrawn at the end of 20 min.

VM = Volume of medium

Following abbreviations are common in all the calculation types :-

AT = Absorbance of Levocetirizine HCl in test sample

AS = Absorbance of Levocetirizine HCl in standard preparation

WS = Weight of Levocetirizine HCl WS in mg

P = % age purity of Levocetirizine HCl WS (as is basis)

LC = Label claim of Levocetirizine HCl (5 mg/tablet)

4.2.2.4.5. Acceptance criteria

F_2 Value calculation:- The F2 test is a statistical test used to compare dissolution profiles. When the drug released more than 85 % within 15 min, then the test and reference profiles can be considered similar without further statistical evaluation.

If dissolution takes more than 15 min, then the statistical tests F_2 must be calculated to show that the two dissolution profiles are equivalent or similar. The F_2 is a similarity function over the full profile. Acceptance criteria for F_2 value must be between 50 to 100 (Laxman *et al*.,2014).

F2 = Between 50 and 100 the two dissolution profile are similar.

Similarity factor (F_2) is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the % (%) mean dissolution between the two profiles. F_2 measured by using **Equation 27**.

$$F2 = 50 \bullet \log \{[\, 1 + (1/n)\Sigma_{t=1}^{n} (R_t - T_t)^2 \,]^{-0.5} \bullet 100\} \qquad \textbf{Equation:27}$$

Where

n= Number of time points

∑= Summation of overall time points

R_t = Dissolution value of the reference batch at time t

T_t = Dissolution value of the test batch at time t

4.2.2.5. Bioanalytical method development

For the quantitative determination of Levocetirizine HCl in rabbit plasma and the proposed tablet dosage form, a straightforward, quick, selective, exact, validated, and sensitive reverse phase HPLC technique was devised. Many iterations of a modern, rapid, and sensitive assay for the determination of Levocetirizine HCl in rabbit plasma were conducted. The developed procedure was evaluated and validated according to ICH guidelines in order to gauge its validity and potential value.

4.2.2.5.1. Chromatographic conditions

Mobile phase components included a pH 5.0 ammonium acetate buffer (20 M), 25 % methanol, 50 % acetonitrile, and 5 % acetonitrile, respectively, for chromatographic analysis. A 0.45 membrane filter was used to filter the mobile phase, and sonication was used to get rid of any remaining bubbles. At room temperature, the prepared mobile phase was pumped isocratically at a flow rate of 1 mL/min. Eluent was monitored at 232 nm on a Thermo C-18 column (4.60 x 250 mm, 5-micron particle size), and the run time was 10 min.

4.2.2.5.2. Selection of mobile phase

System suitability parameter like RT, tailing factor, theoretical plates and HETP, the mobile phase found to be most suitable for analysis of Levocetirizine HCl was acetonitrile: methanol: 20 mM ammonium acetate buffer (pH 5) in the ratio of 25:55:20 v/v/v. The mobile phase was filtered through 0.45µ filter paper to remove particulate matter and then degassed by sonication. Flow rate employed for analysis was 1 mL/min (Deepak *et al.*,2011).

4.2.2.5.3. Preparation of standard stock solution

Perfectly weigh and add 10 mg of Levocetirizine HCl working standard into 50 mL dry and cleaned volumetric flask. Add 40 mL quantity of diluents (mobile phase) and perform sonication to dissolve it completely. Visually inspection to be done. Make volume up to the mark of volumetric flask with same solvent (stock solution). Further pipette out 5 mL of above stock solution in to a 10 mL VF and dilute it upto the mark with remaining diluents. Further pipette 0.20 to 1 mL of remaining stock solution into

a 10 mL VS and dilute up to the mark with the diluents. This gives the solutions of 2-10 µg/mL for drug (Ashok *et al.*,2011).

4.2.2.5.4. Extraction of blank plasma liquid

Take 1 mL of plasma, 4 mL of acetonitrile was added; then solution was mixed thoroughly with shaker and left to stand still for 10 min at normal room temperature. After 10 min the solution was centrifuged at 15000 rpm for 15 min at 5 °C. The clear transparent supernatant liquid was cleaned off, filtered the solution through 0.22 µ syringe filter and injected directly into HPLC system (Bhaskaran *et al*.,2002).

4.2.2.5.5. Standard plasma stock solution preparation

To formulate calibration standards and quality control testing samples, suitable known quantities of the numerous diluted standard solutions add to blank plasma to obtain drugs in the concentrations varies from of 2-10 µg/mL for Levocetirizine HCl. Samples were stored at 20 °C and 20 µL volume of each sample was injected and analyzed (Nettis *et al.*,2009).

4.2.2.5.6 % Drug assay

To measure the amount of the drug in the developed formulations, twenty number of marketed tablets of Licet MD, R Dimex, India Ltd. were taken weighed and ground to a fine powder in mortar pestle; amount equal to 5 mg of Levocetirizine HCl was taken in 50 mL VF before 50 mL diluents was added. The content of the flask was shaken for about 60 min in flash shaker instrument. This obtained solution was filtered through whatman filter paper to separate out the residual which are insoluble in nature, and further dilutions were carried out to obtain the required concentration. Final prepared solutions were filtered through a 0.45-µm Millipore filter before analysis of same from the HPLC to prevent blockage and results error (Alexander *et al.*,2014).

4.2.2.6: Biopharmaceutical evaluation of orodispersible tablets of Levocetirizine HCl

The investigations will compare the pharmacokinetic properties of orally administered Levocetirizine HCl to those of a test formulation of orodispersible tablets. In order to

quantitatively compare the pharmacokinetic profile of a produced trial to that of a reference drug solution, pharmacokinetic investigations in rabbits are essential. It was previously reported that male New Zealand rabbits have been employed frequently in pharmacokinetic investigations of ODTs, and this is because of their small size and high reproductive rate. Tablet formulations are feasible for administration in these patients because of their big size and relatively long oesophagus, allowing for several blood samples to be taken at varying intervals. Furthermore, while doing in vivo pharmacokinetic investigations, several publications have found that rabbits provide an excellent statistical association between *in-vitro*drug release and *in-vivo %* age drug absorption from the formulation.

A novel medicine's pharmacokinetic profile cannot be completed without analysing the concentration of the drug in plasma as a function of time. Only with the help of suitable animal models we can obtain quantitative data on medication absorption and excretion kinetics in real time. Due to their larger size compared to rats, rabbits have been frequently utilized as a viable animal model for pharmacokinetic investigations. This is because many blood samples can be taken at different time intervals, and the formulation can be easily administered thanks to the rabbits' big oesophagus. The dispersible tablet has a diameter of around 8 mm, making it tricky to provide to tiny animals (Aljimaee *et.al.,* 2015).

In the pharmaceutical sciences, rabbits are frequently used as an appropriate model for the oral administration of the planned formulation, followed by blood sampling at regular intervals to evaluate the pharmacokinetic parameters associated with the formulation.

Protocols for animal experiments were approved by an institutional ethics committee and carried out in accordance with the guidelines established by the "Committee for the Purpose of Control and Supervision of experiments on Animals (CPCSEA)," Ministry of Social Justice and Empowerment, Government of India. Protocol number: GDGU/IAEC/2022/04. The animal study was performed in GD Goenka University Gurugram, Haryana.Twelve New Zealand rabbits weighing 4-4.50 Kg were used in the experiment. During their 1.50 weeks in animal house, rabbits will be fed a conventional diet and given supplemental heat to help them adapt. In preparation for

the experiment, twelve rabbits will be split into two groups, and each will fast for 24 h. Group-I will get 10 mg of Levocetirizine HCl in 5 mL of purified water (PW) (a pure solution), while Group-II will receive orodispersible tablets equivalent to 10 mg of Levocetirizine HCl. Fasting done and animals will be able to drink water throughout the study. Carefully inserting a paediatric catheter into the marginal ear of vein, 1 mL plasma blood samples will be taken. In heparinized added centrifuged tubes, blood samples were taken at 0 min before sample dose, 15, 30, 40 and 90 min following dosing 2, 4, 8, 12 and 24 h afterwards. The total amount of blood extracted from a rabbit's ear will not significantly exceed the maximum safe blood collecting limit, which is between 6.50 and 7.50 mL/kg of body weight. It is a standard practise to collect blood samples in centrifuge tubes containing 0.40 mL of a 2.60 % w/v citrate based solution. Collecting plasma samples required centrifugation at 3000 rpm for 10 min to separate the plasma liquid. The plasma will be transported to a new set of test tubes, where it will be frozen until analysis.

In order to maintain a baseline, a collection of plasma blood samples was taken with no dosage. The samples were filtered via a 0.25 m nylon filter (Millipore). The following high performance liquid chromatographic method was used to analyse the concentration of Levocetirizine hydrochloride in human plasma samples. 200 µL of liquid plasma sample was combined with 1.0 mL of ACN and centrifuged for 15 mins at 3000 rpm from the entire obtained sample. Evaporating the above volatile sample with a stream of nitrogen and heat, the residue was dissolved in 300 µL of high performance liquid chromatographic method mobile phase, and samples were injected into on a Thermo C-18 column (4.60 × 250 mm, 5 micron, HPLC instrument equipped with an internal UV detector. During the experiments, a mobile phase consisting of phosphate buffer (Acetonitrile: methanol: 20 mM ammonium acetate buffer (pH 5.0) in a ratio of 25: 55: 20 v/v/v/) was used at a flow rate of 1 mL/min (Devi *et al.*, 2013).

4.2.2.6.1. Pharmacokinetic studies in rabbits and its analysis

Levocetirizine HCl plasma drug concentration data at different time points obtained from the rabbits were imperiled to pharmacokinetic examination to calculate numerous parameters such as peak plasma drug concentration (C_{max}), time to peak

concentration (T_{max}) and area under the curve ($AUC_{0-\infty}$). C_{max} and T_{max} values were directly taken from the graph of plasma drug concentration of Levocetirizine HCl vs. time (Stops *et al.*,2008).

4.2.2.7: Stability studies:

The stability of optimized formulation was tested according to ICH guidelines Q1A(R2). The orodispersible tablets of Levocetirizine Hydrochloride was stored at accelerated (40 ± 2 ºC/75 ±5 % RH) condition in stability chamber. The stability studies were performed on 0, 3 and 6 months. Tablets were tested for physical appearance, assay and dissolution (Kulkarni *et al*.,2001).

CHAPTER 5

Results and Discussion

5.1 Development and evaluation of Wurster processed extended-release platform technology for MUPS tablet of S (-) Metoprolol succinate (Part A)

5.1.1. Preformulation study

5.1.1.1. Organoleptic properties:

S(-) Metoprolol succinate was observed as white, crystalline powder.

5.1.1.2. Solubility of drug:

S (-) Metoprolol succinate was freely soluble in purified water. It is soluble in methanol and buffer i.e phosphate buffer pH 6.80 and 0.10 N HCl. Solubility of S (-) Metoprolol succinate declines as pH increases. The pH of distilled water is 7.0. The different pH solution was prepared by using of 0.1 N HCl, Acetate buffer, phosphate buffer etc. (Jarannath *et.al*,2013). S (-) Metoprolol succinate is BCS class I category drug. In BCS class I category drug is having high solubility and high permeability. S (-) Metoprolol succinate is having good solubility and permeability as shown in **Table 35** (IP-2022).

Table 35. Solubility of S (-) Metoprolol succinate

S.No	pH	Concentration (mg/mL) (n=3)	Observations
1	1.20	99 ± 0.19	Soluble
2	2	95.16 ± 0.18	Soluble
3	4.50	94.15 ± 0.21	Soluble
4	6.80	93.05 ± 0.15	Soluble
5	7.20	90.12 ± 0.23	Soluble
6	7.40	86.22 ± 0.23	Soluble
7	7.80	82.15 ± 0.13	Soluble
8	Distilled water	159 ± 0.18	Freely soluble
9	Methanol	97.14 ± 0.18	Soluble

5.1.1.3. Determination of bulk density and tap density

The bulk density and tapped density are important aspects of the material. Bulk and tapped density interferences with the occupancy of the equipment. Bulk density is the ratio of the untapped weight of the powder and volume. Bulk density contributes to void volume (particles to particles). The tapped density is the ratio of the tapped weight of the powder for a definite period and volume of powders tapped. It contributes to an increase in bulk density, powder cohesiveness and powder flow property. The bulk and tapped density of the Metoprolol succinate were found to be 0.37 ±0.02 and 0.52 ±0.03 g/mL, respectively (Salve, *et al.*,2021).

5.1.1.4. Compressibility index and Hausner's ratio

The Carr Compressibility Index (CI Index) and Hausner Ratio (H) were used to measuring a property of powder and measure of interparticulate friction of the powder to be compressed. It also reflects the importance of the interaction of interparticle material. These interactions are usually less important for a free-flowing powder, for which the bulk and tapped densities will be proportional to each other. Less flowing materials are characterized by the occurrence of larger interparticle interactions, which contributes in significantly difference between bulk and tapped densities. The CI of S(-) metoprolol succinate is approx. 31 ± 0.33 % , which reflects powder poor flow properties as shown in **Table 36.** The H for S (-) metoprolol succinate was found to be 1.43 ± 0.08, which also reflects poor powder property (Salve, *et al.*,2021).

Table 36. Compressibility Index and Hausner's Ratio

Parameter	Compressibility index (CI) in %	Hausner's ratio (H)
Observed	31 ± 0.33	1.43 ± 0.08

5.1.1.5. Drug identification

5.1.1.5.1. Fourier transform infrared (FTIR)

Metoprolol succinate has several significant peaks **(Figure 6)** the peak at 1240 cm^{-1} is symbolic of the bridging of the two different ring in systems *viz.*, both pyrazolopyrimidine and piperazine ring presence of band in spectra are crucial as it

confirms that the two ring in the systems are attached. Another crucial peak is the broad band found in the IR spectrum that appears at a wave number of 1581 cm^{-1} and is attributed to the C=O functional group situated on the pyrazole ring system.

The band observed at 3650 cm^{-1} represents NH symmetric and asymmetric stretching in the structure. The enlargement of peaks in the range 3650-2710 cm^{-1} is mainly due to the presence of hydrogen bonds in the complex of citrate. The three important peaks observed in this range are 3650 cm^{-1}, 2321 cm^{-1} and 2870 cm^{-1} and are attributed to the =C-H aromatic, CH3 asymmetric and CH3 symmetric vibrations present in the molecule (Okunlola, A, *et al.*,2020). The S (-) Metoprolol succinate was studied using X-ray diffractometer (PW 1729, Philips, Finland). The diffraction pattern of Metoprolol succinate shows different peaks at 2 Ø = 8.05, 12.82, 14.10, 16.20, 19.42, 24.23, 26.20 as shown in **Figure 9**. The peaks data indicate that S (-) Metoprolol succinate is crystalline in nature. (Wasekar, N., *et al*,2022)

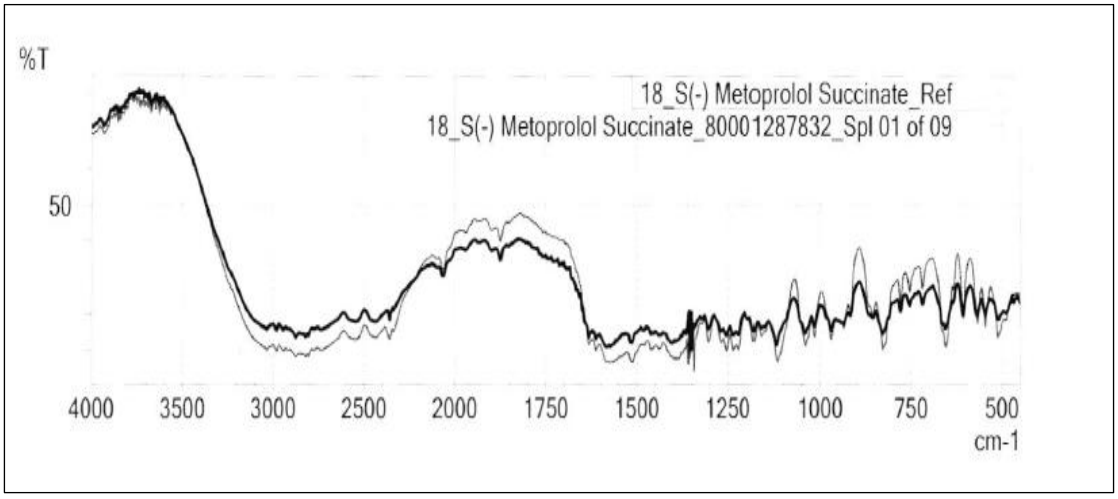

Figure 6. Infrared absorption spectrum of S (-) Metoprolol succinate

The frequencies (absorption band) used for the interpretation of IR spectra are listed in **Table 37.**

Table 37. Frequency and functional group assignment for MS

Wave number (cm^{-1})	Assignment (s)
3650-2321	Aromatic CH and-OH Aliphatic, NH2
1585	R-COOH (Carboxylic acid)
1581, 1520	C_6H6 (Aromatic ring)
1240, 1012	H-O-H (Aromatic ring)
1101	Aliphatic-ether
850	1,4- benzene ring

5.1.1.5.2: By HPLC

The identification of the S(-) Metoprolol done using HPLC method. Mobile Phase was used in combination of buffer: glacial acetic acid: triethylamine: phosphoric acid: acetonitrile (810: 10: 2: 3: 146), for buffer, weigh about 3.90 g of ammonium acetate in 810 mL water. Conditions for Chromatographic Column: Inertsil ODS - 3, 250 mm x 4.6 mm, 5 micron or equivalent. Flow rate was 1.50 mL/min, wavelength: 280 nm, run time was 30 min, inject 20 µl each of blank, standard preparation and sample preparation on HPLC, using HPLC condition of assay and record the retention time of the principal peak in HPLC chomatograph. The retention time of the metoprolol Standard: is 14.08 min. The retention time of the metoprolol sample: 14.08 min. Both sample and the standard preparation retention time match (Phale, M. D., *et al*, 2009).

5.1.1.6. By UV spectrophotometer

UV is important method used for the identification of the drug molecule. An ultraviolet spectrum, generated using a UV-1601 UV Visible Spectrometer (Shimadzu Corporation). The λ max of S(-) metoprolol succinate in 6.80 pH phosphate buffer was found at 275 nm shown in **Figure.7** The observed value is closer to mentioned in the literature (Patel, D. M.,*et al*,2019), (Jagannath., et.al,2013)

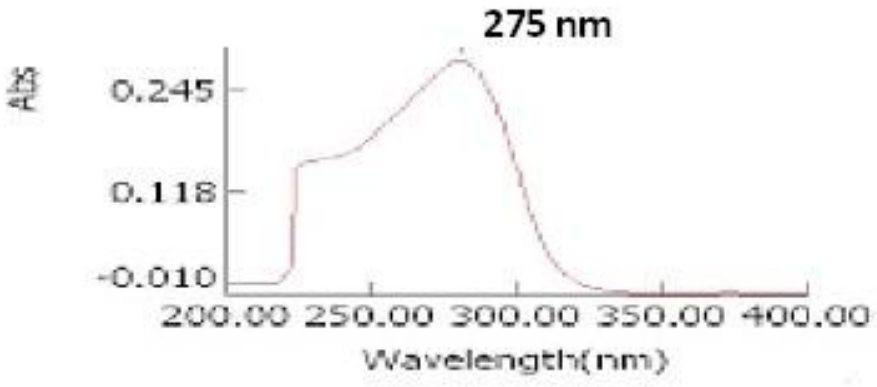

Figure 7. Ultraviolet absorption spectrum of S (-) Metoprolol succinate

5.1.1.7. Melting point determination

a) The melting point of S (-) Metoprolol was determined by capillary method. The melting point of S (-) Metoprolol was determined by capillary method. The melting point observed is 122.50 °C ±0.51 °C which is closer with the standard. i.e 120 °C (PubChem).

b) The DSC thermogram for MS has a melting endotherm peak at 121.54°C shown in **Figure 8.** Melting point also confirm the identification of the drug molecule (Patil, A.,*et al*,2022). It can concluded that the bulk drug is pure in nature and to be used for formulation development purpose.

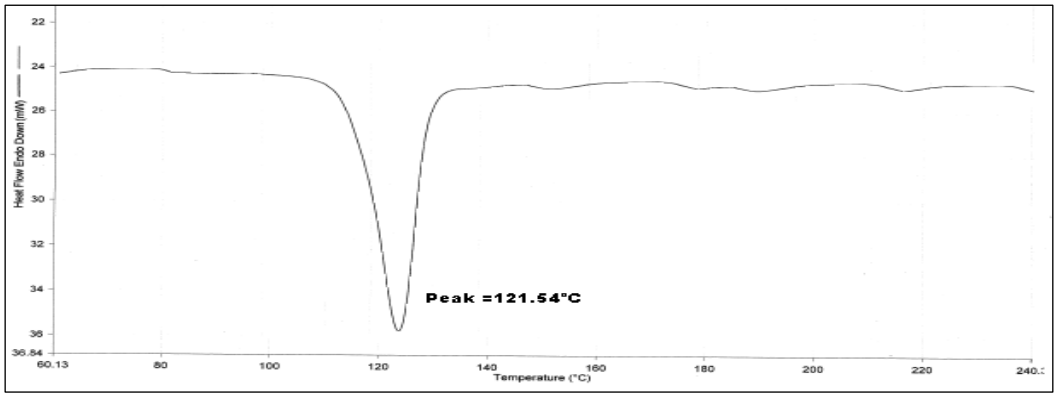

Figure 8. DSC thermogram of S (-) Metoprolol succinate

5.1.1.8. Powder X-Ray diffractometry (PXRD)

The S (-) Metoprolol succinate was studied using X-ray diffractometer (PW 1729, Philips, Finland). The current and voltage applied were 34 mA and 36 V. The diffraction pattern of Metoprolol succinate shows different peaks at 2 Ø = 8.05, 12.82, 14.10, 16.20, 19.42, 24.23, 26.20 as shown in **Figure 9**. The peaks data indicate that S (-) Metoprolol succinate is crystalline in nature. (Wasekar, N., *et al*,2022)

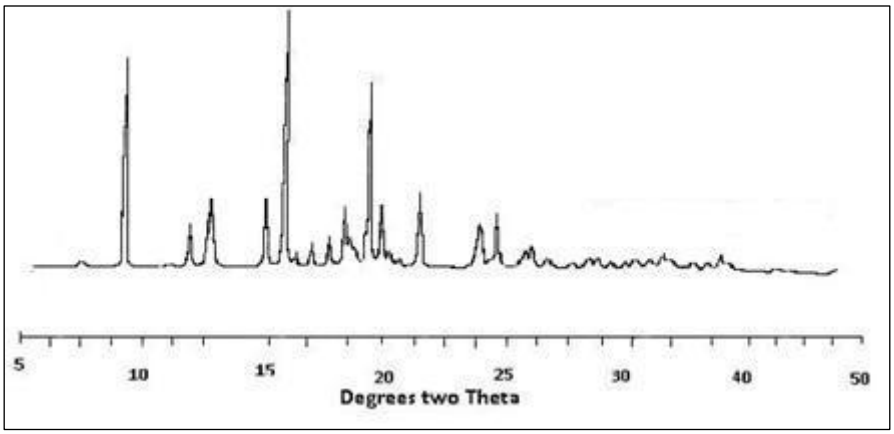

Figure 9. PXRD of S (-) Metoprolol succinate

5.1.1.9. Related substance (RS) and drug assay (By HPLC)

The potency and purity of the drug was evaluated by assay and releated substance. The mobile phase used for the testing, Buffer: Glacial acetic acid: triethylamine: phosphoric acid: acetonitrile (810: 10: 2: 3: 146) and column Inertsil ODS - 3, 250 mm x 4.60 mm, 5 micron or equivalent. The RS results of the Metoprolol Succinate for highest impurity found to be 0.15 % and for total impurity is 0.26 % which were well with in the limit i.e NMT 2 %. We can further use the API for processing. The assay was found to be 99.09 %. Assay and RS of the S(-) Metoprolol succinate reflects and ensure the API to be used in the formulation is having identity, potency, quality and purity (Emam. *et al,* 2020).

5.1.1.10. Sieve analysis

The particle size of the API is very critical for the development of sustained release dosage form. The % retention observed in the 20#, 30 # and 40# is less than 5 % as

shown in **Table 38** which confirms the fine nature of the S (-) Metoprolol succinate. The fine name of the API is ideal for preparing sustained release tablet by optimizing the drug-polymer ratio. Based on the outcomes now next part is to design our formulation with respect to the selection of excipients (Zidan *et al*.,2022).

Table 38. Seive analysis of S (-) Metoprolol succinate

S.No	Seive Number	% Retained (n=3)
1	20 #	0
2	30 #	0.20 ± 0.01
3	40 #	1.20 ± 0.07
4	60 #	7.80 ± 0.06
5	80 #	34.60 ± 0.15
6	100 #	56.40 ± 0.12

5.1.1.11. Standard calibration curve

The absorbance of all the prepared solutions of 5-60 µg/mL were measured comparison to blank in 6.80 pH phosphate buffer at λ max 275 nm. The samples were analyzed using double beam spectrophotometer UV-1601 UV Visible Spectrometer (Shimadzu Corporation). A standard calibration plot of absorbance (nm) v/s drug concentration (µg/mL) was plotted and observed to follow Beer Lambert's law over the concentration range of 5-60 µg/mL (**Table 39**). It showed r^2 value of 0.99 shown in **Figure 10** (Salve, *et al.*,2021).

