Comparative Evaluation of Fast Dissolving Tablets of Aceclofenac by Different Techniques

A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE

REQUIREMENTS FOR THE DEGREE OF

MASTER OF PHARMACY

IN

PHARMACEUTICS

By

MODDU VINOD KUMAR

(Reg. No. 11309856)

Under the guidance of

Supervisor

Sujit Bose

Lecturer

SCHOOL OF PHARMACEUTICAL SCIENCES

LOVELY PROFESSIONAL UNIVERSITY

PUNJAB, 144411

APRIL, 2015

INDIA'S LARGEST UNIVERSITY

LOVELY PROFESSIONAL UNIVERSITY

Transforming Education, Transforming India

School of: PHARMACEUTICAL SCIENCES, LPU

DISSERTATION TOPIC APPROVAL PERFORMA

Name of the Student: M. VINOD KUMAR Registration No: 11309856

Batch: ..... Roll No. V1307A09

Session: ..... Parent Section: PHARMACEUTICS

Details of Supervisor: Designation: LECTURER

Name SUJIT BOSE Qualification: M. PHARMACY

U.ID 18699 Research Experience: .....

SPECIALIZATION AREA: PHARMACEUTICS (pick from list of provided specialization areas by DAA)

PROPOSED TOPICS

1. Comparative Evaluation of fast dissolving Tablets of Aceclofenac, Prepared by Different techniques.
2. Enhancement of Dissolution of Aceclofenac Fast dissolving Tablets by using Different watersoluble carriers.
3. Development & optimization of Aceclofenac Gel.

Signature of Supervisor Sujit Bose 07/09/2014

PAC Remarks: Approved by PAC

APPROVAL OF PAC CHAIRPERSON: Signature: Monica Gulati Date: 2/9/14

*Supervisor should finally encircle one topic out of three proposed topics and put up for approval before Project Approval Committee (PAC)

*Original copy of this format after PAC approval will be retained by the student and must be attached in the Project/Dissertation final report.

*One copy to be submitted to Supervisor.

DECLARATION BY THE CANDIDATE

This is to submit that this written submission in my thesis entitled "Comparative Evaluation of Fast Dissolving Tablets of Aceclofenac by Different Techniques" represents original ideas in my own words and where others' ideas or words have been included, I have adequately cited and referenced the original sources. I also declare that I have stuck to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the school and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when required.

Patents related to API, process, product, method and equipment, if any, have been examined to ensure non-infringing approach to the existing patents.

This thesis encompasses the information generated by me based on experimental work carried out in the Institute. I assure and hold full responsibility for its genuineness.

_____

Moddu Vinod Kumar

Forwarded Through

Sujit Bose
Lecturer
Domain of Pharmaceutics
School of Pharmaceutical Sciences
Lovely Professional University
Punjab,144411

CERTIFICATE

The work described in this thesis entitled "Comparative Evaluation of Fast Dissolving Tablets of Aceclofenac by Different Techniques" has been carried out by ModduVinod Kumar under my supervision. I certify that this is his bonafide work. The work described is original and has not been submitted for any degree to this or any other university.

Date:

Place:

Sujit Bose
Lecturer
Domain of Pharmaceutics
School of Pharmaceutical Sciences
Lovely Professional University
Punjab, 144411

CERTIFICATE BY SCHOOL

This is certified that the work described in this thesis entitled "Comparative Evaluation of Fast Dissolving Tablets of Aceclofenac by Different Techniques" has been carried out by ModduVinod Kumar at the School of Pharmaceutical Sciences, Lovely Professional University, Punjab.

Dr. S. Tamilvanan
Head of Domain
School of Pharmaceutical Sciences
Lovely Professional University
Punjab, 144411

Dr. Monica Gulati, Ph.D.
Sr. Dean and Head of School
School of Pharmaceutical Sciences
Lovely Professional University
Punjab, 144411

ACKNOWLEDGEMENT

First and foremost, I would like to take this golden opportunity to thank Almighty God for His blessing and bestowing upon me for all his kindness that has helped me throughout the journey of my life and those people who had helped me through this project. The success of my project is based on the support and encouragement of all those people.