Table 39. Standard calibration curve of S (-) Metoprolol succinate in 6.80 pH phosphate buffer

Concentration(µg/mL)	Absorbance (nm) n=3
5	0.09 ± 0.01
10	0.17 ± 0.02
15	0.25 ± 0.02
20	0.32 ± 0.04
25	0.40 ± 0.03
30	0.47 ± 0.01
35	0.54 ± 0.02
40	0.61 ± 0.04
45	0.70 ± 0.04
50	0.76 ± 0.03
55	0.83± 0.02

Concentration(µg/mL)	Absorbance (nm) n=3
60	0.91± 0.05

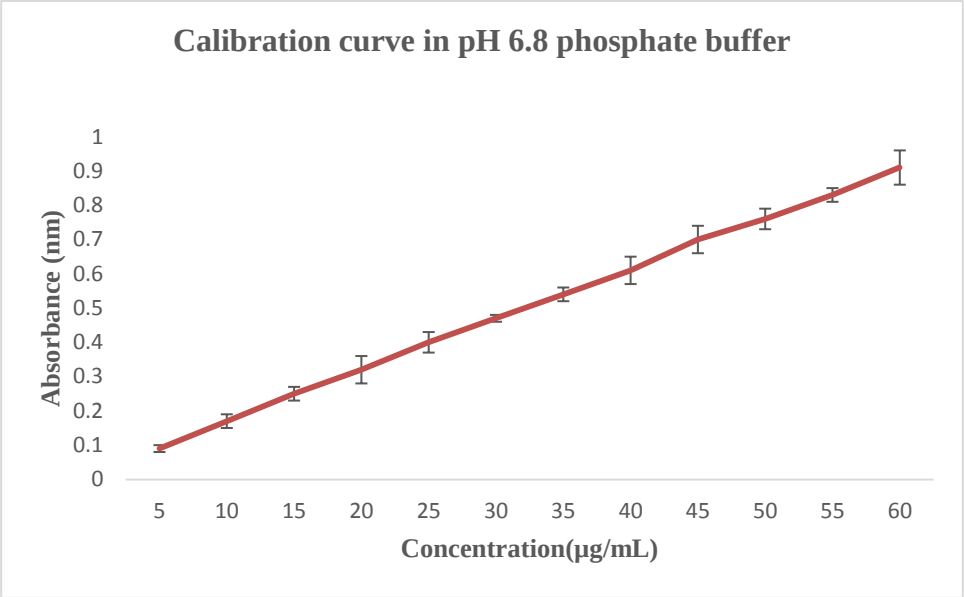

Figure 10. Calibration curve of S (-) Metoprolol succinate in pH 6.8 phosphate buffer

5.1.1.12. Drug excipient compatibility

Compatibility of API with excipient was studied by keeping metoprolol succinate individually and mixing metoprolol succinate individually with all excipient in 1:1 ratio and kept it exposed to 25°C ± 2°C/ 65 % RH ± 5 % RH, 40°C ± 2°C /75 % RH ± 5 % RH and 60°C ± 2°C for 30 days. Details of physical observations are provided in **Table 40.**

Table 40. Drug excipient compatibility

Ingredients	25°C ± 2°C/ 65 % RH ± 5 % RH	40°C ± 2°C /75 % RH ± 5 % RH	60°C ± 2°C
S(-) Metoprolol succinate	White coloured powder	White coloured powder	White coloured powder
API + MCC Pellet	White coloured powder	White coloured powder	White coloured powder
API + Povidone	White coloured powder	White coloured powder	White coloured powder

Ingredients	25°C ± 2°C/ 65 % RH ± 5 % RH	40°C ± 2°C /75 % RH ± 5 % RH	60°C ± 2°C
API + Talc IP	White coloured powder	White coloured powder	White coloured powder
API + Hypromellose	White coloured powder	White coloured powder	White coloured powder
API + Ethyl cellulose	White coloured powder	White coloured powder	White coloured powder
API + Eudragit	White coloured powder	White coloured powder	White coloured powder
API + Methocel K-100 M	White coloured powder	White coloured powder	White coloured powder
API + Hypromellose, K4-M	White coloured powder	White coloured powder	White coloured powder
API + Pregelatinized Starch	White coloured powder	White coloured powder	White coloured powder
API+ Hydrogenated castor oil (Lubritab)	White coloured powder	White coloured powder	White coloured powder
API + Mannitol	White coloured powder	White coloured powder	White coloured powder
API + Crospovidone	White coloured powder	White coloured powder	White coloured powder
API + Ceolus KG 802	White coloured powder	White coloured powder	White coloured powder
API + Aerosil	White coloured powder	White coloured powder	White coloured powder
API +Sodium steryl fumurate	White coloured powder	White coloured powder	White coloured powder
API +MCC 102	White coloured powder	White coloured powder	White coloured powder
API + Magnesium stearate	White coloured powder	White coloured powder	White coloured powder

From the physical observation there was no significant impact of temperature and humidity observed on the materials.

5.1.1.13. Chemical analysis by DSC:

Drug-excipient compatibility by Differential Scanning calorimetry (DSC) study plays significant role in the development of new formulation which ensure no interaction among the API and exciepients used in the formulation. DSC is rapid method for analysis of interaction among API and Exciepients. The incidence of a new peak in the drug exciepients mixture, the disappearance of the API peak, or a change in melting temperature (for eg. change in shape of peak, position of peak, or enthalpy of peak) shows interaction of API and Exciepients. DSC thermograms were measured at temperature range between 32 ºC and 254 ºC using a Model DS-60(Shimadzu®, Tokyo, Japan) with equipment and PC control unit TAC 60 (Shimadzu®, Tokyo, Japan) which woks at a heating rate of 15 ºC/min and a nitrogen flow rate of 25 mL/min. Data analysis was undertaken using the latest Manager Software. Version 2.0. DSC of Drug and exciepients shown in **Figure 11a** and DSC of MUPS tablets of shown in **Figure 11b**. DSC study showed that endotherm of metoprolol succinate was found around 122.80 ^{0}C. While endotherms of metoprolol succinate with other excipients were found in the range of 110 ^{0}C -130 ^{0}C. No substantial shifting of the endotherms was observed; this shows that the metoprolol succinate is compatible with excipients used in the formulation (Thombre, *et al.*,2020).

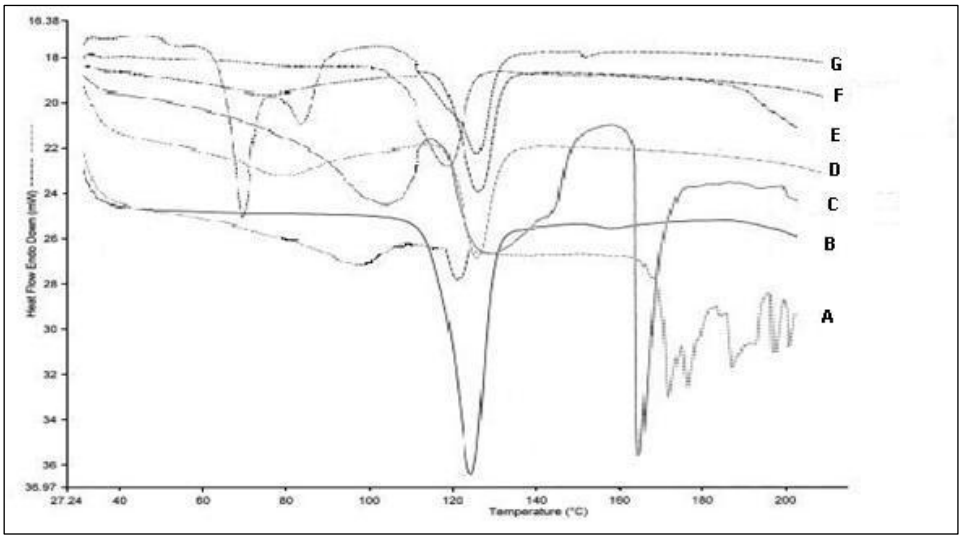

Figure 11a. DSC study of Metoprolol succinate with different excipients

A-HPMC, B-Metoprolol succinate, C-Povidone, D-Ethylcellulose, E-MCC; F-Crosspovidone, G- Magnesium stearate

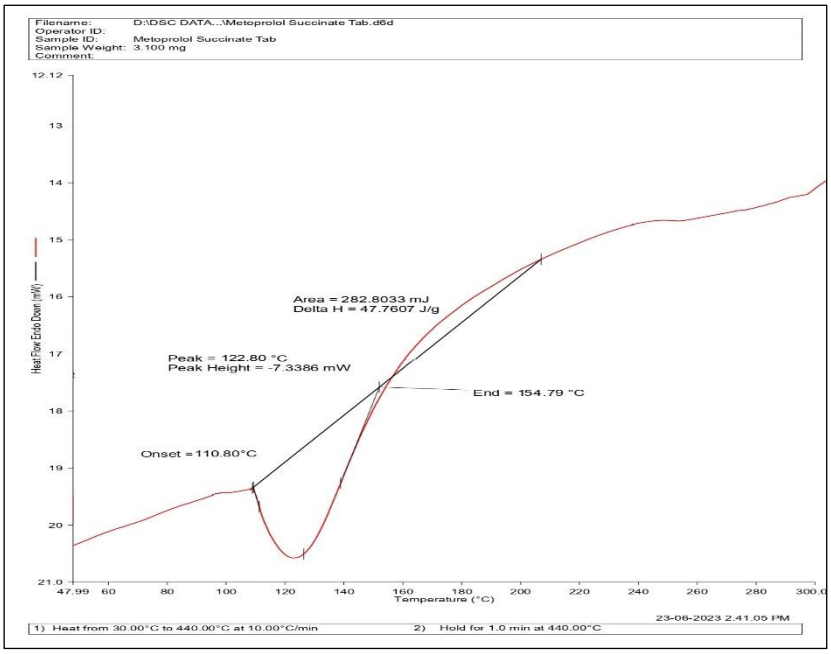

Figure 11b. DSC study of MUPS tablet of S (-) Metoprolol succinate

5.1.2. Marketed product characterization

Seloken XL 25 mg, Batch No. ACT002, Mfg. AstraZeneca, Sweden. Product was procured form market and evaluated for its size, shape, weight, and chemical analysis such as assay and dissolution. Physicochemical properties are highlighted in **Table 41.**

Table 41. Physicochemical evaluation of Marketed product

Parameters	Results
Brand name	Toprol XL 25 mg
Generic Name	Metoprolol succinate sustain release Tablets 25 mg
Strength	25 mg
Batch no.	SXV010
Mfg date	Dec, 2021
Exp date	Nov, 2023
Mfg by	AstraZeneca Sweden
Weight	250 mg
Dimensions	9 mm
Colour	White
Shape	Round
Hardness	6.80 Kg/cm^2
Dissolution	
2 hs. (NMT 25 %)	15.02 ±2.10 %
4 hs. (20-50%)	34.57 ± 1.90 %
8 hs. (35-70%)	52.39 ±1.40 %
20 hs. (NLT 70 %)	93.21 ±2.20 %

5.1.3. Development and Characterization of MUPS tablet of S(-) Metoprolol succinate.

5.1.3.1. Drug loading

Different trials were conducted, and drug loading was evaluated. The formulation PT-8 contains talc, and hypromellose shows maximum drug loading. Amount of drug in

pellets was found to be 99.20 % ±0.50 %. The details of results and formulation are shown in **Table 42.**

Table 42. Physical and chemical parameters of drug coated pellets

Formulation	PT-1	PT-2	PT-3	PT-4	PT-5	PT-6	PT-7	PT-8
Bulk Density	0.74±0.02	0.67±0.05	0.78±0.03	0.74±0.05	0.78±0.05	0.69±0.03	0.74±0.02	0.72±0.04
Compressibility Index (%)	14.15±0.14	16.21±0.22	16.28±0.13	15.21±0.16	15.26±0.10	14.28±0.14	13.48±0.12	12.57±0.15
Angle of Repose	26.17±0.11	27.15±0.22	24.15±0.12	26.14±0.18	26.47±0.18	26.57±0.14	26.45±0.13	27.45±0.17
Drug Content	96.20±1.02	93.50±1.33	97±1.24	95.40±1.46	95±1.50	97.50±1.23	95.10±1.11	99.20±0.50

5.1.3.2 Functional coating of sustained release polymer over drug-loaded pellets

In the modified release dosage form the selection of polymer was key to success. In the present study, we studied ethylcellulose, hypromellose, methacrylate derivative (Eudragit), Methocel K4M and Methocel K100 M etc. The most important segment on account of any controlled release system is the release controlling segment. In the current examination, the degree sustained release was achieved with the drug: polymer proportion in the matrix. In the current formulation, PT17, drug release achieved with in the specification by the utilization of Methocel K4M and Methocel K100 polymer. The test formulation results are shown in **Table 43** (Sun, X., *et al*, 2020)

Table 43. Physical and chemical parameters of functional coated pellets.

Formulation	PT-9	PT-10	PT-11	PT-12	PT-13	PT-14	PT-15	PT-16	PT-17
Bulk Density (g/cc)	0.77 ±0.04	0.71 ±0.03	0.75 ±0.09	0.74 ±0.07	0.69 ±0.02	0.71 ±0.04	0.71 ±0.04	0.74 ±0.03	0.69 ±0.05
Compressibility Index (%)	15.47 ±0.11	14.58 ±0.21	14.42 ±0.23	15.68 ±0.19	13.48 ±0.13	14.58 ±0.17	13.47 ±0.12	14.15 ±0.21	14.21 ±0.13
Angle of Repose Θ	24.29 ±0.09	26.14 ±0.11	25.19 ±0.08	25.74 ±0.12	27.15 ±0.15	26.18 ±0.08	26.74 ±0.13	25.97 ±0.12	27.11 ±0.06
Dissolution Profile (%)									
2 h (NMT 25 %)	35.20 ±1.22	29.20 ±2.02	32.40 ±1.60	26.14 ±1.14	24.50 ±1.33	20.54 ±1.19	22.11 ±1.02	18.71 ±1.17	17.77 ±0.23
4 h (20-50%)	53.10 ±1.13	48.10 ±1.02	46±1.33	43.47 ±1.12	47.10 ±1.22	41.50 ±1.16	47.24 ±1.19	41.71 ±1.15	33.57 ±1.02
8 h (35-70%)	76 ±1.31	69.60 ±1.42	67.50 ±1.13	64.64 ±0.17	67.60 ±1.34	61.90 ±1.54	67.17 ±1.13	62.10 ±1.19	52.72 ±0.55
20 h (NLT 70 %)	98.50 ±1.33	95.40 ±1.22	89±1.16	94.34 ±1.44	91.90 ±1.11	92.44 ±1.36	93.10 ±1.14	94.14 ±1.34	95.77 ±1.01

5.1.3.2.1. Effect of low viscosity Ethylcellulose 5 cps

Ethylcellulose is a non-toxic, stable, compressible, inert, hydrophobic polymer that is widely used in the manufacture of pharmaceutical dosage forms. Properties of ethylcellulose sustained-release products such as film-coated tablets, microspheres, microcapsules and matrix tablets have been reported for both soluble and sparingly soluble drugs. Trials PT9 and PT10 were manufactured with plain ethylcellulose 5 cps with different concentrations. The powder flow properties and physical parameters of Trial PT9 and PT10 found satisfactory. Effect of low viscosity Ethylcellulose on dissolution was observed. Form results initially the Ethyl cellulose (EC) at 15 and 30 mg/tablets resist the drug release upto certain extent but desired pattern of release was not found. Flow properties shown in **Table 44** and effect of Ethyl cellulose shown in **Table 45** (Nadendla,*.et al*.,2011).

Table 44. Flow properties of functional coated pellets PT9 and PT10

Parameters	PT9	PT10
Bulk density (g/cc)	0.77 ±0.04	0.71 ±0.03
Compressibility index (%)	15.47 ±0.11	14.58 ±0.21
Angle of repose (θ)	24.29 ±0.09	26.14 ±0.11

Effect of low viscosity Ethylcellulose on dissolution was observed. Form results initially the EC at 15 mg and 30 mg/tablets resist the drug release upto certain extent but desired pattern of release was not found.

Table 45. Effect of low viscosity of Ethylcellulose on dissolution

Time (h)	Specification	PT9 (%)	PT10 (%)
1	**NMT 25 %**	35.20 ±1.22	29.20±2.02
4	**20-50%**	53.10 ±1.13	48.10±1.02
8	**35-70%**	76 ±1.31	69.60±1.42
20	**NLT 70 %**	98.50 ±1.33	95.40±1.22

5.1.3.2.2. Effect of Ethylcellulose (EC) 10 cps

During the past development the dissolution profile was not as per specifications, so trial planed with EC 10 cps to control the drug release. Trial PT10 and PT11 planned with EC 15 mg/tablets and 30 mg/tablets respectively. Compared with PT10, trial PT11 was found better but results were on borderline. Powder flow properties found satisfactory as shown in **Table 46.** (Nadendla*,.et al.*,2011). The viscosity or molecular weight grade of EC can impact drug release rates. Drug release is retarded with increasing molecular weight (viscosity) of EC. The retardation in drug release can be attributed to an improvement in the mechanical properties of the film. Lower molecular weight grades yield solutions of lower viscosity, allowing faster spray application, while higher molecular weight grades provide films of higher mechanical film properties. Coating formulations which yield the desired film properties, as well as afford a faster spray application, would be most advantageous. It is observed that samples coated with the lower molecular weight (viscosity) grades had faster release

rates than samples coated using higher viscosity grades of EC. This is consistent with other literature reports.

Table 46. Flow properties of functional coated pellets PT11 and PT12

Parameters	PT11	PT12
Bulk Density (g/cc)	0.75 ±0.09	0.74 ±0.07
Compressibility Index (%)	14.42 ±0.23	15.68 ±0.19
Angle of repose (θ)	25.19 ±0.08	25.74 ±0.12

Dissolution results were not found satisfactory at intermediate time points drug release was not as per desired release pellets as shown in **Table 47.**

Table 47. Effect of ethylcellulose 10 cps on dissolution properties

Time	Specification	PT11(%)	PT12 (%)
1 h	**NMT 25 %**	32.40±1.60	26.14±1.14
4 h	**20-50%**	46.00 ±1.33	43.47±1.12
8 h	**35-70%**	67.50±1.13	64.64±0.17
20 h	**NLT 70 %**	89.00 ±1.16	94.34±1.44

5.1.3.2.3. Effect of Eudragit on drug release

Eudragit NE 30D is an aqueous type dispersion combination of a neutral copolymer based on ethyl acrylate and methyl methacrylate, widely used to obtain reservoir-type sustained release formulations. insoluble, but swells in water and has low permeability). Water-soluble additives can be included in the film to increase the permeability of the membrane when the product is exposed to an aqueous environment during the dissolution stage.

Trial PT13 and PT14 were manufactured with ethylcellulose 15 mg and 30 mg per tablets concentrations of eudragit NE30D in functional coating. The powder flow properties and physical parameters found satisfactory as mentioned in **Table 48** (Quinten, T., *et al*,2012). The prepared pellets have good flow properties.

Table 48. Flow properties of functional coated pellets PT13 and PT14

Parameters	PT13	PT14
Bulk density (g/cc)	0.69 ±0.02	0.71 ±0.04
Compressibility index (%)	13.48 ±0.13	14.58 ±0.17
Angle of repose	27.15 ±0.15	26.18 ±0.08

The amount of Eudragit has not remarkably make the difference in the dissolution pattern.

5.1.3.2.4. Effect of Methocel K100 M

Trial was planed with high-viscosity grade HPMC, which was used along with reservoir-coated pellets. All physical parameter was found satisfactory. Results described in **Table 49** and **Table 50** (Gohel, M.*et al*.,2009). The prepared pellets have good flow properties which are ideal for compressing the pellets in tablets.

Table 49. Flow properties of PT15 formulation

Parameters	PT15
Bulk density (g/cc)	0.71 ±0.04
Compressibility index (%)	13.47 ±0.12
Angle of repose (θ)	26.74 ±0.13

Dissolution results were found satisfactory but 8th h interval on the higher side which may lead to failure in validation batches.

Table 50. Effect of Methocel K100M on dissolution properties

Time	Specification)	PT15 (%)
2 h	**NMT 25 %**	22.11±1.02
4 h	**20-50%**	47.24±1.19
8 h	**35-70%**	67.17±1.13
20 h	**NLT 70 %**	93.10±1.14

5.1.3.2.5. Effect of viscosity of Methocel K4M

Effect of HPMC used functional coating have much advantages. Due to its lack of toxicity, extensive availability in many chemically substituted forms, high hydration rate, and adaptability in terms of viscosity, HPMC is frequently utilized as a rate-controlling polymer in oral ER dosage forms. HPMC's performance in the ER matrix

system is determined by its gel layer viscosity and the speed with which it forms following hydration. The total rate of drug release is controlled by the viscosity of the gel layer formed during the gelation process. In addition, 15 mg/Tab concentration of Methocel K4M concentration from results in broad differences in dissolution profiles as compared to ethyl cellulose and eudragit. All physical parameter was found satisfactory, results was well described in **Table 51** and **Table 52** (Gohel, M.*et al*.,2009).

Table 51. Flow properties of functional coated pellets PT16 formulation

Parameters	PT16
Bulk density (g/cc)	0.74 ±0.03
Compressibility index (%)	14.15 ±0.21
Angle of repose (θ)	25.97 ±0.12

Dissolution results were found satisfactory but 8th h interval on the higher side which may lead to failure in validation batches. So combination of polymer required to get the mean release in middle value of the specification.

Table 52. Effect of Methocel K4M on dissolution properties

Time (h)	Specification	PT16
2	**NMT 25 %**	18.71±1.17
4	**20-50%**	41.71±1.15
8	**35-70%**	62.10±1.19
20	**NLT 70 %**	94.14±1.34

5.1.3.2.6. Effect of combination of Methocel K100 M and Methocel K4M on drug release

Hydrophilic matrices in sustained-release tablets often start with cellulose ethers like hydroxypropylmethylcellulose (HPMC). Research from the 1960s describes their application, but only lately have their characteristics and efficiency been measured to any great extent. To effectively regulate medication release, formulations often rely on their gelling ingredients, which are hydrated to produce layers of gel that are resistant to diffusion and erosion. Matrix carriers for extended-release solid dosage forms often make use of hydrophobic materials. Particularly challenging and fruitless

has been the creation of regulated drug delivery systems for highly water-soluble medicines, which often exhibit zero-order release kinetics.

The design flaws in this delivery system can be attributed to three factors:

There is insufficient management of the time-dependent polymer relaxing and detangling processes that accompany medication breakdown and diffusion.

It's not easy to compensate for the longer diffusion paths that occur with time. Sustained-release dosage forms may be created for medications that are extremely water-soluble by combining hydrophobic polymers with hydrophilic matrices. There are several advantages to using hydrophobic polymers, including their proven safety and high stability over a wide range of pH and moisture conditions. Fluorescein, a highly water-soluble chemical, improves the gel thickness and swelling rate by creating an extra osmotic gradient in the HPMC matrix. The glassy matrix eventually changes into a rubbery swelling gel in the presence of solvent due to increased mobility of the polymer chains. With an increase in polymer loading, the gel matrix becomes more viscous, decreasing the drug's effective diffusion coefficient. Differences in water penetration rate, water absorption capacity, and polymer swelling have also been documented to contribute to variations in drug dissolution patterns as a consequence of changes in total polymer concentration. PT17 was created with the same concentrations of the Methocel K4M and Methocel K100M. The powder flow properties and physical parameters of PT17 found satisfactory. The details described in **Table 53** and **Table 54** (Gohel, *et al*.,2009).

Table 53. Flow properties of functional coated pellets PT17

Parameters	PT 17
Bulk Density (g/cc)	0.69 ±0.05
Compressibility Index (%)	14.21 ±0.13
Angle of repose (θ)	27.11 ±0.06

The dissolution profile of PT17 found satisfactory.

Table 54. Effect of Methocel K100 M and Methocel K4M on drug release

Time	Specification	PT 17
2 h	NMT 25 %	17.77± 0.23
4 h	20-50%	33.57± 1.02
8 h	35-70 %	52.72± 0.55
20 h	NLT 70 %	95.77± 1.01

5.1.3.2.7. QTPP and CQA for S (-) Metoprolol succinate MUPS tablets formulation

The QTPP and CQA for S (-) Metoprolol succinate MUPS tablets are presented in **Table 55** along with the rationale for selected quality attributes. Drug release (NMT 25 % at 2 h, 20 % to 50 % at 4 h, 35 % to 70 % at 8 h, 70 % or higher at 20 h) is considered a CQA for Metoprolol succinate MUPS Tablets. These were essential features for the desired dosing regimen and efficacy of metoprolol succinate.

Table 55. QTPP and CQA for S (-) Metoprolol succinate MUPS tablets formulation.

QTPP Elements	Target	CQA	Justification
Adminstration route	Oral route	No	Formulation designed for oral administration
Dosage	MUPS tablet	No	Maintain plasma concentration
Strength	25 mg	No	Dose of drug
Product profile	Description: White to off white Punch: 9.0 mm circular. Hardness: NLT 3 Kg/cm^2 Assay: 90-110 % Dissolution: (NMT 25 % at 2 h, 20 % to 50 % at 4 h, 35 % to 70 % at 8 hs, 70 % or higher at 20 h)	Yes	Assay, Dissolution important CQA which directly impacting product profile and its efficiency.
Stability	As per ICH guidelines ICH Q1B	No	Regulatory requirement

QTPP Elements	Target	CQA	Justification
Packaging system	Suitable for drug product	No	To maintain quality and integrity of drug storage.

5.1.3.3. Compression of MUPS tablets

MCC PH 102, MCC PH 200, aerosil, sodium stearyl fumarate, lubritab were taken and mixed to prepare cushioning agents. Optimized Functional coated pellets were mixed with these cushioning agents. Compress lubricated MUPS (Multiple unit pellets system) blend in single rotary compression machine at different RPM as well as hardness and thickness over the parameters as follows; white to off white tablets of 250 mg and 3.60 ±0.40 mm thickness, turret speed: 12 RPM and hydraulic pressure: NLT 15 pounds.

Compaction Properties and Heckel analysis

S (-) Metoprolol succinate compacts were prepared by using MCC PH 102, MCC PH 200, aerosil, sodium stearyl fumarate and lubritab. The compaction behaviour of the two materials was also evaluated using the compressibility-tabletability compactibility (CTC) profile presented below. The compressibility plot (Fig. 12 a) relates the effect of compression pressure on porosity and shows a gradual decline in porosity for both materials as the compression pressure increases.

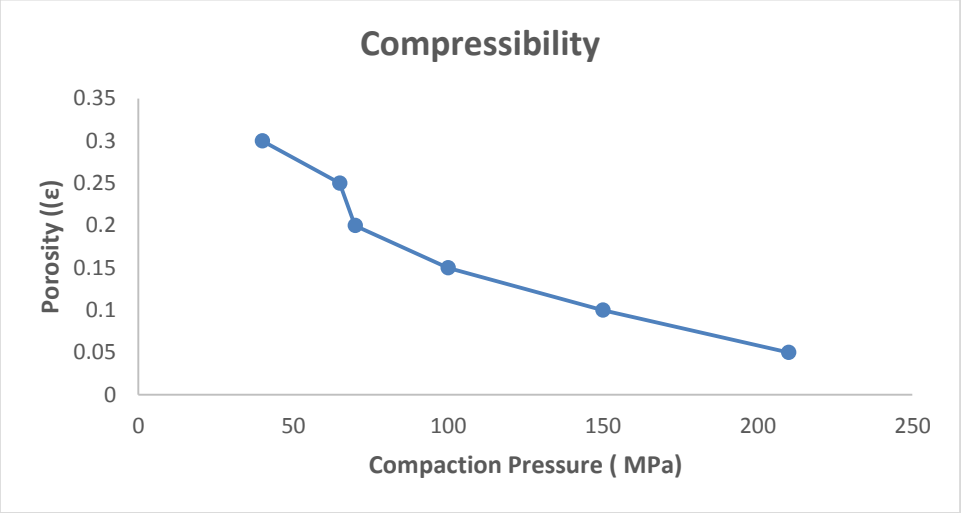

Figure 12 a: Compressibility Plot

The compactibility plot (Fig. 12 b) shows the relationship between tensile strength and porosity of compacts. Tensile strength increased with decreasing porosity. The tensile strength were higher at all porosities (0.1–0.4). Compacts produced the lowest porosity value at maximum compaction pressure.

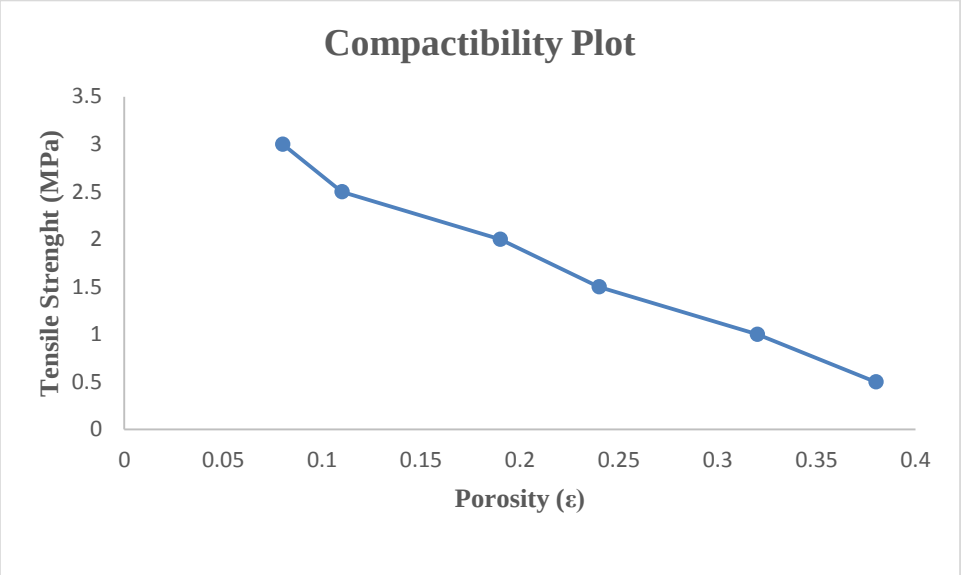

Figure 12 b: Compactibility Plot

The Tabletability profile for both materials represented by a plot of tensile strength against compression pressure (Fig. 12 c) shows that tensile strength increased as the compression pressure increased. Powders under the efect of an external mechanical stress are subject to either elastic deformation, plastic deformation, viscoelastic deformation, or fragmentation as the main mechanism for deformation. Plastic deformation has been recognized as the most important deformation mechanism that facilitates tablet formation (Apeji YE *et.al*, 2019).

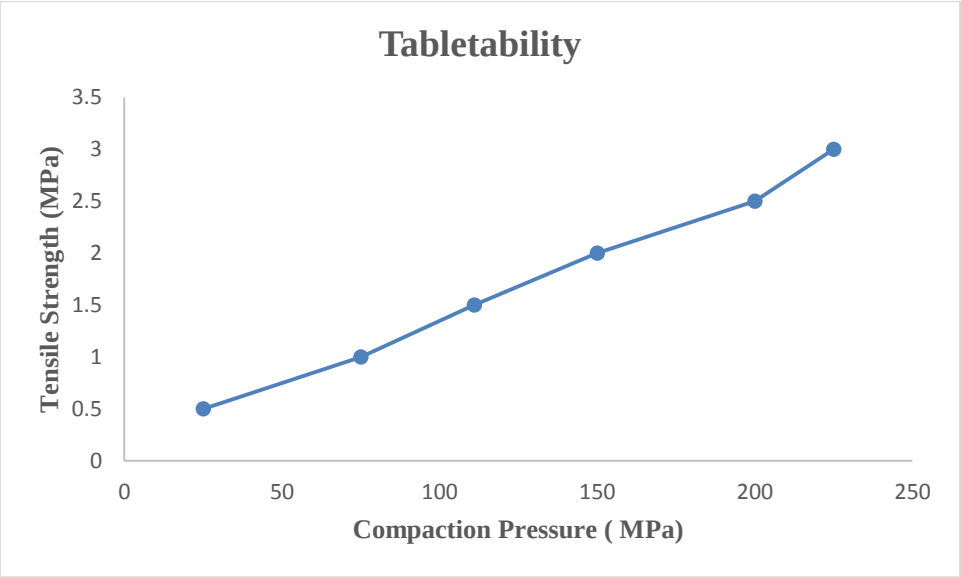

Figure 12 c: Tabletability Plot

Due to particle rearrangement and fragmentation within the MUPS lubricated blend. The is no linearity found at the start of the initial stage of the compression process. Heckel plots shows non-linearizer behaviour. Lubricated MUPS granules of S (-) Metoprolol succinate shows maximum die filling reflected by A values. Bridges and arches formation in the powder blends leads to prevention of close packing when blend stored at bulk containers. Higher original compact volume observed reflected higher level of fragmentation. Parameters such as Mean yield pressure (Py) and Relative density (Da) should be determined from the Heckel plot. At Pressure (12 Kg/cm3), relative density found to be 0.747 and at (24 Kg/cm3), relative density found to be 0.857.

When the pressure was kept at low the larger granules breaks in small granules and facilitate rearrangement. With gradual increase in the compaction force showed plastic deformation of the compacted blend. Better compressibility observed reflects greater plasticity indicated by slope in Heckel plot shows in **Figure 12.d.**

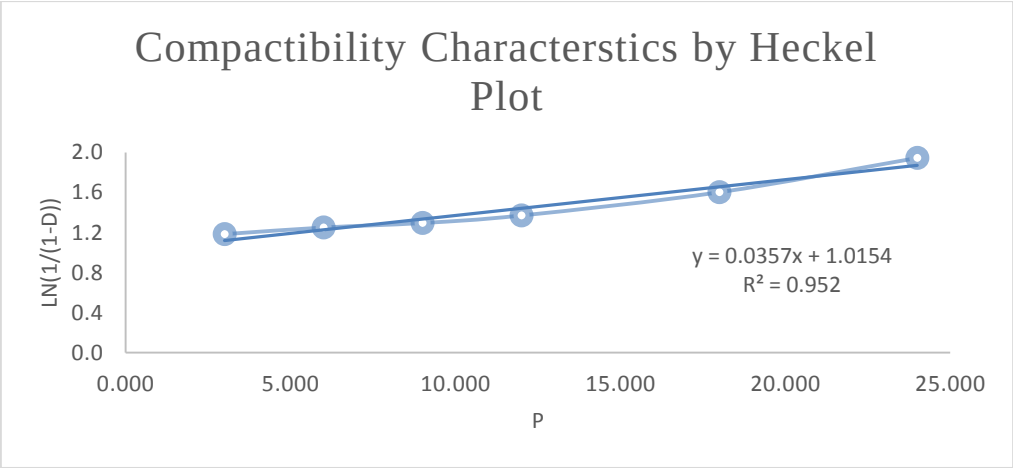

Figure 12 d: Compatibility characteristics by Heckel Plot

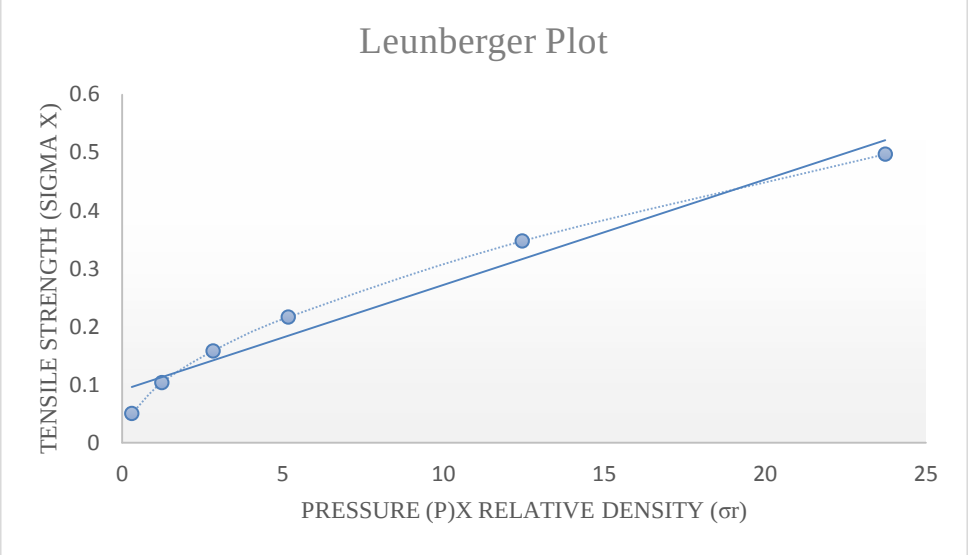

Figure 12 e : Leunberger Plot

5.1.3.3.1 Characteristics of tableting blend and Pellets

5.1.3.3.1.1. Content uniformity

Content uniformity was calculated by taking 10 tablets of random weights were chosen for analysis of drug content and enlisted in the below table, these results were showing the homogeneous blending of the pellets with the help of filling the void spaces by using cushioning agents. Cushing agents also protect direct contact with other pellets by developing a layer around the pellet surface which prevents the segregation of pellets. Methocel K100 and Methocel K4 M were used as controlled

release polymer which provides strength to pellets during compression and protects them from getting segregated. Various crushing excipients been used to prevent the rupturing of Pellets during compression. The optimized formulation contains Hydrogenated castor oil, Crosspovidone, Aerosil and SSF which help to provide elasticity to the tablets. RPM of the compression machine also plays an important factor while compressing the MUPS tablets. Physical and chemical parameters shown in **Table 56** (Reddy, G. L, *et al*,2016).

Table 56. Evaluation parameters of S(-) Metoprolol succinate MUPS tablets

Parameters	**FT1**	**FT2**	**FT3**	**FT4**	**FT5**
Thickness (mm)	3.60 -3.80	3.65-3.70	3.34-3.50	3.5-3.80	3.8-3.90
Hardness (kg/cm^2)	3.21-4.10	3.21-4.34	3.14-4.21	3.74-4.85	3.62-4.22
Friability (%)	0.45±0.04	0.38±0.06	0.50±0.06	0.37±0.07	0.13±0.06
Drug content (%)	99.62±0.14	95.97±0.22	96.77±0.19	98.92±0.11	99.9 %±0.06
Comp RPM	20	20	20	20	20
Dissolution					
2 h (NMT 25 %)	33.2±0.15	27.2±0.18	28.1±0.19	26.14±0.11	16.77±0.08
4 h (20-50%)	51.1±0.12	54.1±1.14	45±1.15	51.47 ±1.64	36.57±0.09
8 h (35-70%)	73.6±1.11	69.6 ±1.16	69.5±1.54	63.64 ±1.16	54.42±1.43
20 h (NLT 70 %)	98.5±1.32	95.4±0.12	95 ±1.32	94.34 ±1.19	95.77±1.10
Content Uniformity in %	88.5-96	75-109	88.5-105	86-96	96-103

5.1.3.3.1.2. Drug Assay

Drug assay was calculated using HPLC from the method. Mobile Phase was used in combination of buffer: glacial acetic acid: triethylamine: phosphoric acid: acetonitrile (810: 10: 2: 3: 146), for buffer, weigh about 3.90 g of ammonium acetate in 810 mL water. Conditions for Chromatographic Column-: Inertsil ODS - 3, 250 mm x 4.6 mm, 5 micron or equivalent. Flow rate was 1.50 mL/min, wavelength: 280 nm, run time was 30 min, Injection Volume: 20 µl, Approximate retention time: S (-) Metoprolol Succinate: About 14.50 min. The calculated amount of drug in pellets in

FT5 was found to be 96 to 103 % estimated spectrophotometrically (Yang, Z., *et al*, 2016).

5.1.3.3.1.3. Drug Dissolution

The pattern of drug release showing that coating with Methocel will increase its lipophilic and water solubility decreased so water uptake rate was decreased, in our study, almost 95 % drug content release from the drug-coated pellets and same from the MUPS tablets were found after dissolution with sustained action by releasing NMT 25 % in 2 h, 4 h (20-50 %), 8 h (35-70 %) and NLT 70 % in 20 h. FT5 formulation Figure s state the release rate of the drug from pellets and showing sustained action with up to 20 h of release in the 6.80 phosphate buffer (Yang, Z., *et al*, 2016).

5.1.3.3.1.4. Drug excipients compatibility by using FTIR:

FTIR was done using instrument Perkin Elmer. Data analysis was done using Perkin Elmer spectrum IR version 10.6.1. IR absorption spectroscopy used to confirm molecule and also help to identify the molecular structure. It is widely used in the pharmaceutical industry in raw material testing. The frequencies (absorption band) used for the interpretation of IR spectra are listed in **Table. 57** and **Figure 13.**

MUPS tablets has several significant peaks of Metoprolol succinate which confirm that there is no significant sift in the peak which shows that exciepiets are compatible with the API. Additional peaks are there for exciepients due to drug exciepients intraction, weak Van der walls forces and hydrogen bonding.

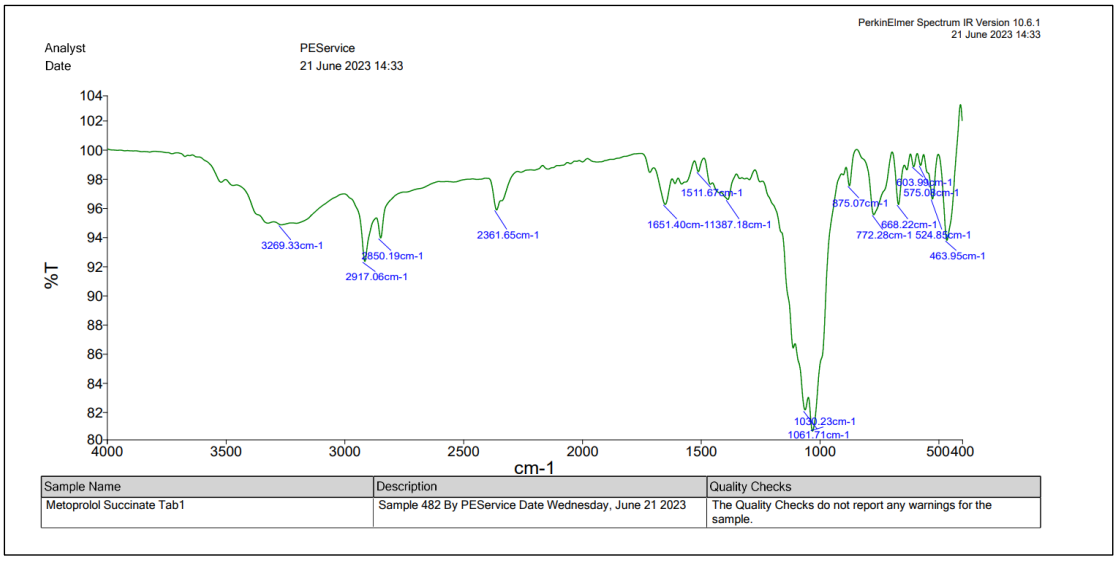

Figure 13 FTIR study of S(-) Metoprolol succinate tablets

Table 57. Frequency and functional group assignment for MUPS Tablets

Wave number (cm^{-1})	Assignment (s)
3269.33-2361.65	aromatic CH and-OH Aliphatic, NH2
1511	R-COOH (Carboxylic acid)
1651.40	C_6H6 (Aromatic ring)
1030,1061.71	H-O-H (Aromatic ring)
1101	Aliphatic-ether
875	1,4- benzene ring

5.1.3.4. Effect of process variables on dissolution

To develop the robust process, different variables have been studied such as type of pellets, size of pellet, inlet temperature, nozzle diameter, fluidization air pressure etc.

5.1.3.4.1. Effect of type of pellets

In the present study, CR1: microcrystalline cellulose pellets (MCC), CR2: non peril seeds and CR3: starch pellets were taken. The selected pellet was evaluated for powder flow properties. Powder flow properties and physical properties of MUPS of S (-) Metoprolol succinate given in **Table. 58** all the properties were satisfactory.

Table 58. Flow properties of different types of coated pellets of S (-) Metoprolol succinate

Parameters	CR1	CR2	CR3
Bulk Density (g/cc)	0.67±0.02	0.72 ± 0.05	0.76 ± 0.09
Compressibility Index (%)	14.91±0.12	14.78 ± 0.16	16.99 ± 0.12
Angle of repose (θ)	26.75±0.11	27.50 ±0 .22	27.18 ± 0.10

The physical parameters of compressed tablets were found significant and having good flow properties as shown in **Table 59.**

Table 59. Physical properties of MUPS tablets by using different types of pellets of S (-) Metoprolol succinate

Parameters	CR1	CR2	CR3
Thickness (mm)	3.29 ± 0.10	3.28 ± 0.15	3.32 ± 0.11
Hardness (Kg/cm^2)	4.21-6.12	4.11- 6.21	4.15 – 6.12
Friability (%)	0.67 ± 0.04	0.38 ± 0.10	0.54 ± 0.07

MCC pellets shows better performance compared with NPS and starch pellets. An extensive study was carried out on microcrystalline cellulose (MCC) by many researchers both as powdered and granulated forms, and revealed that MCC shows plastic deformation during compression and provides better protection to the coated particles as powder and granules. Dissolution results as shown in Table 60 Zakowiecki, D., *et al*,2020)

Table 60. Dissolution of MUPS tablet by using different types of pellets of S (-) Metoprolol succinate

Time	Specification	CR1	CR2	CR3
1 h	NMT 25 %	19.71 ±1.11	16.48 ± 1.04	26.48 ± 0.21
4 h	20 -50 %	33.47 ±1.21	32.87 ±1.06	42.87 ± 0.98
8 h	35 -70%	50.82 ±1.16	51.02 ± 1.05	71.02 ± 1.11
20 h	NLT 70 %	94.14 ±2.10	91.74 ±1.22	99.74 ± 1.03

On MCC pellets compression force shows impact on the surface and results in deformation of the surface and alters the release characteristics.

5.1.3.4.2. Effect of pellets size

Studied the effect of MCC pellets size on the flow properties and physicochemical properties of tablets. In the present investigation we screened the thee different sizes of pellets as, CR4: 20 #-30 #, CR5: 30 #- 40 # and CR6: 50 #-100 #. As the particle size gets smaller, the amount of coating material required for the desired thickness becomes much higher. As the coating material must be applied using media with a solids concentration in the liquid range of 10 %- 30 %, the amount of liquid also increases as a result of the reduction in particle size. Another complicating issue is that as particle size decreases, agglomeration becomes highly dependent on coating fluid formulation and die. This is inevitable. Therefore, we decided to use an average particle size that gives reasonably desirable results. The flow properties of CR4, CR5 and CR6 were insignificants as high bulk density which may lead to hamper the flow properties mentioned in **Table 61** and physical property mentioned in **Table 62** reflects good flow properties.

Table 61. Flow properties of coated pellets of S (-) Metoprolol succinate

Parameters	CR4	CR5	CR6
Bulk density (g/cc)	0.88 ± 0.02	0.81 ±0.4	0.74±0.01
Compressibility index (%)	15.11 ± 0.12	14.08 ± 0.22	17.55 ± 0.18
Angle of repose (θ)	26.75±0.12	27.5±0.15	27.18±0.11

Table 62. Physical properties of MUPS tablets of S (-) Metoprolol succinate manufactured from different sizes

Parameters	CR4	CR5	CR6
Thickness (mm)	3.38 ± 0.05	3.18 ± 0.06	3.28 ± 0.12
Hardness (kg/cm^2)	4.21-5.43	4.15- 5.43	4.12– 5.32
Friability (%)	0.62 ± 0.17	0.52 ± 0.14	0.38 ± 0.13

The dissolution study of CR6 showed significant variation in each time point, the particle size (50 #-100 #) shows more significant results compared with CR4 and CR5. The functional coated pellets of CR4 and CR5 not followed the dissolution pattern required as per metoprolol succinate extended release tablets USP as shown in **Table 63** (Yang *et al*, 2016).