Though words are seldom sufficient to express gratitude and feelings but no words to express my gratitude to my parents ***Mrs. Tirupatamma*** and ***Mr. Nageswara Rao*** *and my brother* ***Thirumalarao*** *and sister* ***Malleswari*** *for their love, affection, sacrifice, encouragement and endless support throughout my course, which helped me a lot to complete my work.*

I humbly owe my sincerest gratitude to my teacher and guide, ***Surjit Bose****, who has supported me throughout my thesis with his patience and knowledge whilst allowing me the room to work in my own way. His mentorship was paramount in providing a well-rounded experience consistent my long term career goal. He encouraged me to grow like an independent thinker and inspired me to do the work in more lucrative and result oriented manner.*

I would like to thank my institute, ***Lovely Professional University****, Phagwara, Punjab, India, which has provided opportunity to thousands like me to explore the vast ocean of knowledge and in the process provided them great career opportunity.*

I am also thankful to ***Mr. Gopal Krishan****, Deputy Superdentant, Lovely Professional University, Phagwara, Punjab, India for providing us the laboratory requirements and his sustained encouragement which helped me in completing the task.*

I extend my sincere thanks to all my ***friends*** and ***classmate Supreet, Neha Sahiti, Pavitr, Pankaj Mukesh*** *for their friendship and for making my stay at LPU an enjoyable and giving me wonderful memories which I will cherish throughout my life.*

Lastly, but not least, I would like to thank all those who were directly or indirectly assisted in completion of this work.

Moddu Vinod Kumar

DEDICATED TO.....
MY FAMILY

CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

Abbreviation	Description
API	Active Pharmaceutical Ingredient
CDER	Centre for Drug Evaluation and Research
FDA	Food and Drug Administration
FDT	Fast Dissolving Tablet
HCl	Hydro Choric Acid
ODT	Oral Disintegration Tablet
SSG	Sodium Starch Glycolate
Kg/cm^2	Kilogram per centimetre square
KBr	Potassium Bromide
M	Molar
mg	milligram
ml	millilitre
µg/ml	microgram per millilitre
nm	nanometre
rpm	rotation per minute

INTRODUCTION

Chapter 1

INTRODUCTION

The idea of Fast Dissolving Tablets (FDT's) came into perspective with a target of expanded patient consistence. As the expense for creating a non specific atom is excessively high, the examination is consistently done on the novel dosage forms for having better agreeability as contrasted with the diverse dose manifestations of which the oral course serves to make an attribution. Few subjects, especially children and old age patients, experience issues gulping or biting solid delivery forms. For an instance, an elderly patient will most likely be unable to devour an everyday dosage of anti depressant as a tablet. A child with anaphylaxes could utilize a more suitable measurement structure than antihistamine syrup. An adult lady experiencing radiation help for breast disease may be so squeamish it would be impossible gulp her H2-blocker. FDT's are an immaculate suitable for these patients. Quick dissolving medication approaches have quickly picked up acknowledgement as a paramount better approach for overseeing medications. A quick dissolving medication approach is a formulation that breaks down or crumbles in the mouth cavity without the assistance of water or chewing.

1.1. Definition:

The Centre for Drug Evaluation and Research (CDER), United State (US)Food and Drug Administration (FDA)defined Fast Dissolving Tablets (FDT) as "A solid dosage form containing medicinal substances, which disintegrates rapidly, usually within a matter of seconds, when placed upon the tongue".

FDT's deteriorated and/or disintegrate momentarily in saliva with no utilization of water. A few formulations are intended to break down in saliva astoundingly quick, inside a couple of moment, and are genuine FDT's. Remaining constitutes operators to improve the velocity of tablet breaking down in the oral cavity, and is all the more fittingly termed quick deteriorating tablets, as they may take up to a moment to totally disperse. After placing in oral cavity, this tablet deteriorates quickly, discharging the medication, which disintegrates or scatters in the saliva.

1.2. Ideal Properties of FDT's:

1. Need no water for administration.
2. Should be rigid and less friable.
3. Have an agreeable flavour covering property
4. Display low compassion to environmental conditions

1.3. Advantages of Fast Dissolving Tablets:

1. No difficulty in administration in the patients who are unable to gulp.
2. Good mouth perception property
3. The hazard of blocking or suffocation is avoided, thus providing enhanced safety.
4. Useful where a special quick onset of action required.