Table 63. Dissolution profile of CR4, CR5 and CR6 batches

Time	Specification)	CR4	CR5	CR6
1 h	NMT 25 %	28.87 ± 0.12	25.75± 0.19	16.48± 1.10
4 h	20 % -50 %	41.55 ± 0.18	39.74± 0.13	31.08± 0.29
8 h	35 % -70 %	69.77 ± 0.13	60.14± 0.11	52.74± 1.15
20 h	NLT 70 %	92.11 ± 0.10	87.15± 2.01	92.78± 1.43

5.1.3.4.3. Effect of inlet temperature

In this research we studied the effect of inlet temperature on manufacturing process and on dissolution pattern of metoprolol succinate tablets. We had selected the inlet temperature i.e CR7: 45°C ± 5 °C, CR8:60 °C ± 5 °C and CR9:70°C ± 5 °C. Prior studies were carried out using OFAT (One Factor at a time) approach. The selection of the temperature was selected based on literature survey and product temperature kept in industry for different range of pellets coating of aqueous and non-aqueous solvent system. (Husar, S., et al.,2019). Requirement of inlet temperature depends on spray speed, solvent type and solution viscosity, which directly affect product moisture and product temperature. Aqueous solvents require high temperatures to avoid particle agglomeration, while non-aqueous solvents require low temperatures to dry at low temperatures. For substrates that tend to melt or decompose at high temperatures, too high a temperature can also cause agglomeration. Therefore, the temperature is set taking into account various properties of the substrate as well as the solvent medium. Generally, 55-65 °C for organic solutions and 65-75°C for aqueous solutions work well at the start of the spray cycle. Prepared pellets reflect good flow property as shown in **Table 64.**

Table 64. Flow properties of coated pellets of S (-) Metoprolol succinate manufactured at different temperatures

Parameters	CR7	CR8	CR9
Bulk Density (g/cc)	0.69 ± 0.05	0.74 ± 0.02	0.78 ± 0.0.6
Compressibility index (%)	14.11 ± 0.15	13.79 ± 0.64	14.19± 0.11
Angle of repose (θ)	24.9 8± 0.08	27.11± 0.05	26.11± 0.04

The physical parameters for CR8 and CR9 were found satisfactory. During the manufacturing of CR7, the inlet temperature was set low i.e. 45°C ± 5 °C at this temperature sticking observed and the pellets were sticking with each other, also agglomerates formation observed, further it was difficult to manufacture the batch. Manufacturing of CR8 and CR9 batches was found satisfactory as shown in **Table 65.**

Table 65. Physical properties of MUPS tablet of S (-) Metoprolol succinate at different temperatures

Parameters	CR8	CR9
Thickness (mm)	3.21 ± 0.05	3.21 ± 0.10
Hardness (kg/cm^2)	4.41 – 5.21	4.32 – 5.14
Friability (%)	0.32 ± 0.11	0.33 ± 0.09

The trial CR8 and CR9 was compressed as MUPS tablets, the dissolution results shown in **Table 66.** The temperature CR 8: 55 °C was found satisfactory and results obtained in the middle of the specification while CR9 formulation intial results are lower due to over heating of the pellets (Vanhoorne, V., *et al*.,2016).

Table 66. Dissolution study of CR8 and CR9 formulation

Time	Specification	CR8 (%)	CR9 (%)
1 h	NMT 25 %	18.75 ± 0.11	9.15 ± 0.19
4 h	20-50 %	34.11 ± 0.16	37.17 ± 0.11
8 h	35-70 %	50.71 ± 0.18	59.11 ± 0.14
20 h	NLT 70 %	89.93 ± 0.16	87.11 ± 0.13

5.1.3.4.4. Effect of nozzle diameter of gun

Effect of nozzle diameter of gun on the manufacturing of pellets was studied. We have used three different types of gun diameter i.e. CR10: 0.50 mm, CR11:1.20 and CR12: 2.0 mm. For the selection of nozzle, The smaller the nozzle insert, the more uniform the spray mist. However, a smaller nozzle insert can clog the nozzle. Wurster coaters require a finer atomization of the coating solution than tablet pan coaters to avoid agglomeration. The nozzle to be used must be able to atomize the coating liquid even if the supply speed of the coating liquid is increased. Large droplets of coating fluid produced by low-power nozzles do not spread evenly over the material being

coated and do not dry as quickly as smaller droplets. Very small droplets dry quickly. Some droplets may contact the surface of the tablet or bead, but may dry out before they can disperse, creating an uneven surface on the core material. In order to maintain uniform atomization, when the spray velocity exceeds the capacity of the nozzle, large droplets of coating liquid will appear along with small droplets, and large droplets will lead to the formation of agglomerates. Multi-unit nozzles should be used for large product batches to avoid agglomeration. The prepared blend reflects good flow properties **(Table 67).**

Table 67. Evaluation of lubricated blend of S (-) Metoprolol succinate manufactured by different nozzle diameter

Parameters	CR10	CR11	CR12
Bulk density (g/cc)	0.72 ± 0.06	0.74 ± 0.08	0.78 ± 0.05
Compressibility index (%)	14.5± 0.12	13.9± 0.19	14.19± 0.13
Angle of repose (θ)	25.10± 0.12	28.12± 0.17	24.56± 0.10

The physical parameters found satisfactory and details are described in **Table.68.**

Table 68. Physical properties of MUPS tablet of S (-) Metoprolol succinate by different nozzle diameter

Parameters	CR10	CR11	CR12
Thickness (mm)	3.20± 0.10	3.20± 0.12	3.20± 0.09
Hardness (Kg/cm^2)	4.12-5.15	4.24- 5.44	4.09-6.24
Friability (%)	0.32± 0.21	0.32± 0.18	0.33± 0.14

The effect of gun nozzle diameter had impact on dissolution, in CR10 where the nozzle diameter 0.50 require more time for functional coating compared with CR12. The details for dissolution was described in **Table 69**.

Table 69. Dissolution profile of CR10, CR11 and CR12 formulations

Time (h)	Specification	CR10	CR11	CR12
1	NMT 25 %	16.90 ± 2.17	14.50 ± 2.12	12.50 ± 0.50
4	20 -50 %	40.11± 2.19	35.80 ± 2.45	30.0 0± 1.01
8	35-70 %	58.50 ± 2.30	50 ± 2.55	49 ± 1.15
20	NLT 70 %	90 ± 2.18	91 ± 2.11	86 ± 0.60

Trial CR12 shows the drug release on higher side as compared with CR10 and CR11. During the drug loading process of CR12 we faced the sticking problem and hence the peristaltic pump RPM was decreased. Due to this it takes a lot of time to achieve the desired drug loading %age on pellets. 0.55 mm Nozzle Diameter: Spray rate less and more time taken for coating and by 2 mm: Droplet bigger inadequate spraying sticking and twining of the pellets (Vanhoorne, V., *et al*.,2016).

5.1.3.4.5. Effect of fluidization air pressure

Effect of fluidization air pressure was studied with three different air pressures viz. CR13:2500 CFM, CR14: 3000 CFM and CR15: 3500 CFM. The inlet pressure was chosen based on the prior experimental trials. The inlet air volume is not for drying the product, but should be used to achieve the desired fluidization pattern. Product drying can be achieved by adjusting the temperature. For non-aqueous coatings, effervescent underfloor turbulence is recommended to minimize the generation of static electricity and particle friction, whereas for aqueous coatings, more severe turbulence is recommended to achieve higher drying efficiency. is required. At low air velocities, some of the particles begin to move upwards as the air flow increases, so air passes through the bed without disturbing the solid particles. When the airflow increases to a certain level, the particles start moving upwards and fall through the inner cylinder like a fountain. Meanwhile, the pressure drops and remains constant, causing the particles to move regularly.

Fluidization air pressure (CFM) plays an important role in the fluidization of Pellets inside the Fluid bed equipment. Low Fluidization pressure leads to non-uniform drug and controlled release coating on pellets and also generates sticking of Pellets. High air pressure lead to less weight gain of pellets. Hence optimium range of fluidization air pressure required to achieve uniform coating and critical quality attributes well within limits.

During the manufacturing of CR13, as the fluidization air pressure was set low i.e. 2500 CFM at this pressure sticking observed and the pellets were not fluidized properly. They stick with each other and agglomerates formed, further it was difficult

to manufacture. Formulation CR13, CR14 and CR15 was found satisfactory as shown in **Table 70-72** (Mundada, P. K., *et al*,2017).

Table 70. Evaluation of lubricated blends of CR13, CR14 and CR15 formulations

Parameters	CR13	CR14	CR15
Bulk density (g/cc)	0.69± 0.08	0.71± 0.06	0.71± 0.09
Compressibility index (%)	13.48± 0.19	14.58± 0.25	13.47± 0.21
Angle of repose (θ)	27.15± 0.15	26.18± 0.18	26.74± 0.19

Table 71. Physical properties of MUPS tablets of CR13, CR14 and CR15 formulation.

Parameters	CR13	CR14	CR15
Thickness (mm)	3.29± 0.09	3.28± 0.10	3.30± 0.08
Hardness (Kg/cm^2)	4.12- 6.45	4.45 – 6.15	4.34 – 6.46
Friability (%)	0.40± 0.05	0.39± 0.10	0.67± 0.09

Table 72. Dissolution profiles of CR13, CR14 and CR15 formulations

Time	Specification	CR13 (%)	CR14 (%)	CR15 (%)
1 h	NMT 25 %	17.37± 1.43	15.54± 1.05	19.11± 0.65
4 h	20-50%	42.75± 1.15	36.77± 0.69	40.24± 1.15
8 h	35-70%	64.91± 2.11	66.47± 1.43	58.17± 1.24
20 h	NLT 70 %	87.71± 1.05	92.44± 1.56	93.10± 1.43

5.1.3.4.6. Effect of height (position) of Wurster

Height of wurster process is critcal paramter which need to be optimized. The height of the wurster coating above the orifice plate. The height of wurster optimized based on the material load of pellets in the container. It is substrate dependent. Height of wurster direcly affect drying efficency, drug loading and functional coating process. **Table 73** suggested standard conditions for partition height for drug and fuctional coating. (Mundada, P. K., *et al*,2017).

Table 73: Standard conditions for partition height for drug and functional coating

Substrate partition height	
Tablets coating	24–55 mm in small machines
	45–100 mm in 16" wursters and larger
Pellets coating	10–30 mm small machines
	25–65 mm in 24" wursters and larger.
Powder	Approximately 20–45 mm in all machines

Trial CR16, CR 17 and CR 18 were planned with different height position CR 17 trial was found satisfactory. Height positions i.e. lower (CR16) and higher (CR18) markly affect the coating and pattern of fluidization. Evaluation results shown in **Table 74**, **Table 75** and **Table 76**. The height of column has significantly role in the drug loading and functional coating. In CR16 column height kept less fludization and more sticking of the pellets observed while in CR18 column height was kept more then more fluidization occurs and non uniform coating take place. In CR17 formulation optimum coloumn height was kept and uniform results obtained.

Table 74. Evaluation of lubricated blends of CR16, CR17 and CR18 formulations

Parameters	CR16	CR17	CR18
Bulk density (g/cc)	0.72± 0.05	0.75 ± 0.04	0.77± 0.08
Compressibility index (%)	13.1± 0.14	11.99± 0.10	11.08± 0.15
Angle of repose (θ)	25.55± 0.12	26.75± 0.15	26± 0.14

Table 75: Physical properties of MUPS tablets of of S (-) Metoprolol succinate CR16, CR17 and CR18 formulation

Parameters	CR16	CR17	CR18
Thickness (mm)	3.29 ± 0.16	3.29± 0.19	3.28± 0.10
Hardness (Kg/cm^2)	4.11 - 6.32	4 .34 – 6.34	4.34 -6.55
Friability (%)	0.37± 0.14	0.33± 0.19	0.41± 0.12

Table 76: Dissolution details of CR16, CR17 and CR18 formulation

Time	Specification	CR16	CR17	CR18
1 h	NMT 25 %	21.17± 0.23	19.15± 0.18	22.14± 0.11
4 h	20-50 %	36.14± 0.32	33.14± 0.32	39.15± 0.15
8 h	35-70 %	55.16± 0.22	53.1± 1.11	59.19± 0.16
20 h	NLT 70 %	89.11± 0.14	93.75± 0.16	89.14± 0.10

5.1.3.5. Comparative dissolution profile (CDP) of test product and marketed Product of S (-) Metoprolol succinate MUPS tablets

Comparative dissolution profile was done to check the similarity between the release behaviour of prepared test sample and the marketed sample. It is also regulatory requirement before launch of the product in the market. Comparative dissolution profile of of MUPS tablets of S (-) Metoprolol succinate of approved (Toprol-XL 25) AztraZenica (Reference) was performed in all dissolution media i.e. a) Sodium Phosphate Buffer pH 6.80 with agitation speed 50 RPM b) 0.10 N hydrochloric acid with agitation speed 50 RPM and d) Acetate buffer pH 4.50 with agitation speed 50 RPM. Hence, the Multimedia dissolution profiling results of the marketed samples are similar to that of test sample in term of F2 Value i.e. greater than 50 (Note: If F2 value more than 50 : Dissolution similarity is there) as shown in **Table 77-79** (Mundada, P. K.,*et al*,2017).

5.1.3.5.1. CDP of test product and marketed product in sodium phosphate buffer pH 6.80

Table 77. F_2 value of MUPS tablets in 900 mL in sodium phosphate buffer pH 6.80/ USP II (Paddle) with sinkers / 50 RPM

Dissolution limits 2 h (NMT 25 %) 4 h (20-50%) 8 h (35 -70%) 20 h (NLT 70 %)	Test Sample FT5		Marketed sample Seloken XL 25	
	2 h	16.77±1.42	2 h	15.18±2.10
	4 h	36.57 ±1.56	4 h	40.21 ±1.21
	8 h	54.42 ±1.42	8 h	56.42 ±1.52
	20 h	95.77± 1.32	20 h	94.77± 1.12
F2 Similarity factor	**92**			

5.1.3.5.2. CDP of test product and marketed product in pH 4.50 acetate buffer / USP II (Paddle) / 50 RPM

Table 78. F2 Value of MUPS tablets in 900 mL in pH 4.5 acetate Buffer / USP II (Paddle) / 50 RPM

	Test Sample FT5 (25 mg)		**Marketed sample Seloken XL 25**	
F2 Similarity factor	2 h	12.12± 1.17 %	2 h	13.16 ± 1.20 %
	4 h	27.18 ±1.19 %	4 h	28 ±1.11 %
	8 h	42.22 ±1.21 %	8 h	44.12 ±1.15 %
	20 h	81.12± 1.18 %	20 h	84.21± 1.14 %
	84			

5.1.3.5.3. CDP of test product and marketed product in 0.1N HCl / USP II (paddle) / 50 RPM. (Seal coated Pellets)

Table: 79 F2 Value of 900 mL of 0.1N HCl / USP II (Paddle) / 50 RPM

	Test Sample FT5 (25 mg)		**Marketed sample** Seloken XL 25	
F2 Similarity factor	2 h	8.15± 1.01 %	2 h	9.10± 1.14 %
	4 h	20.13 ±1.32 %	4 h	22.15 ±1.42 %
	8 h	35.15 ±1.16 %	8 h	38.13 ±1.15 %
	20 h	65.31± 1.09 %	20 h	68 ± 1.05 %
	69			

5.1.3.6: Formulation process validation of MUPS tablet formulation.

From this study, we can say that pharmaceutical process validation is the most important and most recognized parameter of cGP. cGP regulations require manufacturing processes to be designed and controlled to ensure that in-process materials and final products meet and consistently meet specified quality requirements. Products must be built robust enough to withstand the variability of the manufacturing process, and the manufacturing process must have the ability and stability to continue to ensure a well-functioning and safe product. . Process validation consists of a series of activities that take place over the life cycle of products and processes as shown in **Table 80** (Abhishek, P. *et al*,2012).

Table 80. In process results of process validation batches of metoprolol succinate modified release MUPS tablets

Test	Specification	SCL001	SCL002	SCL003
Drug Loaded pellets				
Description	White to off-white colour pellets	Complies	Complies	Complies
Sieve analysis	NMT 5 % should not retained on 24 #	2.35 ± 1.22	2.12 ±1.15	2.17 ±1.20
	NLT 95 % should retained on 30 #	97.12 ± 1.10	98.10 ±1.05	97.50 ±1.32
Assay in %		99.10 ± 0.50	100.5 ± 0.44	99.12 ± 0.50
Functional coated pellets				
Description	White to off-white colour pellets	Complies	Complies	Complies
Sieve analysis	NMT 5 % should not retained on 24 #	3.23 ± 1.10	3.10 ± 1.05	3.50 ±1.13
	NLT 95% should retained on 30 #	98.10 ± 1.52	98.20 ±1.42	99.10 ±1.25
Assay in %		99.10 ±1.22	98.50±1.52	98.20 ±0.50
Dissolution				
1 h	NMT 25 %	17.15 ±2.11	16.43 ±1.32	17.01 ±1.21
2 h	20-50%	35.17 ±1.34	37.52 ±1.23	33.12 ±1.54
8 h	35-70%	58.42 ±1.29	56.12 ± 1.42	57.41 ±1.20
20 h	NLT 70 %	92.15 ±1.43	94.23±1.17	95.11 ±1.25
Compressed MUPS tablet				
Description	White to off-white colour circular shape	Complies	Complies	Complies
Average weight (mg)	250 mg ± 3 %	250.10	250.12	251.15
Thickness (mm)	3.70 ± 0.30	3.81-3.95	3.82-3.93	3.80-3.92

Test	Specification	SCL001	SCL002	SCL003
Hardness	NLT 3 Kg/cm^2	3.40-6.14	3.34-5.65	3.34-5.45
Friability	NMT 1 %	0.12 ± 0.02	0.15 ± 0.03	0.21 ± 0.08
Assay	90-110 %	99.10 ± 1.16	98.60 ± 1.55	98.60 ± 1.32
Dissolution				
1 h	NMT 25 %	18.20 ± 1.42	17.21 ± 1.21	16.02 ± 1.10
2 h	20-50 %	34.29 ± 1.54	38.12 ± 1.13	36.22 ± 1.34
8 h	35-70%	56.41 ± 2.32	55.22 ± 2.08	56.21 ± 1.32
20 h	NLT 70 %	93.19 ± 2.15	94.11 ± 2.07	93.21 ± 1.12

5.1.4. Bioanalytical method development

A simple, specific, sensitive, and rapid reversed-phase high-performance liquid chromatography (RP-HPLC) method was developed and validated for the quantification of S (-) metoprolol succinate in small amounts of rabbit plasma. A mobile phase containing plasma was run through the column to give a plasma peak with a retention time of 9.12 min.

5.1.4.1. Standard curve of S (-) Metoprolol succinate in rabbit plasma

A sample chromatogram of plasma S(-) metoprolol is shown in the Figure 14 , and the retention time of plasma metoprolol was 9.12 ± 0.01 min. A standard plot of metoprolol against plasma was also drawn showing a linear range of 0.020 µg/mL to 0.100 µg/mL and a regression of 0.99. Standard curve data for metoprolol in plasma are presented in Figure 14.

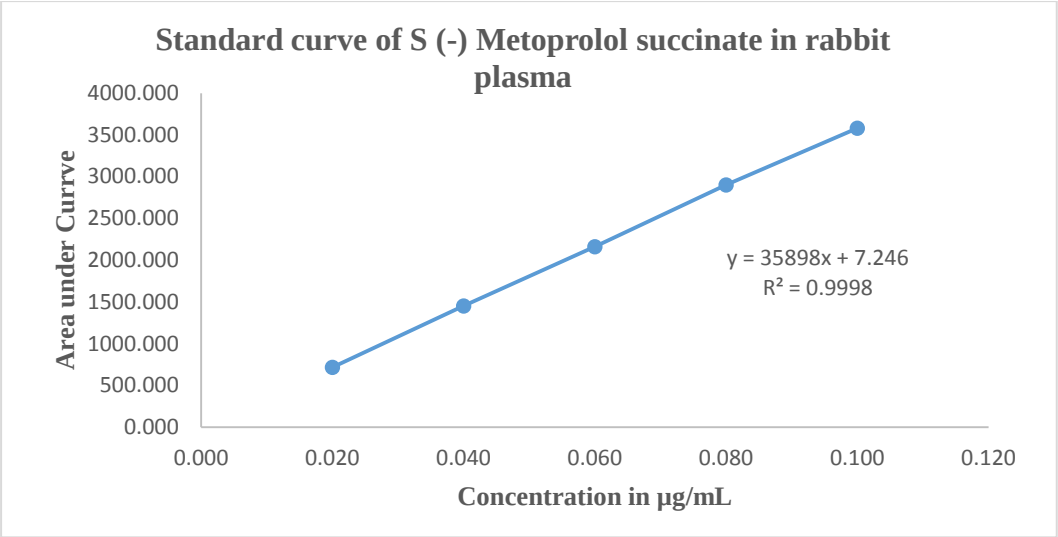

Figure 14. Calibration curve of S(-) Metoprolol succinate in plasma

5.1.4.2 System suitability parameters

Separation variables were adjusted and the column was saturated with mobile phase at 1 mL/min. After fully saturating the column, a working standard of 0.10 µg/mL S(-) metoprolol succinate was injected in 6 replicates. Peak and column performance reports were recorded for all chromatograms as shown in **Table 81.**

Table 81: System suitability parameters of S (-) Metoprolol succinate

System suitability	Retention time	Area under curve	No. of Theoretical plates
1	9.12	3582	2951
2	9.12	3585	2954
3	9.12	3582	2950
4	9.14	3583	2954
5	9.13	3584	2952
6	9.12	3584	2951
Mean	**9.12**	3584	**2952**
SD	**08**	**1.15**	**1.52**

5.1.4.3.Validation of developed method

5.1.4.3.1.Linearity

The linearity of an analytical method is the ability (within a certain range) to obtain an assay that is directly proportional to the area of the analyte within the sample. The

standard curve was contracted after analysis of 5 different concentrations (0.020-0.100 µg/mL), the area of each concentration was plotted 5 times and the average area was calculated. From the observed AUC and the mean of each concentration value, response ratios (response factors) were determined by dividing the AUC by each concentration **(Table 82)** (Bhowmick, M.,*et al*, 2015).

Table 82: Response ratio data for Linearity for S(-) Metoprolol succinate

Replicates	Concentration (µg/mL)	Area under curve (n=5)	Response ratio (n=5)
1	0.020	716	35.810
2	0.040	1455	36.370
3	0.060	2210	36.830
4	0.080	2899	36.230
5	0.100	3586	35.860
Mean			**36.220**
SD			**0.372**
%RSD			**0.010**

5.1.4.3.2. Specificity

Method specificity was performed to unambiguously assess the analyte presence of possible constituents such as impurities, degradation products and matrix constituents.

5.1.4.3.3. Accuracy

A recovery study was performed to validate the accuracy of the developed method. Defined concentrations (120 % level) of standard drugs were spiked into pre-analytical sample solutions and their recoveries were analyzed as shown in **Table 83** (Bhowmick, M.,*et al*, 2015).

Table 83: Recovery study S(-) Metoprolol Succinate (120 % Level)

Replicates	Concentration (µg/mL)	Added amount (µg/mL)	Conc found in (µg/mL) n=3	% Mean concentration
1	0.020	0.024	0.0238	99.170
2	0.040	0.048	0.0477	99.360
3	0.060	0.072	0.0716	99.440
Mean				99.323
SD				0.113
% RSD				01

5.1.4.3.4. Precision

The precision are established in three differences:

1. Repeatability

Linearity ranges for S(-) metoprolol succinate Five replicate measurements at five concentrations with linear ranges of 0.020, 0.040, 0.060, 0.080, and 0.100 µg/mL demonstrated precision at short intervals under the same operating conditions. rice field. Reproducibility results are shown in **Table 84** (Bhowmick, M.,*et al*, 2015).

Table 84 : Repeatability of S(-) Metoprolol succinate

Replicates	Concentration (µg/mL)	Mean conc found in (µg/mL) n=5
1	0.020	0.020
2	0.040	0.039
3	0.060	0.058
4	0.080	0.082
5	0.100	0.098
SD		0.028
% RSD		0.474

2. Intermediate precision

a) Day to day precision

Intermediate precision was performed within laboratory variation on different days with 5 replicates at 5 concentrations. Daily intermediate precision results for S(-) metoprolol succinate as shown in **Table 85** (Bhowmick, M.,*et al*, 2015).

Table 85: Day to day precision of S(-) Metoprolol succinate

Replicates	Concentration (µg/mL)	Mean conc. found in (µg/mL) n=5
1	0.020	0.019
2	0.040	0.039
3	0.060	0.061
4	0.080	0.081
5	0.100	0.099
SD		**0.029**
% RSD		**0.478**

b) Analyst to analyst precision

Analyst to analyst variation was performed by different analyst in five replicate at five concentrations as shown in **Table 86.**

Table 86 : Analyst to analyst precision of S(-) Metoprolol succinate

Replicates	Concentration (µg/mL)	Conc found in (µg/mL) n=5
1	0.020	0.018
2	0.040	0.038
3	0.060	0.060
4	0.080	0.078
5	0.100	0.098
SD		**0.028**
% RSD		**0.485**

3. Reproducibility

Reproducibility was assessed by chemical-to-chemical variability (using Rawchem chemicals instead of Merck chemicals) in five replicates at five concentrations as shown in **Table 87 (**Bhowmick, M.,*et al*, 2015).

Table 87 .Reproducibility of S(-) Metoprolol succinate

Replicates	Concentration (µg/mL)	Conc found in (µg/mL) n=5
1	0.020	0.019
2	0.040	0.038
3	0.060	0.062
4	0.080	0.079
5	0.100	0.099
SD		**0.028**
% RSD		**0.479**

5.1.4.3.5. Robustness

Small, deliberate changes in mobile phase concentration were made according to ICH standards to ensure that the method was unaffected. The mobile phase ratio was changed from ACN:methanol:ammonium acetate buffer pH-5 (25:55:20 % v/v/v) to (25:54:21 % v/v/v). Robustness results are shown in the **Table 88** (Bhowmick, M.,*et al,* 2015).

Table 88. Robustness of S(-) Metoprolol Succinate

Replicates	Concentration (µg/mL)	Conc found in (µg/mL) n=5
1	0.020	0.018
2	0.040	0.039
3	0.060	0.061
4	0.080	0.079
5	0.100	0.098
SD		**0.028**
% RSD		**0.480**

5.1.5. Pharmacokinetic studies of MUPS tablet of S(-) Metoprolol succinate

After oral administration of plain 5 mg and test formulation of S(-) metoprolol succinate 5 mg MUPS tablet. The in vivo data were obtained, and these were plotted against time. The pharmacokinetic parameters C_{max}, T_{max} and AUC_{0-t} were summarized in **Table 89.** The pharmacokinetic parameters T_{max} and $AUC_{0-\infty,}$ are related to the rate and extent of absorption, respectively, while C_{max} is related to both the processes. The extent of absorption is a key characteristic of a drug formulation, and therefore $AUC_{0-\infty,}$ is an important parameter for analysis in a comparative bioavailability study.

It is evident from **Figure 15,** that plain S(-) Metoprolol succinate could produce no sustained effect. The test formulation of S(-) Metoprolol succinate 5 mg MUPS tablet showed significantly lower C_{max} than plain S(-) Metoprolol Succinate and it required more time (T_{max} 8 h) to reach C_{max} (0.083 µg/mL) as compared with plain S(-) Metoprolol succinate (T_{max} 1 h) C_{max} (0.185 µg/mL). The area under the curve increased nearly 1.7 times higher in Test formulation of MUPS tablet than plain S(-) Metoprolol succinate. C_{max} and T_{max} values of formulated Test formulation of MUPS tablet and marketed SR matrix tablets were comparable as per literature, and AUC_{0-t} of Test formulation of MUPS tablet was higher than the marketed SR matrix tablets.

These pharmacokinetic parameters (lower Cmax and prolonged Tmax) indicated that drug release maintained smooth extended absorption of drug and sustained pseudo-steady state concentration of MS in plasma level with minimal fluctuations up to 36 hs. However, there was a lag time of approximately 1–2 h before blood levels could be measurable (Bhowmick, M.,*et al*, 2015). The test formulation compared with the marketed formulation and based on literature shows both are equivalent in nature.

Table 89. Pharmacokinetic parameters of S(-) Metoprolol succinate in 'New Zealand rabbits' (n=6), orally administrated with pure drug solution (PDS) 5 mg Test formulation 5 mg, marketed formulation.

Plain S(-) Metoprolol Succinate			Test formulation		
T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)	T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)
10	0.186	0.402	80	0.081	1.928
10	0.195	0.444	80	0.082	1.956
10	0.180	0.430	80	0.081	2.033
10	0.179	0.440	80	0.084	1.993
10	0.193	0.463	80	0.085	2.025
10	0.176	0.421	80	0.086	2.023
Average	0.185	0.433	Average	0.083	1.993
SD	08	0.021	SD	02	0.043
% CV	4.238	4.852	% CV	2.570	2.139

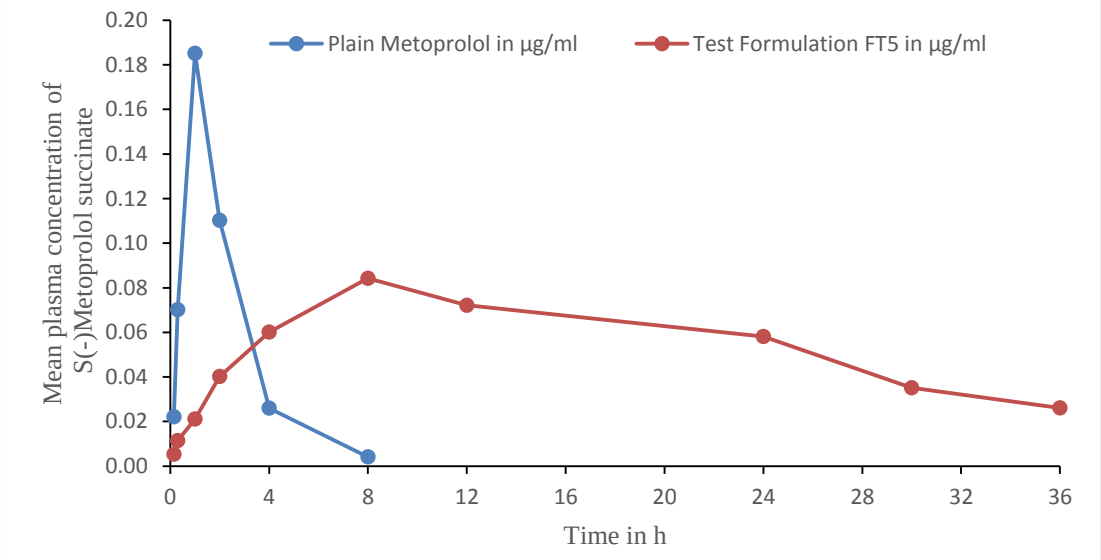

Figure 15 : Plasma concentration of S(-) Metoprolol Succinate in male new zealand rabbits (n=6) following oral adminstration of plain S(-) Metoprolol

Succinate and MUPS tablet of S(-) Metoprolol succinate

5.1.6. Stability studies of MUPS tablet of S (-) Metoprolol succinate

Stability studies were conducted according to ICH Guidelines Q1A(R2), the optimized formulation was packed and stored in accelerated conditions in a stability chamber. The samples were evaluated for assay and dissolution studies at regular intervals. The stability studies were carried out according to ICH guidelines for optimized formulation. The stability studies were carried out under conditions 40 ˚C ±2 ◦C/75 % ±5 % RH. Then the MUPS tablets were stored under accelerated conditions and the samples were withdrawn at 0, 3 and 6 months and evaluate the MUPS tablets for hardness, assay and dissolution. In 0-month initial hardness i.e 3.10 ±0.28, at 3 months it is 3.15 ±0.16 and in six months it is 3.20 ±0.12. There is slight increase in the hardness in w.r.t time but well with limits. For drug assay 0 month i.e 99.50 ±1.60, at 3 months it was 98.50 ±1.21 and in six months it was 97.20 ±1.92. There is also slight decrease in assay value from initial but within the specification limit. For dissolution 0 month at 20 hr 95.77± 1.32, at 3 months it is 93.21 ±2.20 and in six months it is 90.17 ± 1.70. There is also slight decrease in dissolution value from initial but within the specification limit. Based on the stability it can be concluded that developed formulation is stable. Results shown in **Table 90** (Mundada, P. K., *et al,*2017).

Table 90. Accelerated stability studies (40±2 ^{0}C/75% ±5% RH)

Month	Hardness (n-=3) in Kg/cm^2	Assay (n-=3) in %	Dissolution with limit (n-=3) in %
0	3.10 ±0.28	99.50 ±1.60	16.77±1.42 Limit: 2 h (NMT 25 %) 36.57 ±1.56 Limit: 4 h (20.0-50%) 54.42 ±1.42 Limit: 8 h. (35-70) 95.77± 1.32 Limit: 20 h (NLT 70 %)
3	3.15 ±0.16	98.50 ±1.21	15.02 ±2.10 Limit: 2 h (NMT 25 %) 34.57 ± 1.90 Limit: 4 h (20-50%) 52.39 ±1.40 Limit: 8 h (35-70 %) 93.21 ±2.20 Limit: 20 h (NLT 70 %)
6	3.20 ±0.12	97.20 ±1.92	14.05± 2.20 Limit: 2 h (NMT 25 %) 30.41± 1.42 Limit: 4 h (20-50%) 49.20 ± 1.65 Limit: 8 h (35-70 %) 90.17 ± 1.70 Limit: 20 h (NLT 70 %)

5.2 Screening and evaluation of spray dried fluid bed processed orodispersible platform for Levocetirizine HCl (Part B)

5.2.1: Preformulation study

5.2.1.1. Organoleptically property

Levocetirizine HCl was observed as white, crystalline powder.

5.2.1.2. Solubility

Levocetirizine HCl discovered to be completely soluble in distilled water, it is also soluble in ethanol, acetone, 0.10 N HCl and phosphate buffer having pH 6.80 as shown in **Table 91**.

Table 91. Solubility of S (-) Metoprolol succinate

S.No	pH	Concentration (mg/mL) (n=3)	Observations
1	Distilled water	98.15 ± 0.14	Soluble
2	Ethanol	97.21 ± 0.13	Soluble
3	Acetone	95.13 ± 0.17	Soluble
4	0.1 N HCl	90.12 ± 0.15	Soluble
5	Phosphate buffer	91.31 ± 0.12	Soluble

5.2.1.3. Bulk and Tapped density

Bulk and Tapped density for the Levocetirizine HCl found to be 0.42 g/mL and 0.59 g/mL (Akhtar, *et al,*2020).

5.2.1.4. Compressibility index and Hausner ratio

The flow property indicator both CI (compressibility index) found to be 36 and H (Hausner ratio) 1.45 indicates very poor flow properties (Akhtar, *et al,*2020).

5.2.1.5. Identification

5.2.1.5.1 Fourier transform infrared (FTIR)

FTIR absorption spectrum of Levocetirizine HCl was measured by mean of a absorbance. The IR spectrum, obtained at a wave-number series of 4000 –600 cm^{-1} and at a tenacity of 4 cm^{-1}, is shown in Figure 34. -CI peak obtained at

781.14,807.79,844.60 in cm^{-1}, -COO-ar at 1745.35 cm^{-1}, -C-O- at 1135.95 cm^{-1} and -C-N- at 1355.76 cm^{-1}. All the obtained peaks match with the reference which conforms identification of Levocetirizine HCl. Band assignments of Levocetirizine HCl are summarized in the **Figure 16** and **Table 92** (Jahangir, M. A., *et al*, 2014).

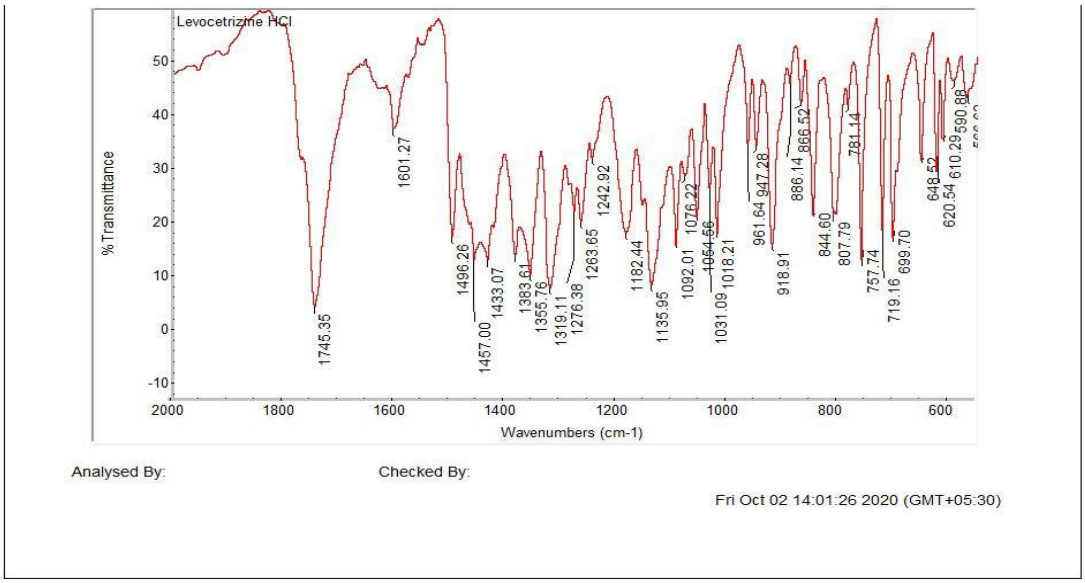

Figure 16. FTIR absorption spectrum of Levocetirizine HCl

Table 92: FTIR absorption spectrum band assignments of Levocetirizine HCl

S.No	Assignment	Wave number in cm^{-1}
1.	-CI	781.14,807.79,844.60
2.	-COO-ar	1745.35
3.	-C-O-	1135.95
4.	-C-N-	1355.76

5.2.1.5.2. HPLC Method

The retention time of the Levocetirizine HCl Standard: **12.46** min and the Retention time of the Levocetirizine HCl: **12.47** min as shown in **Figure. 17** and **Figure 18**. Both sample and the standard preparation retention time matches which confirms the identification of the Levocetirizine HCl (Basavaiah, K., *et al*,2012).

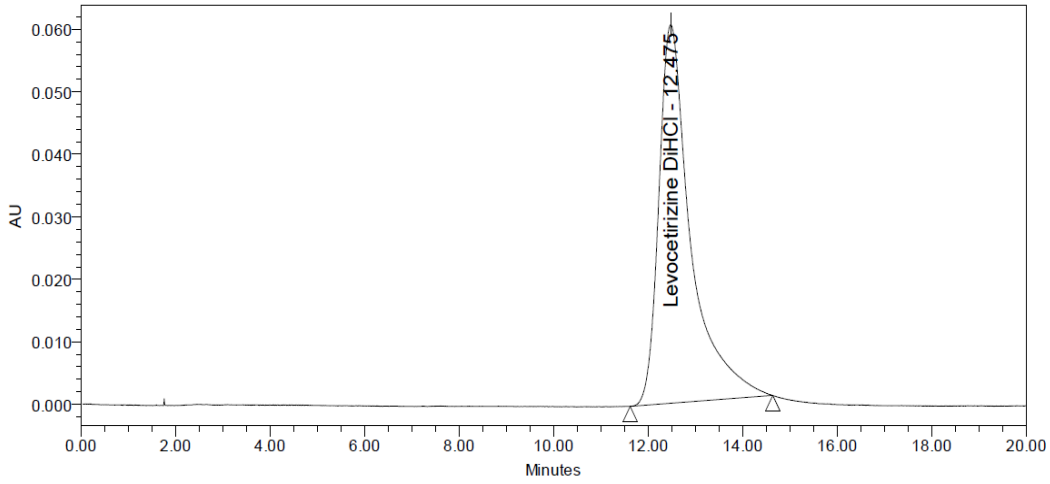

Figure 17. Sample chromatogram of Levocetirizine HCl

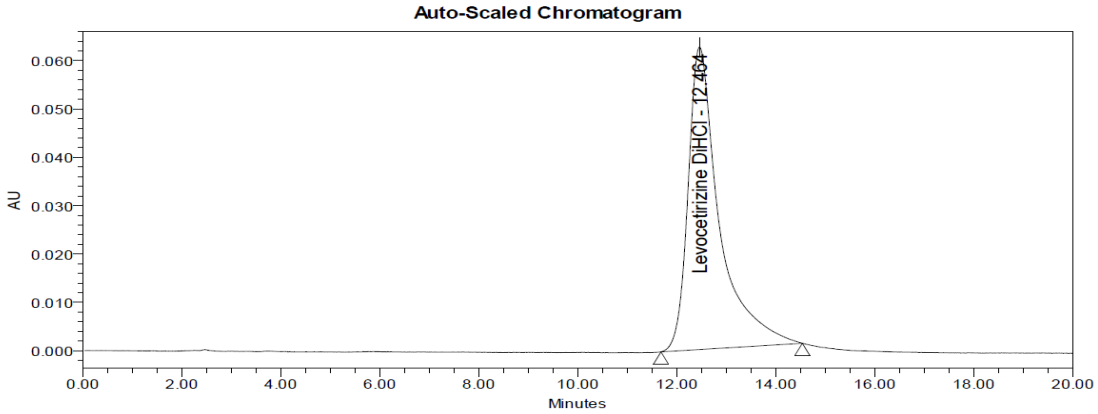

Figure 18. Standard chromatogram of Levocetirizine HCl

5.2.1.6 UV Spectroscopy determination of λ_{max} Levocetirizine HCl

From the stock solution, a suitable concentration of Levocetirizine HCl i.e 10 µg/ mL was made in distilled water and Ultravoilet scan was taken for above stock solutions between the wavelengths of 200- 400 nm. (Gupta, M., *et.al* ,2014) The Absorbance of Levocetrizine HCl in 6.80 pH phosphate buffer was found to be 231 nm. (Figure 19) which is matching with reported value (Jahangir, M. A., *et al*, 2014).

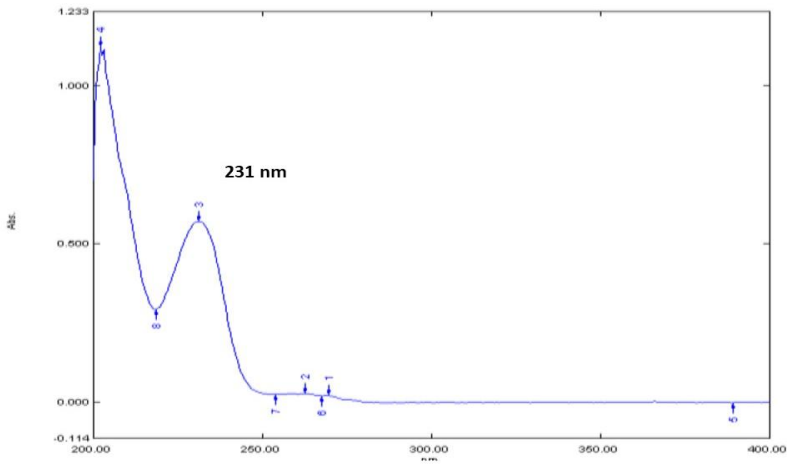

Figure. 19: UV spectrophotometer: λ_{max} of Levocetirizine HCl

5.2.1.7. pH

2 g of sample in a 100 mL beaker, add to it 100 mL of distilled water. Stir well to dissolve and check the pH at 25°C. The pH of Levocetirizine HCl was found to be 5.40 against standard limit i.e. 4.50-6.50 (Jahangir, M. A., *et al*, 2014).

5.2.1.8. Melting point determination

In DSC study, endotherm of Levocetirizine HCl found around 215.45 0C as shown in the Figure 20 which indicates purity and identity of drug. (Vijay,et.al., 2012). The Levocetirizine HCl is having the impurity well within the limit. The observed values shown in Table 98. The results found were well with the specification limit for single max impurity i.e. 0.06 limit (NMT 0.5 %) and for total impurity i.e. 0.26 limit (NMT 1.0 %).

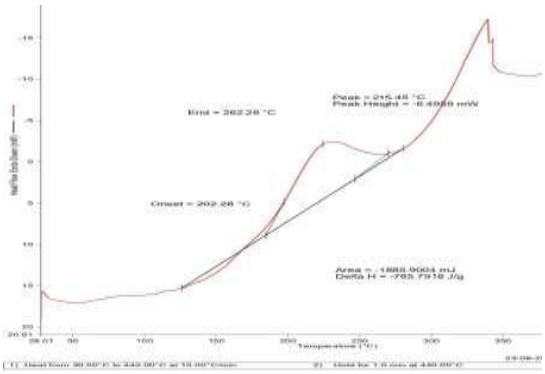

Figure 20. DSC thermogram of Levocetirizine HCl

5.2.1.9. Loss on drying

The observed value of LOD was found to be 0.42 ±0.05 % which reflects the API is having less moisture which is ideal for preparing orodispersible tablet which avoid sticking problem during compression (Al-Kubati, *et al*, 2022).

5.2.1.10. Sieve analysis

The main objective of sieve analysis was to test the different size of API particles present. Series of standard sieve were kept one another, so that the mesh with larger mesh size subjugate up position followed by sieve of decreasing trend pore size towards the bottom. From Sieve analysis data we can conclude that API is fine in nature as shown in **Table 93** (Shah, A. P., *et al,* 2021).

Table 93. Sieve analysis of Levocetirizine HCl

S.No	Sieve number (#)	% Retained
1.0	20	0
2.0	40	3.25 ± 0.21
3.0	60	16.32 ± 0.16
4.0	80	30.51± 0.18
5.0	100	49.92± 0.10

5.2.1.11. Drug assay

The observed assay value was 98.72 against the standard limit i.e. 98 %–102 % on the dried basis. The Assay of the Levocetirizine HCl complies w.r.t specification and chromatograms shown in **Figure 21, 22 and 23** (Basavaiah, K., *et al,*2012).

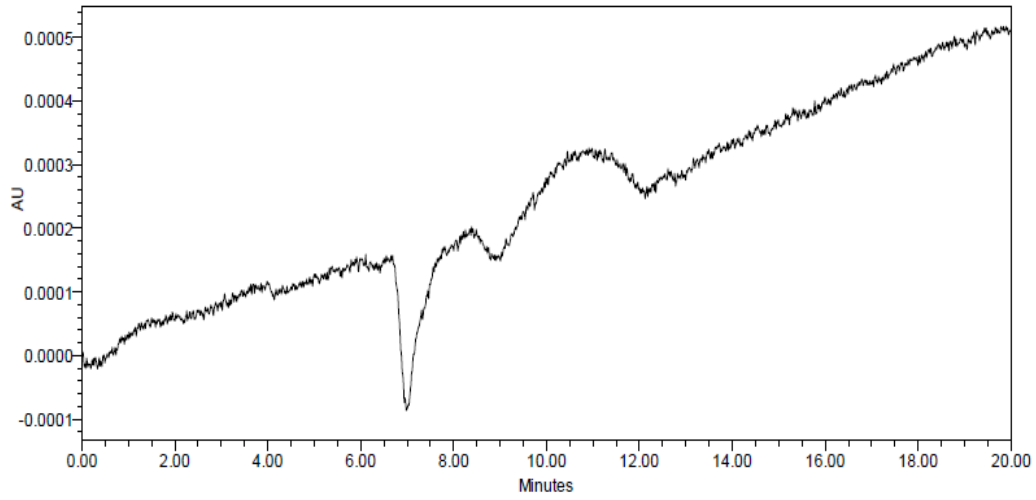

Figure 21. Blank chromatogram of Levocetirizine HCl

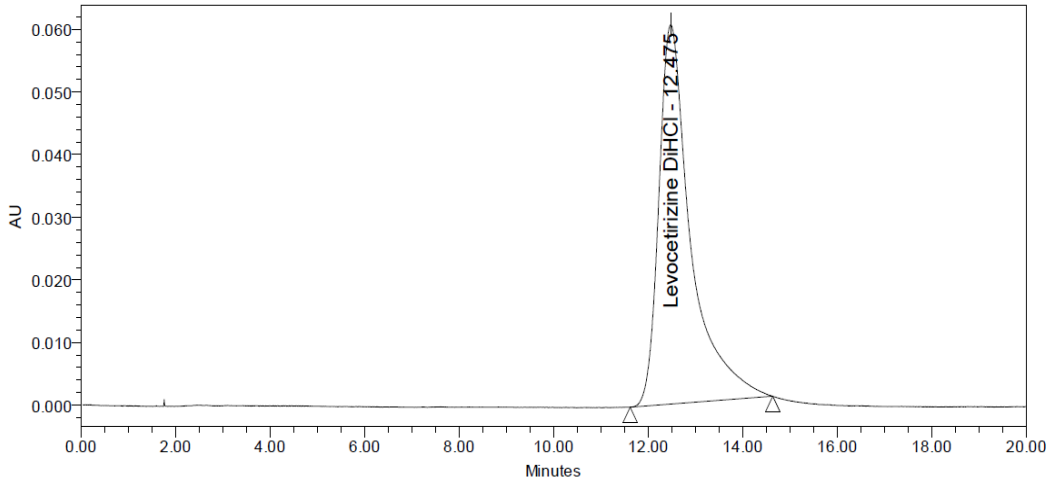

Figure 22. Sample chromatogram of Levocetirizine HCl

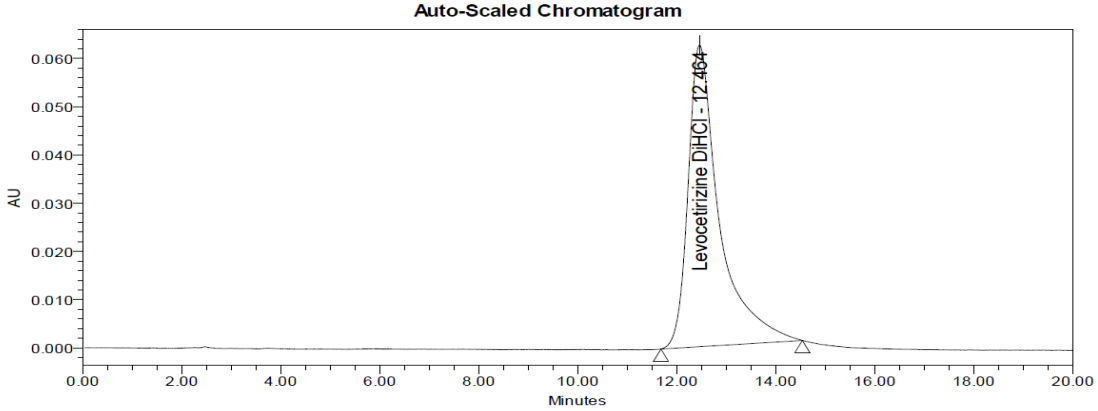

Figure 23. Standard chromatogram of Levocetirizine HCl

5.2.1.12. Related substances of Levocetirizine HCl

Dissolve 20 mg of the substance under examination in 100 mL of mobile phase and filter. Reference solution (a): A 0.02% w/v solution Levocetirizine HCl mobile phase. Reference solution (b): Dilute 1 mL of reference solution to 100 mL with mobile phase. The Levocetrine HCl is having the impurity well within the limit. The observed values shown in **Table 94.** The results found were well with the specification limit for single max impurity i.e 0.06 limit (NMT 0.5 %) and for total impurity i.e 0.26 limit (NMT 1.0 %). From the observed value API can be used for the manufacturing of the orodispersible tablets of Levocetirizine HCl (Birendra, Y., *et al*,2010).