1.4. Limitations of FDT's:

1. Inadequate mechanical strength so that precautions are to be taken while handling.
2. Specific packaging is required which aids in stabilization and safety.

1.5. Ideal Drug Candidates for Fast Dissolving Tablets

1. The quantity should not be $\geq$ 20 mg.
2. Partially ionized medicament at oral pH is required
3. Permeation of drug should be through the mucosal route.

1.6 Potential candidates for fast dissolving tablets

There are no specific confinements providing it is used as an Active Pharmaceutical ingredient (API).

Table 1.1 Medications which are formulated as FDT's:

Analgesics and Anti-inflammatory	**Anti-depressants**	**Anti-Hypertensive**	**Anti-Neoplastic Agents and Immuno suppressants**	**Corticosteroids**
Aloxiprin	Amoxapine	Amlodipine	Amsacrine	Budesonide
Benorylate	Ciclazindol	Benidipine	Busulphan	Dexamethasone
Diflunisal	Maprotiline	Carvedilol	Cyclosporin	Flunisolide
Etodolac	Nortiptyline	Darodipine	Dacarbazine	Hydrocartisone
Fenbufen	Trazodone	Felodipine	Etoposide	Prednisone

1.7. Selection of Additives:

Additives parity the assets of API in quick liquefy dosage systems. This requests intensive facts of the science of these excipients to anticipate association with the actives. These Excipients when introduced in the formulation, bestow the obliged organoleptic properties and formulation viability.

1.7.1 Bulk Agents:

Bulk operators are huge in the definition of quick dissolving tablets. The chemicals

provide capacities of a diluents, filler and expense reducer. They enhance the surface qualities that thusly upgrade the deterioration in the mouth, other than including mass additionally diminishes the amassing of the active in the formulation. Mannitol specifically has high watery dissolvability and great tangible sensation. These are included in the range of 10-90 percent by weight of the final formulation.

- **The excipients could be positioned in descendant orderregarding their fragileness:**
  Microcrystalline cellulose > spread dried lactose > beta lactose > alpha lactose > alpha lactose monohydrate>dicalciumphosphatedihydrate.
  The sugar based excipients which are ordinarily utilized are particularly bulkingagents which show high fluid dissolvability and sweetness, and subsequently grant tasteconcealing property. Mizumito et.al, ordered sugar-based excipients into two sorts on the premise of embellishment and dissolution rate.

Table 1.2 Classes of sugar based excipients:

Class i	Class ii
Lactose and Mannitol low mouldability	Maltose and Maltitol High mouldability

1.7.2 Emulsifying Agents:

These are imperative excipients for forming quick dissolving tablets they support in fast deterioration and medication discharge without biting, gulping or drinking water. Also, consolidating emulsifying specialists are helpful in settling the immiscible mixes and improvingbioavailability. An extensive variety of emulsifying agents are suggested for quick dissolving tablet plan, like alkyl sulfates, PEG esters, lecithin, sucrose esters and others.

1.7.3 Lubricants:

Oils, however not crucial excipients, can additional aid in making these tablets more pleasant following deteriorate in the oral cavity. These agents uproot abrasiveness and aid in the medication moving mechanism starting from the oral cavity into the abdomen.

1.7.4 Flavors and Sweeteners:

Flavors and taste-covering specialists build the formulation with additional agreeable, satisfying for patients. The incorporation of these additives supports in prevails over animosity and obnoxious flavor of some API. Both native and manufactured flavors are utilized to enhance the organoleptic qualities. Pharmacists can browse an extensive variety

of sweeteners.

1.7.5 Superdisintegrants:

Disintegrants are chemicals customarily integrated in tablets and in capsules for advancing waterpenetration and scattering of network of measurements structure in disintegration fluids.Superdisintegrants are by and large utilized at a low concentration, ordinarily 1-10% w/w in respect to aggregate weight of dose unit. By and large utilized Superdisintegrants are (Ac-Di-Sol), Crospovidone (CP), SSG which denote to instance of cross linked cellulose, cross linked polymer and cross linked starch respectively. Ideally, Superdisintegrants ought to root the tablet to disturb, not just into the granules from which it was layered additionally into fine particles from which the granules were readied.