Table 94. Related substances of Levocetirizine HCl

Related substance	Standard	Test
Single Max Impurity	NMT more than 0.50 %	0.06 %
Total Impurity	NMT more than 1 %	0.26 %

5.2.1.13. Calibration curve of Levocetirizine HCl

The absorbance of Levocetirizine HCl in 6.80 pH phosphate buffer was observed to be 231 nm. The absorbance taken from 5 µg/mL concentration to 60 µg/mL **(Table 95).** From the data it revealed that the concentration vs absorbance obeys Beer Lambert's law. It showed R^2 value of 0.9997 **(Figure 24)** (Birendra, Y., *et al*,2010).

Table. 95. Calibration curve of Levocetirizine HCl in 6.80 pH phosphate buffer

Drug conc. (µg/mL)	Absorbance (n=3)
5	0.09 ± 0.01
10	0.16 ± 0.02
15	0.23 ± 0.01
20	0.31 ± 0.03
25	0.39 ± 0.02
30	0.46 ± 0.03
35	0.54 ± 0.03
40	0.62 ± 0.01
45	0.70 ± 0.03
50	0.78 ± 0.03
55	0.86 ± 0.02
60	0.93 ± 0.02

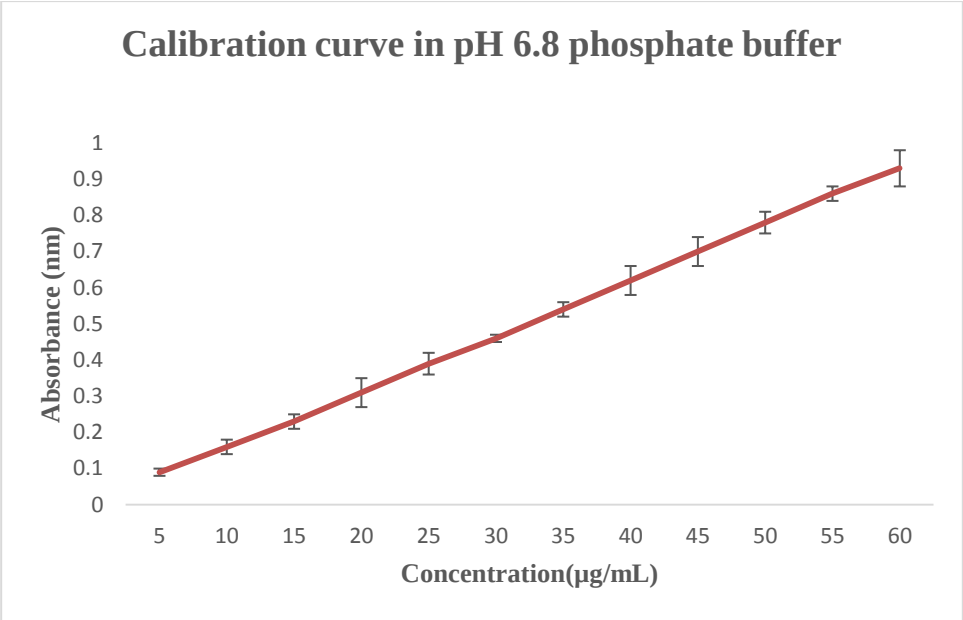

Figure 24. Calibration curve of Levocetirizine HCl in pH 6.80 phosphate buffer

5.2.1.14. Drug excipient compatibility

Compatibility of Levocetirizine HCl (API) with excipient was studied by keeping API individually and mixing Levocetirizine HCl individually with all excipient in 1:1 ratio and exposed to 25°C±2°C /65% RH ± 5 % RH, 40°C±2°C /75% RH± 5 % RH and 60°C±2°C for 30 days in vials as mentioned in **Table 96** (Choudhury, P., *et al*,2016).

Table 96. Preformulation study for Levocetirizine HCl

S.No	Ingredients	25°C±2°C /65% RH ± 5 % RH	40°C±2°C /75% RH± 5% RH	60°C±2°C
1	Levocetirizine HCl (API)	White to off white powder	White to off white powder	White to off white powder
2	API + Mannitol (Perlitol SD 200) Spray Dried	White to off white powder	White to off white powder	White to off white powder
3	API + L-Hydroxypropyl cellulose (LH -11)	White to off white powder	White to off white powder	White to off white powder
4	API + Crospovidone	White to off white powder	White to off white powder	White to off white powder
5	API + Sucralose	White to off white powder	White to off white powder	White to off white powder
6	API + Sodium saccharin	White to off white powder	White to off white powder	White to off white powder
7	API + Aspartame	White to off	White to off	White to off

S.No	Ingredients	25°C±2°C /65% RH ± 5 % RH	40°C±2°C /75% RH± 5% RH	60°C±2°C
		white powder	white powder	white powder
8	API + Povidone	White to off white powder	White to off white powder	White to off white powder
9	API + Colour sunset yellow	Yellow colour powder	Yellow colour powder	Yellow colour powder
10	API + Orange flavor	Yellow colour powder	Yellow colour powder	Yellow colour powder
11	API + Mg. stearate	White to off white powder	White to off white powder	White to off white powder

5.2.1.15. Chemical evaluation by DSC

In DSC study, endotherm of Levocetirizine HCl found around 215.45 ^{0}C. While endotherms of Levocetirizine HCl with other excipients found in the range of 205 – 220 ^{0}C. No substantial shifting of the endotherms was observed; this shows that the levocetirizine HCl is compatible with excipients used in the formulation. **Figure 25** (Labib, G. S.*et al*, 2015).

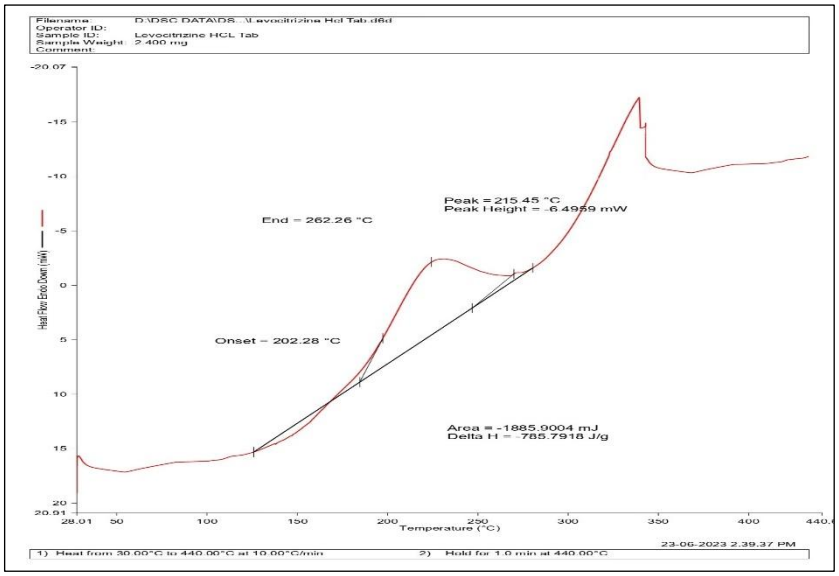

Figure 25: DSC study of levocetirizine HCl with different excipients in orodispersible tablets.

5.2.1.16. Marketed product characterization

Liecet MD XL 25 mg Batch No. SKU1733, marketed by RDimex, India Limited. Product was procured form market and evaluated for its size, shape, weight, and chemical analysis such as assay and dissolution. Physicochemical properties are highlighted in **Table 97** (Kathpalia, H., *et al*,2017)

Table 97. Physicochemical evaluation of marketed product

S.NO	Parameters	Results
1.0	Brand Name	Liecet MD
2.0	Generic Name	Levocetirizine HCl
3.0	Strength	10 mg
4.0	Batch No.	SKU1733
5.0	Mfg Date	Feb, 2020
6.0	Exp Date	Jan , 2022
7.0	Mfg by	RDimex, India Limited
8.0	Weight	100 mg
9.0	Dimensions	6.0 mm
10.0	Colour	White
11.0	Shape	Round
12.0	Hardness	NLT 3 Kg/cm^2
13.0	Thickness	3.80 ± 0.30 mm
14.0	Disintegration Time	35 sec

5.2.2. Blend characteristics of orodispersible tablet of Levocetirizine HCl

Levocetirizine HCl orodispersible tablets was formulated using mixing and direct compression method. Diverse types of disintegrating agents were used named as crosspovidone, croscarmellose sodium, L-HPC and in combination. Spray dried mannitol improves aqueous solubility, good wetting properties, good dispersion and soothning effect. Povidone is inert, non-toxic, temperature resistant, pH stable and water soluble polymer used as a binder in the formulation. Sucralose, sodium saccharin and aspartame taste mask the bitterness of the drug. The sweetners were FDA approved synthetic sugar substitutes, considered as safe and having good taste masking properties (Labib *et al*,2015).

5.2.2.1 Angle of repose

The data attained from the angle of repose of the formulations were discovered in the range of 23.65° and 28.16°. From the data it is concluded that the Levocetirizine HCl API is having good flow property **(Table 98)** (Sumati *et al.,* 2023).

5.2.2.2 Bulk density

The bulk density and tapped density are the important accpect of the material. Bulk and tapped density interferences with the occpancy of the equipments. Density (Bulk) contributes void space (particles to particles). Tapped density contribute to increase in bulk density, powder cohesiveness and powder flow property. The loose bulk density and tapped bulk density for the entire formulation blend varied from 0.37 to 0.47 g/cm^3 **(Table 98)** (Labib *et al*,2015).

5.2.2.3 Hausner ratio

The Hausner Ratio (H) was used to measure property of powder and measure of interparticulate friction of the powder to be compressed. It also reflects the importance of intraction of interparticluate material. These relations are ussally least important for a easy flowing. Less flowing materials are characterized by the occurance of larger interparticle interactions, which contributes in significant difference between bulk and tapped densities. Hausner ratio value obtained between 1.17 % to 1.38 % which shows good flow properties **(Table 98)** (Labib *et al,* 2015).

5.2.2.4. Carr's index

The Carr's index was used to measure property of powder and measure of interparticulate friction of the powder to be compressed. Less flowing materials are characterized by the occurance of larger interparticle interactions, which contributes in significant difference between bulk and tapped densities. The measured data of Carr's index obtained in the varied from 15.09 to 27.77 % reflects good flow property as shown in **Table 98** (Labib, G. S., *et al,*2015).

Table 98. Blend characteristics of orodisperible tablet of Levocetirizine HCl

Form	% Moisture at 105 °C	Bulk density (g/cc)	Tapped density (g/cc)	% CI	H in %	Angle of repose (θ)
PT1	1.57±0.12	0.37±0.02	0.49±0.05	24.48±0.01	1.32±0.04	28.16±0.63
PT2	1.69±0.14	0.39±0.08	0.51±0.03	23.52±0.03	1.30±0.01	27.56±0.24
PT3	1.51±0.10	0.41±0.04	0.49±0.01	16.32±0.08	1.19±0.14	24.84±0.85
PT4	1.61±0.13	0.39±0.08	0.47±0.01	25.61±0.14	1.20±0.05	26.31±0.19
PT5	1.91±0.11	0.37±0.04	0.50±0.04	26±0.26	1.35±0.04	24.19±0.87
PT6	1.27±0.21	0.39±0.03	0.54±0.04	27.77±0.08	1.38±0.03	27.64±0.55
PT7	1.46±0.19	0.42±0.05	0.52±0.01	19.23±0.21	1.23±0.09	25.97±0.48
PT8	1.55±0.18	0.45±0.09	0.53±0.08	15.09±0.17	1.17±0.07	24.97±.0.94
PT9	1.61±0.18	0.38±0.03	0.51±0.09	25.90±0.17	1.34±0.07	26.21±0.28
PT10	1.51±0.16	0.41±0.04	0.49±0.01	16.32±0.08	1.19±0.04	24.84±0.85
PT11	1.80±0.21	0.38±0.04	0.51±0.05	19±0.16	1.25±0.21	23.65±0.56
PT12	1.78±0.16	0.37±0.03	0.56±0.04	20.77±0.11	1.35±0.12	26.32±0.59
PT13	1.46±0.12	0.42±0.05	0.49±0.01	21.23±0.21	1.22±0.10	25.15±0.43
PT14	1.87±0.21	0.46±0.09	0.48±0.02	15.09±0.24	1.19±0.13	27.43±.0.65
PT15	1.76±0.32	0.40 ±0.05	0.53±0.06	25.90±0.30	1.36±0.01	25.22±0.35
PT16	1.71±0.11	0.41 ±0.02	0.51 ±0.09	26.90±0.35	1.30±0.11	23.21±0.45
PT17	1.70±0.13	0.47 ±0.01	0.54 ±0.06	24.90±0.34	1.31±0.09	22.22±0.25

5.2.3. Tablet characteristics of Levocetirizine HCl

5.2.3.1. Hardness

The hardness of the tablets formulated by direct compression method PT17 was obtained in the range of 4 ± 0.34 Kg/cm^2. The hardness value was considered adequate for mechanical stability. Hardness results were tabulated in **Table 99-102** (Dekivadia, M., *et al*,2012).

5.2.3.2. % Friability

The % Friability were performed on different prepared formulation. PT17 formulations fribility value obtained is 0.16±0.04 against NMT 1 %. Results tabulated in **Table 99-102** (Dekivadia, M., *et al*,2012).

5.2.3.3. Thickness

The mean thickness of the developed formuation was (n=3) almost uniform PT17 formulations. The measured values obtained in the range of 3.80 ± 0.08 mm. Results mentioned in **Table 99-102** (Dekivadia, M., *et al*,2012).

5.2.3.4. In-vitrodisintegration time

In-vitrodisintegration time is measured by the time it takes for complete disintegration. Rapid disintegration within mins was observed for all formulations. The in vitro disintegration time of the fast-dissolving tablets manufactured by the direct compression method PT17 was in the range of 28.50 ± 2.50 sec and met the formal requirements listed in **Table 99-102** (Dekivadia, M., *et al*,2012).

5.2.3.5. Wetting time

Wetting time is closely related to the internal structure of the tablet. Wet times of PT17 Levocetirizine HCl direct compressed tablet formulations were found to be in the range of 30 ± 1.90 sec, which resulted in faster dispersion in the mouth as shown in **Table 99-102** (Dekivadia, M., *et al*,2012). The contact angle determination done using Force Tensiometer and the contact angle found to be 42.5 ^{0}. The water droplet completely spreads on the tablets shows contact angle less than 90 ^{0}. The surface is considered as hydrophilic.

5.2.3.6. Drug content

Drug content uniformity was performed for all 17 formulations. All samples were analyzed spectrophotometrically. The drug %age of PT17 was found to be 100.60 ± 0.50 % Levocetirizine HCl as listed in **Table 99-102** (Bagul, U., *et al*, 2010)

5.2.3.7. In-vitrodissolution studies

a) Several dependent and independent factors play an importance role in the release of drug in orodispersible dosage forms. Presence of Superdisintegrants (tablets disintegrates into individual particles) affects dissolution profile of both soluble and insoluble drugs. The primary change in a release from such types of formulations are due to differences in the particle size observed while breaking the tablet. In general,

the dissolution process of orodispersible tablet depends on wetting followed by disintegration. So dissolution profiling required in 6.8 Phosphate buffer. Media pH 6.8 mimic human physiological conditions as well as mentioned on tablet monograph. % Dissolution profile were studied using a USP grade Type II apparatus (50 rpm) taking 900 mL of prepared phosphate buffer pH (6.80) as the dissolution media. The temperature in °C of the dissolution medium was kept at 37 ± 0.50° C and an sample of the dissolved formulation was taken after 30 min. The sample then filtered through 0.45 nylon filter and then absorbance was measured by HPLC apparatus. Drug concentrations were determined using a standard calibration curve. The dissolution of Levocetirizine HCl in tablets is 99.10 ± 1.20 %, which represents the release profile of the drug. This value changed when tablet manufacturing methods changed. The combination of the superdisintegrant crospovidone and L-HPC dramatically increases the solubility of Levocetirizine HCl. Tablets that swell and disintegrate quickly turn into primary particles quickly as mentioned in **Table 100-101** (Labib, G. S.*et al*,2015).

Table 99. Physical and chemical parameters of tablets formulations using different disintegrants

Type	Formulation	Thickness (mm) (n=3)	Hardness (Kg/cm^2) (n=3)	Friability (%) (n=3)	Disintegration time (sec) (n=3)	Wetting time (sec) (n=3)
Crospovidone (XL)	PT1	3.80 ±0.06	4.70 ±0.35	0.65 ±0.14	45 ±1.20	47±1.40
	PT2	3.84 ±0.07	4.80 ±0.41	0.61 ±0.12	43±1.50	42±1.60
	PT3	**3.81 ±0.09**	**4.60 ±0.62**	**0.25 ±0.08**	**41±21**	**42±1.80**
Croscarmellose sodium (CCS)	PT4	3.80 ±0.05	4.90 ±0.24	0.41 ±0.05	59±2.50	57±1.90
	PT5	3.78 ±0.02	5 ±0.49	0.31 ±0.05	55±2.40	54±1.40
	PT6	3.84 ±0.04	5.40 ±0.60	0.40 ±0.10	51±3.10	50±1.70
L HPC	PT7	3.81 ±0.03	5.30 ±0.27	0.21 ±0.15	45 ±1.90	42 ±1.80
	PT8	3.80 ±0.04	5.10 ±0.93	0.24 ±0.12	44 ±1.90	40 ±2.10
	PT9	3.87 ±0.08	5 ±0.25	0.30 ±0.09	40 ±1.90	38 ±2.10
Comb.	PT10	3.80 ±0.06	4.95 ±0.20	0.21 ±0.04	23 ±2.10	26±1.90

Table 100. Physical and chemical parameters of tablet formulations by changing binder concentration

Code	Hardness (Kp) (n=3	Friability (%) (n=3)	DT #(sec) (n=3)	Wetting time (sec) (n=3)	Assay (n=3) in %	Dissolution (sec) (n=3)
PT11	3.10±0.42	1.12±0.47	23.0±2.10	24.0±1.40	98.2 ±2.10	96.2 ±2.70
PT12	4.97±0.54	0.62±0.10	25.0±1.0	27.0±1.6	100.10 ±0.8	98.50±0.60
PT13	4.79±0.62	0.45±0.24	38.0±2.10	35.0±1.80	97.80 ±2.60	97.90 ±2.10
PT14	4.76±0.34	0.20±0.18	49.0 ±2.50	49.0±1.90	97.9±2.80	95.9±2.0

Table 101. Physical and chemical parameters of tablet formulations by changing sweeteners

Code	Hardness (Kg/cm^2) (n=3	Friability (%)	Thickness	DT #(sec) (n=3)	Wetting time (sec) (n=3)	Taste	Assay (n=3)	Dissolution (n=3)
PT15	3.50±0.62	0.24±0.09	3.81 ±0.02	33.0±2.10	35.0±1.80	Good	98.1 ±2.90	97.6±2.60
PT16	3.90±0.34	0.18±0.10	3.82 ±0.03	30.0±2.50	32.0±1.90	Better	98.5±3.20	98.3±3.90
PT17	**4±0.34**	**0.16**±0.**04**	**3.80 ±0.08**	**28.5 ±2.50**	**30.0±1.90**	**Best**	**100.6± 0.50**	**99.1±1.20**

b) In-vitro release studies were carried out using IP apparatus type I (Paddle type) in 900ml 6.8pH simulated salivary fluid as dissolution media at speed of 75rpm and temperature 37±0.5°C. The dissolution test of orodispersible tablets accomplished using Simulated salivary fluid are mentioned in table 102.

Table 102. In-vitro release in simulated salivary fluid

Test Sample PT17	
5 min	**Mean: 72.10 %** **Min: 65.20 %** **Max: 78.20 %**
10 min	**Mean: 93.20 %** **Min: 87.30 %** **Max: 96.10 %**
15 min	**Mean: 99.20 %** **Min: 98.10 %** **Max: 102.14 %**
20 min	**Mean: 100.10 %** **Min: 98.16 %** **Max: 103.17 %**
30 min	**Mean: 101.21 %** **Min: 99.20 %** **Max: 103.14 %**

5.2.3.8. Chemical evaluation by FTIR

The FTIR absorption spectrum of Levocetirizine HCl measureed by mean of a absorbance. The IR spectrum, attined at a wave-number series of 4000 –400 cm^{-1} and

at a tenacity of 4 cm^{-1}. IR Band assignments of Levocetirizine HCl are summarized in the **Table 103.** No substantial shifting of the peaks of Levocetirizine was observed. **Figure 26.** shows that the levocetirizine HCl is compatible with excipients used in the formulation.

Table 103: IR absorption spectrum band assignments of Levocetirizine HCl

S.No	Assignment	Wave number in cm^{-1}
1.	-CI	759.73
2.	-COO-ar	1701.93
3.	-C-O-	1020.09

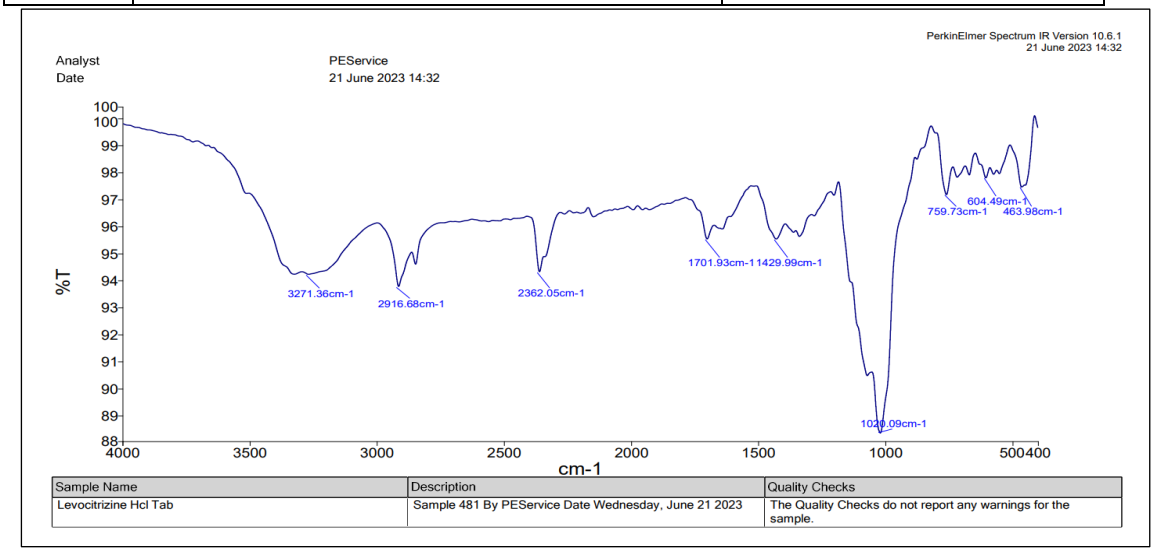

Figure 26. FTIR study of levocetirizine HCl with different excipients in orodispersible tablets

5.2.4. Comparative dissolution profile results of test product and marketed product of orodispersible tablet of Levocetirizine HCl

Multimedia comparative dissolution profiling of Levocetirizine HCl tablets (test vs reference) in 0.1N HCl complies with the specification limits. As the drug released more than 85 % before 15 min in 0.1 N HCl, so there is no need to calculate F_2 value.

The results of multimedia dissolution profiling of Levocetirizine HCl Tablets (test vs reference) in acetate Buffer pH 4.5 (Non specified dissolution medium – 1) complies with the specification limits. As the drug released more than 85 % before 15 min in acetate buffer pH 4.5. So there is no need to calculate F_2 value.

The results of multimedia dissolution profiling of Levocetirizine HCl Tablets (test vs reference) thus phosphate buffer pH 6.8 complies with the specification limits. As the drug released more than 85 % before 15 min in phosphate buffer pH 6.8, so there is no need to calculate F_2 value.

Hence, the multimedia dissolution profiling results of Levocetirizine HCl test formulation are similar to that marketed sample shown in **Table 104-107** and in **Figure 27-29** (Charoo, N. A., *et al*,2023).

Table 104. Comparable dissolution of test sample and marketed sample in dissolution medium of 0.1 N HCl .