1.7.6 Assets of Modified Starches/Celluloses Used in FDTs:

Table 1.3 Properties of starches and cellulose

S.No.	Superdisintegrants	Properties
1.	Croscarmellose sodium	Great swelling ability, effective at low strengths (0.5-2.0%), can be incorporated up to 5%.
2.	Crospovidone	Not soluble in aqueous solution. Immediately diffuse and distend in water, but do not gels even after continuous contact. Effective strengths (1-3%). Micronized grades are available
3.	Sodium starch glycolate	Rapid water absorption swells equal to 6%. High strength leads to crystallizing and loss of disintegration.

1.8 Drug Profile:

1.8.1 Aceclofenac

- **Therapeutic category:**

  It is a Non steroidalAnti inflammatory drug and is specific only for Cox-2 receptor.

- **Chemical name:**

  2-[(2,6-dichlorophenyl)amino] phenylacetoxyacetic acid.

- **Description:**

  White crystalline powder

- **Therapeutic dosage:**

  Generally 100mg is given twice a day through oral route.

- **Drug interaction:**

Table 1.4 Drug interactions

Drug	Interaction mechanism
Digoxin, Lithium, Methotrexate	Plasma concentrations are increased
Anti coagulant	Increase activity
Quinolone antibiotics	Increase nephrotoxicity of cyclosporine

- **Mode of Action:**

  It inhibits the production of Prostaglandin E_2 (PEG2) ,tumor necrosis factor and cytokines which cause inflammation. It also shows its inhibitory effect on Cox-2 receptor.

- **Pharmacokinetics:**

  It is immediately absorbed and high strengths in plasma are observed after 1-3 hrs of oral administration. It highly bounds to plasma proteins upto 99%. The major metabolite of Aceclofenac is 4'-hydroxyaceclofenac. Fundamental route of elimination is through kidney (70-80%).Half life of Aceclofenac is 4hrs.

- **Melting point:** 149-153^{0}C

- **Solubilities:**

Table 1.5 Solubilities

Solvent	Solubility
Water	Insoluble
Acetone	Freely soluble
Alcohol	soluble

- **Physical Properties**

Table 1.6 Physical Properties

S. No.	Property	Value
1.	Melting point	149-153^{0}C
2.	Water solubility	Poorly soluble
3.	Log P	1.23
4.	pKa	4.7
5.	Physiological charge	-1
6.	Hydrogen acceptor count	5
7.	Hydrogen donor count	2
8.	Polar surface area	75.6 A^0

1.9. Excipients profile:[47,48,49]

Table 1.7 Sodium Starch Glycolate

Synonyms	Primogel, Carboxyl methyl starch
Description	White and free flowing powder.
Empirical Formula & Molecular Weight	n($C_{24}H_{44}O_6Na$) 5×10^5 - 1×0^6
Solubility	Soluble in organic solvents and practically insoluble in water
Functional categories	Disintegrants
Melting point	Do not melts
Density (bulk) **Density (tapped)**	0.81g/cm^3 0.98g/cm^3
Stability and storage conditions	Stored n air tight containers
Applications	Suspending agent, disintegrant.

- **Microcrystalline cellulose:**

Table 1.8 Micro crystalline cellulose

Synonyms	Cellulose gel, cellulose microcrystalline
Description	Granular , white, odourless.
Empirical Formula & Molecular Weight	$(C_6H_{10}O_5)_n$
Solubility	Not soluble in water, ethanol, ether, slightly soluble in NaOH solution.
Functional categories	Stabiliser, dispersing agent, emulsifier, anti-cakin agent
Melting point	260-270^{0}C
Density	1.5g/cm^3
Stability and storage conditions	Should be protected from light
Applications	Used as suspending agent, texturizer, fat substitute.

- **Magnesium Stearate:**

Table 1.9 Magnesium stearate

Synonyms	Stearic acid magnesium salt, magnesium salt, magnesium octadecanoate.
Description	Fine white powder
Structural Formula	$[CH_3(CH_2)_{16}COO]_2Mg$
Empirical Formula & Molecular Weight	$C_{36}H_{70}MgO_4$; 591.34
Solubility	Not soluble in water, ethanol & ether
Functional categories	Tablet & capsule lubricant.
Melting point	117- 150 ^{0}C.
Density (bulk) **Density (tapped)**	0.159gm/cm^3 0.286gm/cm^3
storage conditions	stored in well-closed container in a dry place.
Safety	nontoxic. Oral consumption of high amounts may leads to laxative effect.
Applications	Used in cosmetics, food & pharmaceutical formulations and As a lubricant.