Test sample		**Marketed sample**	
5 min	Mean: 95.10 % Min: 92.50 % Max: 95.10 %	5 min	Mean: 94.20 % Min: 89.20 % Max: 94.50 %
10 min	Mean: 98.20 % Min: 94.10 % Max: 100.20 %	10 min	Mean: 97.50 % Min: 93.50 % Max: 99.30 %
15 min	Mean: 100.10 % Min: 98.30 % Max: 102.60 %	15 min	Mean: 99.10 % Min: 97.10 % Max: 104.10%
20 min	Mean: 101.10 % Min: 98.50 % Max: 102.40 %	20 min	Mean: 100.50 % Min: 98.20% Max:103.40 %
30 min	Mean: 100.50 % Min: 99.20 % Max: 103.50 %	30 min	Mean: 101.20 % Min: 97.20 % Max: 104.50 %

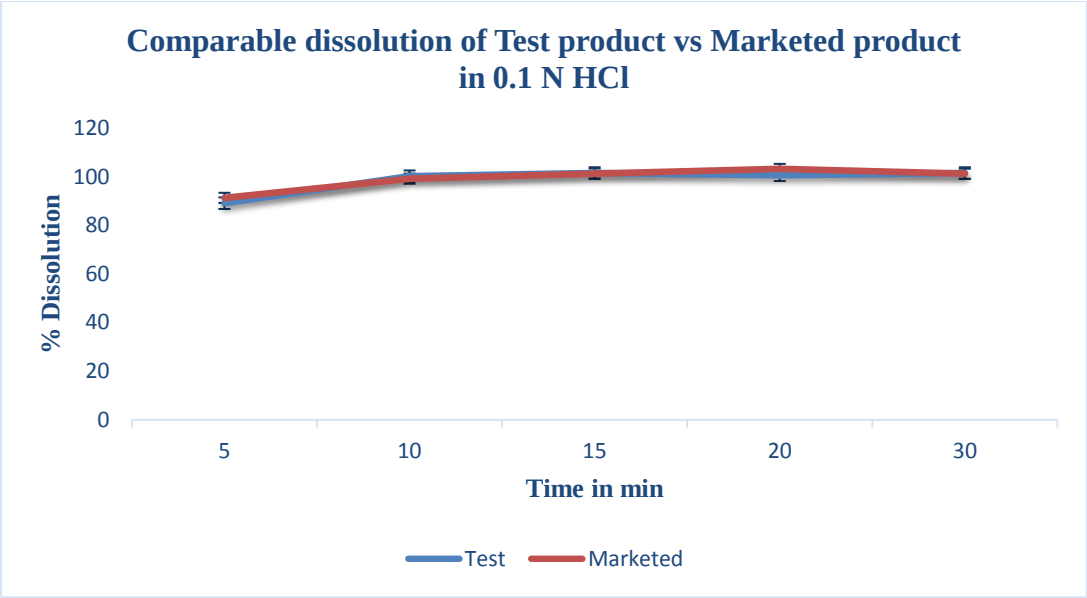

Figure 27. Comparable dissolution of test product and marketed product in dissolution medium of 0.1 N HCl

Table 105. Comparable dissolution of test product and marketed product in dissolution medium of pH 4.5 acetate buffer .

Test sample		Marketed sample	
5 min	Mean: 89.10 % Min: 86.50 % Max: 95.20%	5 min .	Mean: 91.30 % Min: 85.30 % Max: 96.50 %
10 min	Mean: 100.20 % Min: 96.40 % Max: 103.50 %	10 min	Mean: 99.20 % Min: 94.60 % Max: 101.40 %
15 min	Mean: 101.50% Min: 100.20 % Max: 104.50 %	15 min	Mean: 101.30 % Min: 98.20 % Max: 103.50 %
20 min	Mean: 100.60 % Min: 99.20 % Max: 103.20 %	20 min	Mean: 103.20 % Min: 99.40 % Max:104.50 %
30 min	Mean: 101.50 % Min: 100.40 % Max: 104.50 %	30 min	Mean: 101.20 % Min: 99.30 % Max: 104.70 %

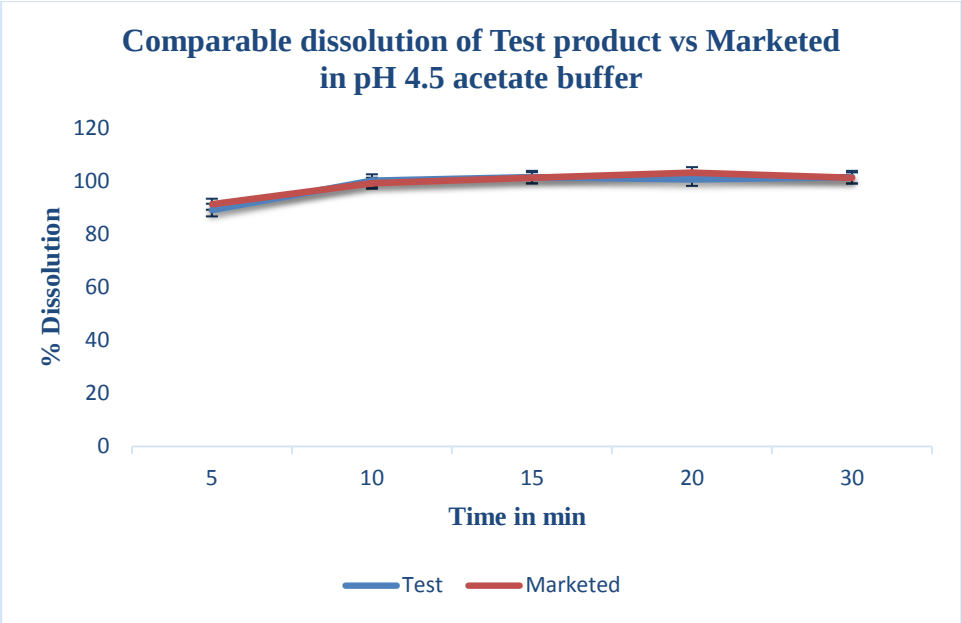

Figure 28. Dissolution profiling comparison chart of pH 4.5 Acetate Buffer

Table 106. Comparable dissolution of test product and marketed product in dissolution medium of of pH 6.8 phosphate buffer.

Test sample		Marketed sample	
5 min	**Mean: 70.20 % Min: 63.10 % Max: 76.50 %**	**5 min**	**Mean: 70.30 % Min: 59.20 % Max: 77.20 %**
10 min	**Mean: 90.10 % Min: 84.20 % Max: 95.20 %**	**10 min**	**Mean: 89.10 % Min: 82.10 % Max: 96.20 %**
15 min	**Mean: 100.10 % Min: 97.20 % Max: 103.40 %**	**15 min**	**Mean: 99.50 % Min: 97.10 % Max: 104.20 %**
20 min	**Mean: 101.50 % Min: 99.50 % Max: 102.10 %**	**20 min**	**Mean: 100.30 % Min: 98.50 % Max: 103.40 %**
30 min	**Mean: 102.50 % Min: 99.50 % Max: 103.20 %**	**30 min**	**Mean: 103.20 % Min: 98.60 % Max: 105.70 %**

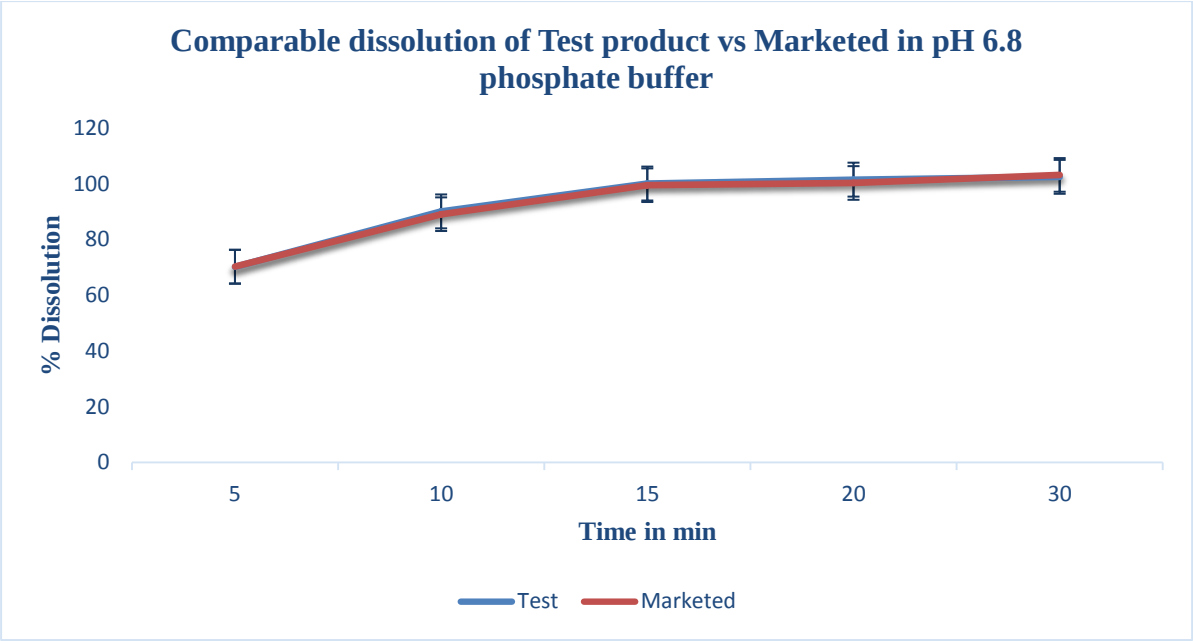

Figure 29. Comparable dissolution of test product vs marketed product in dissolution medium of pH 6.80

5.2.5. Bioanalytical method development

5.2.5.1. Analytical method validation

The analytical method was validated as per ICH guidelines.

5.2.5.2. Linearity and LOD

Linear relationship between peak area and added concentration was established in the concentration range of 2 –10 µg/mL. Shown in **Table 107.** At concentration obtained with signal and noise ratios of 4 and 9. The loss on drying and limit of quantification were determined to be 043 µg/mL and 0.180 µg/mL for Levocetirizine hydrochloride, respectively. The calculated correlation coefficient of this dependence for Levocetirizine HCl was 0.999 (Raikar, P., *et al*,2020).

Table 107. Statistics of Limit of detection (LOD) and Limit of quantification (LOQ)

API name	Correlation coefficient r^2	Limit of detection (n=5)	Limit of quantification (n=5)
Levocetirizine HCl	0.999	043 µg/mL	0.180 µg/mL

5.2.5.3. Precision and robustness

The accuracy of the method was studied at three level: reproducibility, intermediate accuracy (daily and between analysts), and reproducibility of synthetic samples with placebo admixture. Precision was expressed using Mean value ± SD and % age relative standard deviation (% RSD). The capacity of the method to persist unchanged was tested, making small but intentional alterations in the concentration at the time of mobile phase preparation as per ICH guidelines. Mobile phase ratio varied Acetonitrile: methanol: ammonium acetate buffer having pH 5 (25 :55 :20 % v/v/v) to (25 :54 :21 % v/v/v). The values of accuracy along with stability are presented in **Table 108** (Raikar *et al*,2020).

Table 108. Precision and robustness parameters

Parameters	**%age mean (n=5)**	**% RSD**
Repeatability	98.12±0.11	0.068
Reproducibility	98.14 ±0.21	0.076
Robustness	98.33 ±0.15	0.075
Intermediate precision		
Day to day	99.25 ± 0.19	0.088
Analyst to Analyst	99.54 ± 0.17	0.086

5.2.5.4. Accuracy:

The accuracy of the proposed method was evaluated by extraction studies at three different levels. 80 %, 100 % and 120 %. % Recovery testing were performed by adding specific concentrations of Levocetirizine HCl (80 %, 100 % and 120 %) to the samples of the pre-analyzed solutions. The samples were then reanalyzed with the planned method. Average recovery values for Levocetirizine HCl were found to range from 98.13 to 99.22. The total amount of detected drug and the recovery rate were calculated. The results of the recovery study are presented in **Table 109** (Raikar, P., *et al*,2020).

Table 109. Results of recovery study of Levocetirizine HCl

% Recovery	**% age mean (n=5)**	**% RSD**
80	99.22±0.14	0.144
100	98.13± 0.23	0.102
120	98.22±0.24	0.165

5.2.5.5. Specificity

A demonstrative chromatogram was created to show that additional components that may be exist in the sample matrix are separated starting the original analyte. The absence of substantial change in RT of the formulation in the existence and lack of excipients visibly indicates the specificity of testing method used.

5.3.5.6. Application in rabbit plasma

After adding the analyte to the plasma sample, insignificant variation was observed among the amount of Levocetirizine HCl added to the plasma and the amount of Levocetirizine HCl recovered. The recovery of rabbit plasma **(Table 110)** clearly indicates that this method can be applied for the testing method (Raikar, P., *et al*,2020).

Table 110. Precision and accuracy in rabbit plasma.

% Amount of spiked in µg/mL	% RSD in precision	% Accuracy
2	0.901	99.32±0.21
4	11	98.41 ±0.26
6	1.032	98.12 ± 0.29

From all the outcomes gained by the chromatographic study it was established that the method can be performed quickly and easily. Ranges of linearity, precision robustness, LOD, LOQ and specificity were treated to determine method suitability and yield confirmed results. HPLC apparatus has many advantages over UV apparatus, including: B. LOD, LOQ, low size samples with low specificity. Therefore, the established HPLC testing method is fast, inexpensive, and can be projected for routine analytical and quality control purposes.

5.2.6. Pharmacokinetic study

The pharmacokinetics of both the plain Levocetirizine HCl and a test formulation of an orodispersible tablet of Levocetirizine HCl were analyzed. Levocetirizine HCl acquired using both the pure medication and the optimized rapid dissolving tablets. When compared to pure medication administration, the results showed that the parameters were very similar when optimized rapid dissolving tablets were administered. At 0.90 h, the mean C_{max} was 0.418 g/mL for improved fast dissolving tablets and 0.446 g/mL for the commercially available formulation as per literature,

both of which were similar to the C_{max} for the pure drug. The pharmacokietic parameters such as C_{max}, T_{max} and AUC matches when compared with market sample as per literature. Thus, pharmacokinetic investigations showed that fast disintegrating tablets of Levocetirizine HCl had a rapid and increased rate of oral absorption. **Table 111** shows plasma concetration, **Table 112** and **Figure 29** shows pharmacokinetic data (Raikar, P., *et al*,2020).

Table 111. Plasma concentration vs time in h of plain Levocetirizine HCl and test formulation.

Time in h	Plain Levocetirizine HCl (n=6) in µg/mL	Test Formulation (n=6) µg/mL
0.15	0.122	0.212
0.30	0.251	0.302
0.45	0.341	0.352
0.90	0.418	0.457
2	0.337	0.372
4	0.221	0.265
8	0.174	0.205
12	0.111	0.132
24	0.021	0.033

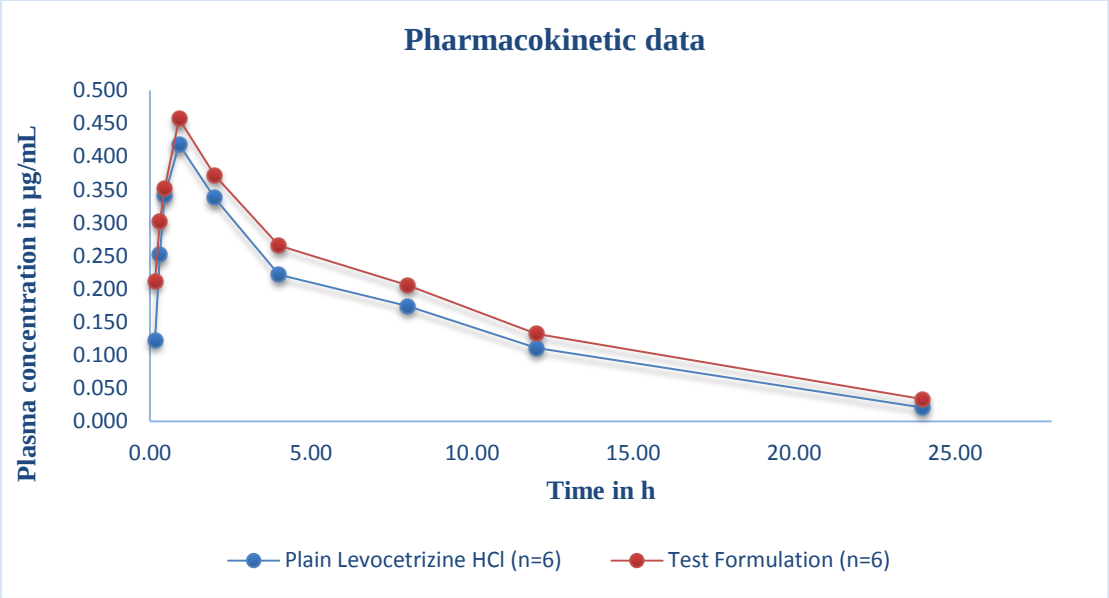

Figure 29: Plasma concentration vs time in h of plain Levocetirizine HCl and test formulation.

Table 112: Pharmacokinetic parameters of Levocetirizine HCl

Plain Levocetirizine HCl			Test formulation		
T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)	T_{max} (h)	C_{max} (µg/mL)	AUC_{last} (h*µg/mL)
0.90	0.400	3.362	0.90	0.455	3.941
0.90	0.410	3.238	0.90	0.458	3.990
0.90	0.420	3.380	0.90	0.459	47
0.90	0.430	3.475	0.90	0.455	3.977
0.90	0.422	3.382	0.90	0.457	42
0.90	0.425	3.402	0.90	0.456	3.985
Average	0.418	3.373	Average	0.457	3.983
SD	0.011	0.077	SD	02	0.024
% CV	2.624	2.282	% CV	0.358	0.593

5.2.7. Stability studies of orodispersible tablets of Levocetirizine HCl

The stability of optimized formulation was tested according to ICH guidelines. The orodispersible tablets of Levocetirizine Hydrochloride was stored at accelerated (40 ± 2ºC/75% RH ±5% RH) conditions in stability chamber. The stability studies were performed on 0, 3 and 6 months. Tablets were tested for disintegration time, assay and dissolution. At 0-month DT i.e 27.60 ±1.50, at 3-month it is 29.40 ±2.60 and at 6-month it is 31.40 ±1.80. There is slight increase in the disintegration time but results meet the specification. At 0-month drug assay i.e 100.60 ±0.50 %, at 3-month it is 100.20 ±0.20 % and at 6-month it is 99.90 ±0.12 %. There is slight decrease in the % Drug assay but results meet the specification. At 0-month % dissolution i.e 99.10 ± 1.20 %, at 3-month it is 98.20 ± 0.62 %and at 6-month it is 97.21 ± 0.30 %. There is slight decrease in the % dissolution but results meet the specification. Results shown in **Table 113.** The formulation is stable upto six month at accelerated stability conditions as there is non significant difference observed between intial and after six month results (Sumati, P., *et al*, 2023).

Table 113. Stability Study of Levocetirizine HCl tablets at accelerated conditions: (40 ± 2ºC/75% RH ±5% RH)

Month	DT #(sec) (n=3)	% Assay	% Dissolution
0	27.60 ±1.50	100.60 ±0.50 %	99.10 ± 1.20 %
3	29.40 ±2.60	100.20 ±0.20 %	98.20 ± 0.62 %
6	31.40 ±1.80	99.90 ±0.12 %	97.21 ± 0.30 %

CHAPTER 6

Conclusion and Future perspective

The platform technology provides a standard framework for release modulator polymer systems that, with some tweaking, can work with any medication, regardless of the drug's physicochemical or pharmacological qualities. Companies can now utilise the designed and optimized drug delivery system for several medication molecules owing to the platform technology. This allows for a higher level of quality control and production efficiency, as well as a shorter time to market and lower overall cost of formulation development and scaling up. The complexity of a system is proportional to its utility.

Part A: MUPS tablets of S (-) Metoprolol succinate

In this research study, a sustained release dosage form of S (-) Metoprolol succinate was developed for the treatment of chonic hypertension. A hydrophilic matrix system was used to manufacture a modified-release MUPS tablet that can be taken as a once-a day dosage unit, especially for patients on long-term beta-blocker therapy.

A modified sustained release matrix tablet formulation designed for sustained release resulted in effective sustained release delay of metoprolol over the 20 h dissolution test period. This matrix formulation was also successfully engineered to produce a multiparticulate pellet system that was compressed into tablets with appropriate levels of coating to attain sustained release profile of S (-) Metoprolol succinate.

Rate and mechanism with drug release have been found to vary with formulation variables including the amount of ethylcellulose used in the functional coating process, drug loading on the inert pellets, and amount of methocel K4M and K100 M contained in the pellets coatings. This indicates that drug release was not completely controlled by the matrix composition itself, but rather by a combination of effects exerted by the hydrophobic ethylcellulose polymer in the formulation.

Using DSC as a tool to identify potential incompatibilities between drug and tableting excipients, a pre-formulation study tested drug and excipients over 30 days under ambient, intermediate, and accelerated conditions.

Comparative dissolution profile of of MUPS tablets of S (-) Metoprolol succinate of approved (Seloken XL 25) AztraZenica (Reference) was performed in all dissolution media. Multimedia dissolution profiling results of the marketed samples are similar to that of test sample in term of F2 Value i.e. greater than 50 and are similar to each other. These pharmacokinetic parameters (lower C_{max} and prolonged T_{max}) indicated that drug release maintained smooth extended absorption of drug and sustained pseudo-steady state concentration of MS in plasma level with minimal fluctuations up to 36 h.

However, after 6 months of storage under extreme temperature and humidity conditions (40 ± 2ºC/75% RH ±5% RH), the drug did not lose potency after exposure to extreme temperatures. The drug appeared to be chemically stable.

Controlled-release oral dosage forms are gaining much more attention today compared to conventional dosages available in the market because they provide sustained drug release that prevents localized gastric irritation. The formulated dosage form eliminates the necessity for multiple daily use of tablet frequencies with improved patient compliance.

The challenges associated with the MUPS tablets is uniformity distribution of pellets, optimization of compaction force to avoid pellets rupture and tooling selection criteria. These challenge in the MUPS tablets affects the Assay and dissolution of the drug product.

Compressing extended-release MUPS pellets into a tablet unit dosage form is difficult because the pellets are brittle, leading to a reputation for polymer and drug coatings. Therefore, the process and formulation are optimized to ensure pellet integrity during compaction and deliver well within the specification in-process and final results. Further research is needed in this area. QbD scaling, validation, and enforcement required to make processes repeatable and robust. MUPS formulations are likely to be the most common dosage form. This result reflects that the prepared MUPS formulation reflects the desired rate of release of S (-) Metoprolol succinate.

Part B: Orodispersible tablets of Levocetirizine HCl

As an alternative to granulation and dry blending, the spray drying fluid bed technique led to the development of a platform technology. Ready-to-use granules with superior flow qualities and physicochemical characteristics including friability, wetting time, and water absorption can be produced using spray drying fluid bed technology. A porous liquid dry material that may transport medications which are unpleasant to the taste buds at low concentrations is an added benefit.

Mannitol (Perlitol SD 200) is used as a solvent, crospovidone (Polyplasdone XL) and L-hydroxypropylcellulose (LH-11) are used as superdisintegrants, and povidone (PVP K-30) is used as a binder in the spray-drying fluid bed platform technology.

Every important material property, including assay, DSC, IR, melting point, particle size, etc., was measured and compared across a range of commonly used excipients and active substances.

We used a tapped and bulk density apparatus to determine the bulk and tapped densities of the API and excipients to evaluate their flow characteristics. Along with the compressibility characteristics, we also calculated the blend's index of compressibility, Hausner ratio, and angle of repose to verify its physical qualities.

To ensure there was no physical or chemical repulsion between the API and exciepients drug exciepients compatibility study was performed.

Orodispersible tablets are best prepared by the dry mixing and direct compression process, with spray dried mannitol as the active ingredient. Many commonly used excipients have been successfully compressed into tablets using the dry mixing and direct compression method, so it was decided to adopt it. This method has the added benefits of requiring fewer manufacturing steps, which lowers the risk of human error, shortens the manufacturing process, saves time, money, and resources, and requires fewer tests.

To ensure the quickest possible disintegration, a platform was created using a variety of super disintegrants, including crosspovidone, L-HPC, and crosscarmellose sodium. Thinners in the form of spray-dried low-moisture mannitol and a binder in the form of

povidone (PVPK-30) were both included. Ingredients include the artificial sweeteners sucralose, sodium saccharine, and aspartame, the colourant sunset yellow supra, and the lubricant magnesium stearate.

Powder blend water absorption ratios increased as they were more saturated with disintegrant in the developed formulation, leading to faster disintegration, wetting, and in vitro dispersion times.

The tablets made by combining the results of all the trials have low friability and high mechanical strength while costing less than their competitors. They also have low crushing strength and disintegration time measured in sec.

The rate of Levocetirizine HCl release from the created orodispersible formulation was evaluated by in vitro dissolution tests. Over 85% of the medication is released within 5 min.

The hardness of 4.0 ± 0.34 Kg/cm^2 was measured in friability testing for the optimal batch of PT17 formulation that was prepared. The tablets were very consistent in how quickly they broke down, with a time of 28.5 ± 2.5 sec.

The results of multimedia dissolution profiling of Levocetirizine HCl tablets (test vs reference) complies with the specification limits. As the drug released more than 85 % before 15 min in phosphate buffer pH 6.80, so there is no need to calculate F2 value. The multimedia dissolution profiling results of Levocetirizine HCl test formulation are similar to that marketed sample. The pharmacokinetics of both the plain Levocetirizine HCl and a test formulation of an orodispersible tablet of Levocetirizine HCl were analyzed. When compared to pure drug administration, the results showed that the parameters were very similar when optimized rapid dissolving tablets were administered and market sample based on literature. Pharmacokinetic results reflects that fast disintegrating tablets of Levocetrizine HCl had a rapid and increased rate of oral absorption

Additionally, ICH-recommended stability studies were conducted in accelerated conditions of 40 ºC ± 2ºC/75% RH ±5% RH for a period of 6 months. Accelerated stability testing was performed to evaluate any alterations to the assay of the tablet dosage form brought on by the presence of a high temperature and humidity

environment. Researchers sped up the testing process to see how changes in physical and chemical quality characteristics over time. The main challenges related to orodispersible tablets are hardness, Disintegration time and friability. So selection of API and exciepients plays an important role.

Future perspectives of present study

- The suggested delivery system has the potential to revitalize the product life cycles of many medications that are widely used in the same dosage form but are in the decline phase of their product life cycle.
- It will improve the pharmaceutical company's bottom line by diversifying its product line, increasing sales, and reaching new customers.
- In the rush to get new drugs to market before rivals, the ability to skip beyond expensive and time-consuming clinical trials is highly attractive.
- This technology helps companies to navigate risk and challenges while development of Critical molecules.
- Platform technology prepares a common base to produce multiple novel therapeutics and add flexibility to develop and enable faster scale up between R&D and commercialization of drug product.
- It helps to produce consistency in product performance and provides simplification of technology transfer activities (From R&D to manufacturing plant).

CHAPTER 7

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List of Publications, patents and presentations

Publications related to research topic

- **Nikhil Gupta,** Sheetu Wadhwa, Vikram Gharge. Formulation and evaluation of Levocetirizine hydrochloride fast dissolving tablets. AIP Conf.Proc.2800,0200081-1-020081.
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- **Nikhil Gupta, Sheetu Wadhwa, Paramjot Maman, Vikram Gharge, Deepshikha.** Development of MUPS sustained release tablets of S (-) Metoprolol Succinate utilizing platform tehnology submitted in Journal of Pharmaceutical sciences.
- **Nikhil Gupta, Sheetu Wadhwa, Paramjot Maman, Vikram Gharge, Samriti.** Orodispersible Tablets: Development technologies, scale-up challenges and recent advancements submitted in Health Science review.
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- Paramjot Maman, **Nikhil Gupta**, Sheetu Wadhwa. Polymer Based Drug Delivery: A Targeted Approach. Think. Ind.Journal.559-578.
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- **Nikhil.Gupta**, Sheetu Wadhwa, Vikram Gharge. Orodispersible tablet of Levocetriziene HCl.

PUBLICATIONS

Development and Evaluation of Spray Dried Fluid Bed Processed OrodispersibleTablet

NikhilGupta[1, a)], SheetuWadhwa[1, b)] ,VikramGharge[2, c)]

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Abstract. The main objective of this work is toprepare and evaluate the orodispersible tablet of Levocetrizine hydrochloride. Seventeen formulations (PT1 to PT17) were formulated by dry mixing method using various superdisintegrants alone and in combination namely crospovidone, croscarmellose sodium, L-HPC and sweeteners such as sucralose, sodium saccharin and aspartame. The developed tablets of Levocetrizine HCl possess fast disintegration and wetting time. Further LevocetrizineHCl tablets were tested for both physical as well as chemical parameters.Precompression parameters like angle of repose, bulk density, tapped density, compressibility index & post-compression parameters like wetting time, water absorption ratio, in-vitro disintegration, drug content and dissolution were determined. Among all developed formulations, PT17 which contains combination of disintegrants (hydroxy propyl cellulose, crosspovidone), binder Povidone and sweetener sucralose meets the criteria of orodispersible tablets. The optimized PT17 formulation shows taste masking, fast disintegration time (28.50 ± 2.50sec),good wetting time (30.1± 1.90 sec), drug assay (100.6 ± 0.50 %) and fast dissolution rate (99.1± 1.20 %) within 5 minutes. The optimized formulation is stable,cost effective,easy to formulate and posseses high quality. The developed stable orodispersible tablets is substitute to the existing market formulation.

Keywords:-Wetting time, precompression, postcompression, Levocetrizine,spray dried, superdisintegrants.

INTRODUCTION

Allergic rhinitis is one of the most common diseases. The main symptom associated with its are inflammation, nasal blockage and irritation in the respiratory system.Earlier antihistaminic drugs which are available in the market used as first line treatment with combination of corticosteriod[1]. But the newly prepared drug is proved to have decongestant effect. Levocetirizine hydrochloride, is antihistaminic drug of second-generation[2] But have few or less sideeffectwhich spress allergic response. TheLevocetrizine hydrochloride possess bitter as well as sour taste[3].Due to the presence of superdisintegrants, the orodispersible tablets possessthe quick dispersion which improves its bioavailabilityand fast absorption by mouth[4].Orodispersible tablets formulation bypass first pass metabolism and shows better bioavailability. The aim and objective of the present study is to develop fast dissolving tablets by using combination of superdisintegrants, binders and sweetneers.The rationale is to enhance the disintegration, dissolution and taste masking of Levocetrizine hydrochloride which improve its bioavailability and avoid the first pass metabolism[5].

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DESIGN AND DEVELOPMENT OF A VALIDATED HPLC METHOD FOR THE QUANTIFICATION OF S (-) METOPROLOL

Nikhil Gupta[1] , Sheetu Wadhwa[1], Paramjot Maman[1], Vikram Gharge[2]* , Mr Vishal Verma[3] & Mrs. Sakshi Soni[3]

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ABSTRACT:

A easy, expeditious and accurate method for the analysis of bulk s(-) Metoprolol succinate and solid tablet dosage form is reversed-phase chromatographic technuique. This technuique has been designed, developed and validated. The method was accomplished with the help of ODS Inertsil- 3, 4.600 mm x 250.000 mm, column having pore size of 5 µm or equivalent. The flow rate kept was 1.5ml/minute, detected at a 280 nm wavelength for a run of 60 minutes. The method development was done as per Q2(R1) ICH guidelines. The method was found to be straightway accurate and error free . The value of Loss on Drying (LOD) and Limit of Quantification (LOQ) over the established range were found to be 0.200 and 0.600 µg.mL-1, individually. The current study was undertaken to design HPLC analysis of the s(-) Metoprolol succinate in bulk as well as its dosage form in a very precise manner.

KEYWORDS: *RP-HPLC, Metoprolol succinate, ICH Q2 , LOD, LOQ, Extrapolated.*

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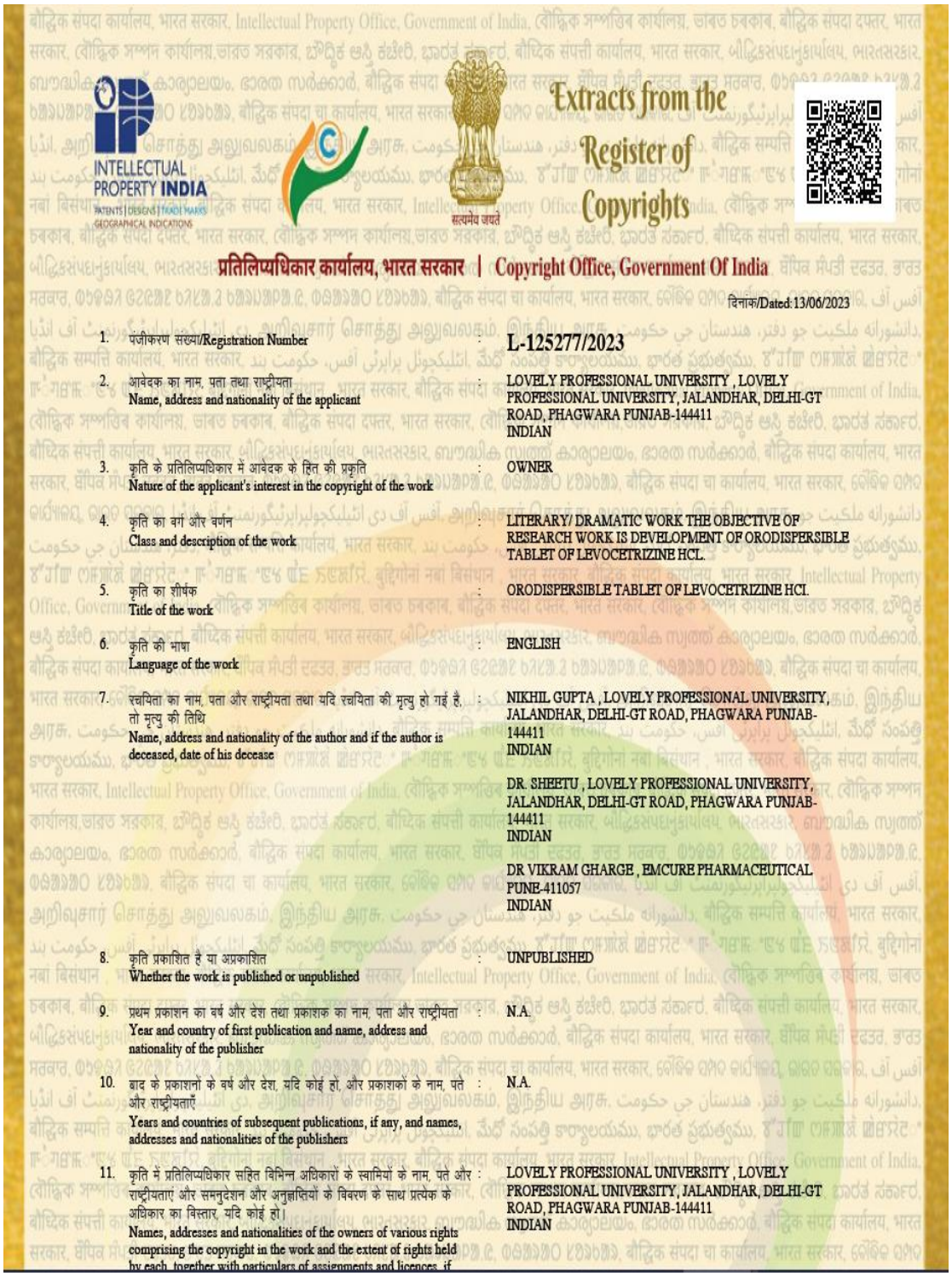

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BOOK CHAPTER

Chapter 1

A Review on Drug Loading: Basic Concepts and Enhancement Techniques

Nikhil Gupta[1,2], Sheetu Wadhwa[1*], Vikram Gharge[2], Sachin Kumar Singh[1], Rajesh Kumar[1], Paramjot Maman[1]

Lovely Professional University, Phagwara (Punjab)
[2] Emcure Pharmaceuticals Limited, MIDC Bhosari, Pune

1. Introduction

Over the last few decades, different type of novel nano-range formulations has been studied extensively in pharmaceutical research. The selection of ideal delivery system depends upon varied physico-chemical and pharmaceutical properties of drug such as solubility, stability, pH, etc. The size, morphology surface texture, and structure of particles can be modified by optimizing and selecting the specific manufacturing methods. But by doing so, there is a change in the different drug release properties like drug loading, drug entrapment and drug release kinetics mechanism. Despite of these rapid and advanced researches, a variety of drug molecules fail during pre-clinical evaluation. This is mainly associated with drug delivery issues which results in poor bioavailability as well as low efficacy. Various biopharmaceutical products like nucleic acids [1], proteins [2] and peptides [3] have often restricted stability and fast clearance from the body. Similarly, various other small molecule drugs may have low solubility, less stability, short time for circulation in body, and may even have non-specific toxicity which limits their therapeutic efficacy.

Recent scientific advancements and techniques lead to the development of varied potential delivery approaches. The effectiveness of the pharmaceutical dosage form depends upon the amount of drug loaded within it. If the drug formulations have less amount of loaded drug then the amount of drug is not up to the level to produce the therapeutic response and thus becomes ineffective. The simplest way to load the drug within the formulation is to use the selective polymer which is compatible with the drug as well as with the other additives. Moreover, the drug gets loaded within that polymer and making the pharmaceutical dosage form effective [4]. Usually, the amount of polymer used with respect to the amount of drug need to be optimized. However, the amount of drug to the amount of polymer used depends upon the size of drug

LIST OF CONFERENCES

1. Disso India. Int Conference. 13-16 May, 2020.

2. Got best Poster Award for presenting my research work on Formulation and Evaluation of Levocetirizine Hydrochloride Fast Dissolving Tablets in Virtual Conference on Current Status and Future Directions held at CT University on 24 July, 2021.

3. Attended and presented my analytical work of S(-) Metoprolol succinate in Recent trends in Pharmacovigilance and Drug Safety 2022 organized by Uttaranchal University.

4. Presenting my research work on Formulation of sustained release MUPS tablet of S (-) Metoprolol succinate using wurster process at 14^{th} Chandigarh Science congress (CHASCON-2020) held at Panjab university on 17^{th} -19^{th} Dec, 2020.

5. Presenting my research paper on Development and evaluation of spray dried fluid bed processed orodispersible tablet in Int conference on Materials for emerging technologies (ICMET-21) at Lovely professional university on 18^{th} -19^{th} Dec, 2022.

CERTIFICATES

1.

2.

3.

Serial No. 155

UTTARANCHAL UNIVERSITY

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INTERNATIONAL CONFERENCE

on

"Recent Trends in Pharmacovigilance and Drug Safety (RTPD-2022)"

April 29-30, 2022

Awarded to Dr./ Prof./ Mr./Mrs./ Ms. Nikhil Gupta

From Lovely Professional University has Presented (Poster/Paper) entitled

Design & Development of Validated HPLC Method for The Quantification of S(-) Metoprolol.

organized by Uttaranchal Institute of Pharmaceutical Sciences (UIPS), Uttaranchal University, Dehradun, Uttarakhand, (India).

Amit S

Organising Secretary
Dr. Amit Semwal
HOD ,UIPS
Uttaranchal University

Convenor
Prof. (Dr.) Vikash Jakhmola
Dean - UIPS
Uttaranchal University

Issue Date 30.4.2022

4.

CRIKC

14TH CHANDIGARH SCIENCE CONGRESS

CHASCON-2020

Certificate of Appreciation

This certificate is awarded to Mr./Mrs./Dr./Prof. Nikhil Gupta for Oral Presentation in 14th Chandigarh Science Congress jointly organised by Panjab University and Chandigarh Region Innovation and Knowledge Cluster on 17th-19th December, 2020.

Presentation entitled- Formulation of sustained release mups tablets of s (-) metoprolol succinate using wurster process

Section- Pharmaceutical sciences

Prof. Desh Deepak Singh
Coordinator

Prof. Ravinder Kumar Singla
DUI

Prof. Sandeep Sehajpal
Co-coordinator

5.

DIVISION OF RESEARCH AND DEVELOPMENT

[Under the Aegis of Lovely Professional University, Jalandhar-Delhi G.T. Road, Phagwara (Punjab)]

Certificate No.240205

Certificate of Participation

This is to certify that **Mr. Nikhil Gupta** of **Lovely Professional University, Phagwara, Punjab, India** has presented paper on **Development and Evaluation of spray dried fluid bed processed OrodispersibleTablet** in the **International Conference on Materials for Emerging Technologies (ICMET-21)** held on February 18-19, 2022, organized by Department of Research Impact and Outcome, Division of Research and Development, Lovely Professional University, Punjab.

Date of Issue: 16-03-2022
Place: Phagwara (Punjab), India

Prepared by
(Administrative Officer-Records)

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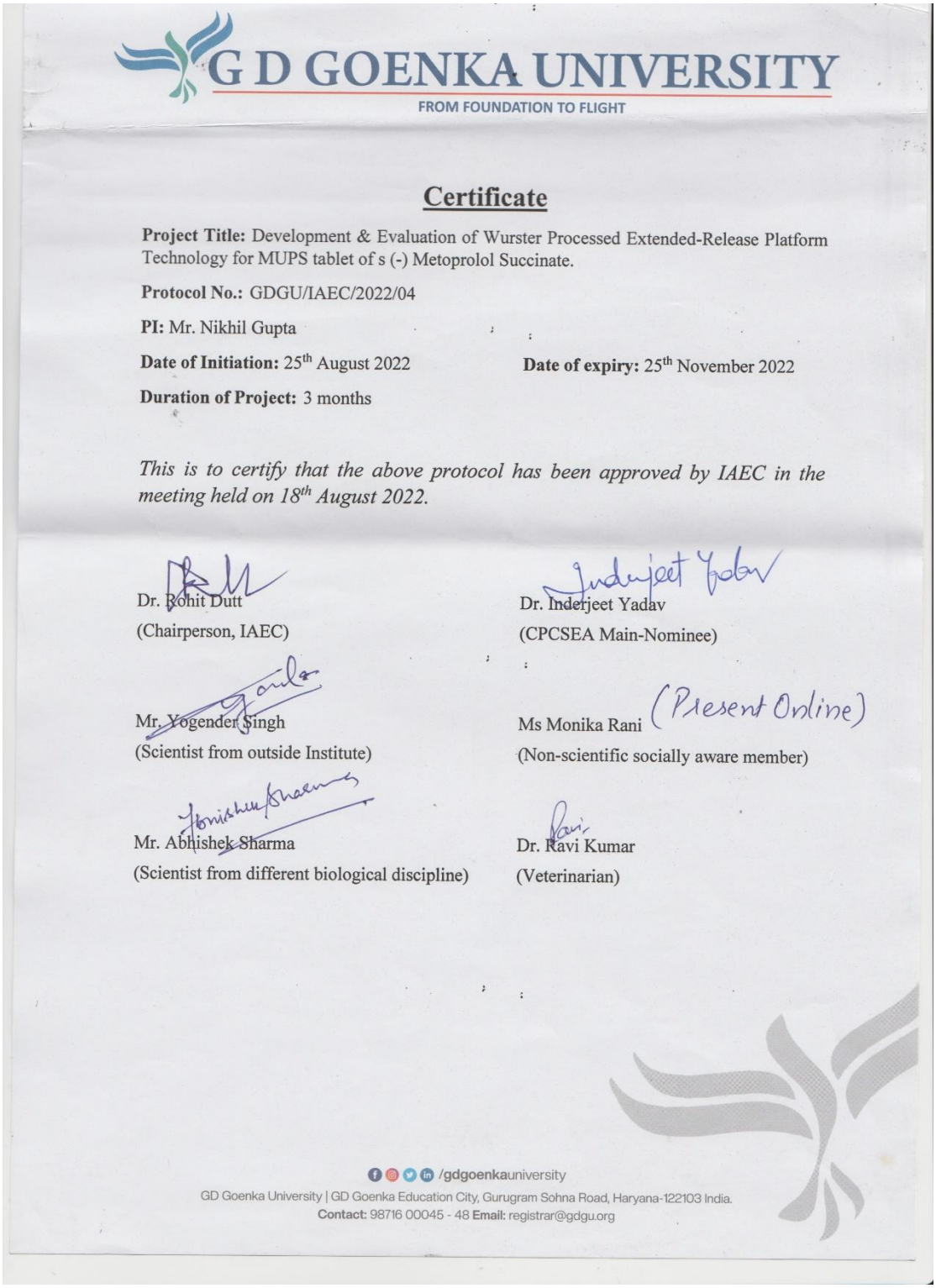
1



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FROM FOUNDATION TO FLIGHT

Certificate

Project Title: Development & Evaluation of Wurster Processed Extended-Release Platform Technology for MUPS tablet of s (-) Metoprolol Succinate.

Protocol No.: GDGU/IAEC/2022/04

PI: Mr. Nikhil Gupta

Date of Initiation: 25th August 2022 **Date of expiry:** 25th November 2022

Duration of Project: 3 months

This is to certify that the above protocol has been approved by IAEC in the meeting held on 18th August 2022.

Dr. Rohit Dutt
(Chairperson, IAEC)

Dr. Inderjeet Yadav
(CPCSEA Main-Nominee)

Mr. Yogender Singh
(Scientist from outside Institute)

Ms Monika Rani (Present Online)
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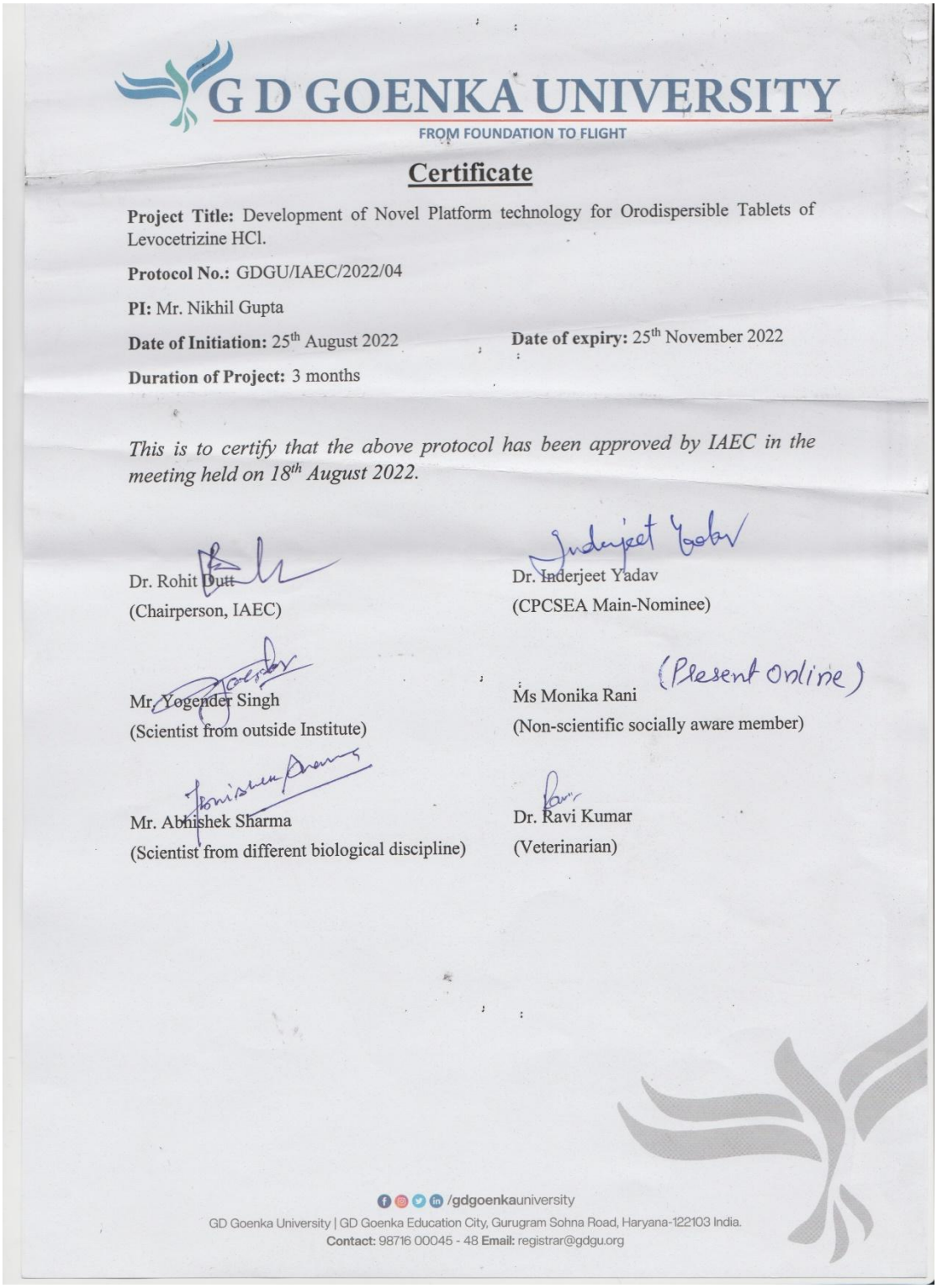
Contact: 98716 00045 - 48 Email: registrar@gdgu.org

2.



G D GOENKA UNIVERSITY

FROM FOUNDATION TO FLIGHT

Certificate

Project Title: Development of Novel Platform technology for Orodispersible Tablets of Levocetrizine HCl.

Protocol No.: GDGU/IAEC/2022/04

PI: Mr. Nikhil Gupta

Date of Initiation: 25th August 2022 **Date of expiry:** 25th November 2022

Duration of Project: 3 months

This is to certify that the above protocol has been approved by IAEC in the meeting held on 18th August 2022.

Dr. Rohit Dutt
(Chairperson, IAEC)

Dr. Inderjeet Yadav
(CPCSEA Main-Nominee)

Mr. Yogender Singh
(Scientist from outside Institute)

Ms Monika Rani (Present Online)
(Non-scientific socially aware member)

Mr. Abhishek Sharma
(Scientist from different biological discipline)

Dr. Ravi Kumar
(Veterinarian)

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