- **Talc:**

Table 1.10 Talc

Synonyms	Magsilosmanthus, Magsil star, Powdered talc, Purified French chalk, soapstone, stealite.
Description	fine, white, odorless, intangible, crystalline powder.
Chemical name	Talc
Empirical formula & Molecular weight	hydrated, magnesium silicate, approximately to the formula $Mg_6(SiO_5)_4(OH)_4$.
Solubility	Almost insoluble in dilute acids and alkalis, organic solvents, and water.
Functional category	Anticaking agent, diluent for tablets and capsules
Specific gravity	2.7-2.8
storage conditions	stored in a well-closed container in a cool, dry place.
Safety	Following oral ingestion talc is unabsorbed systemically and may thus be termed as an vitally non-toxic substance l. However intra nasal or arterial abuse of products And also cause granulomas in body tissues.
Applications	It is mainly used for its lubricant and glidant properties in cosmetics, food and pharmaceutical products. It is also used as dusting powder and tablet and capsule diluent.

- **Polyethylene glycol 6000:**

Table 1.11 Polyethylene glycol 6000

Synonyms	Carbowax, Polyglycol, Macrogol
Description	White, Soild, free floeing powder
Empirical Formula & Molecular Weight	$H(OCH_2CH_2)_nOH$ 6000 D
Solubility	Soluble in water and other organic solvents
Functional categories	Ointment base, suppository base, solvent, lubricants in tablet and capsules
Melting point	$55\text{-}63^0C$
Density	$1.080g/cm^3$
Stability and storage Conditions	Stored in air tight containers
Safety	patients with burns and renal failure should use with precautions.
Applications	Used as vehicle, lubricants in tablets and capsules

- **Sodium lauryl sulphate:**

Table 1.12 Sodium lauryl sulphate

Synonyms	Do decyl sodium sulfate, Sulfuric acid mono dodecyl ester of sodium salt
Description	Cream to white to pale yellow, color crystals, flakes or Powder
Structural Formula	$C_{12}H_{25}NaO_4S$
Empirical Formula & Molecular Weight	288.38 g
Solubility	Freely aqueous soluble, practically insoluble in chloroform and ether.
Functional categories	Anionic surfactant, detergent, tablet and capsule lubricant
Melting point	204-207^{0}C
Density	1.07g/cm^3
Stability and storage Conditions	Stored in air tight containers.
Safety	Causes irritation to Skin, eye, respiratory tract, mucous membrane of stomach
Applications	Used as wetting agent, skin penetration, emulsification.

- **Lactose monohydrate:**

Table 1.13 Lactose monohydrate

Synonyms	Supertab, Tablettose,
Description	White to off white crystalline particles
Empirical Formula & Molecular Weight	$C_{12}H_{22}O_{11}.H_2O$ 360.31g
Solubility	Soluble in water.
Functional categories	Diluents, Binder, filler,
Melting point	201-202^{0}C
Density	1.545 g/cc
Stability and storage conditions	Stored in tightly closed containers, safeguarded from light and moisture.
Safety	Should not be used in patients with lactose intolerance, flatulence, diarrhea
Applications	Used in Lyophilization, tablet and capsule manufacture.

- **Methanol:**

Table 1.14 Methanol

Synonyms	Methyl hydroxide, Mono hydroxy methane, Pyroxylic spirit, Wood alcohol, Wood spirit, methyl carbinol.
Description	Colorless alcohol, hygroscopic
Structural Formula	CH_3OH
Empirical Formula & Molecular Weight	CH_4O 32.04g/mol
Solubility	100% in water.
Functional categories	Antifreeze, solvent, fuel, denaturant for ethanol.
Boiling point	$64.7^{o}C$
Density	$791.80kg/m^3$
Stability and storage conditions	Stored in clean containers made with stainless steel or vulcanized rubber in well ventilated areas or high density polyethylene.
Safety	• Toxic effects are caused when in contact with skin • Irritating to eyes include burning itching and redness. • May cause blindness if inhaled

1.10. Techniques Employed in the Formulation of FDT's:[4,30]

1.10.1. Freeze drying or Lyophilization:

The tablets arranged by freeze drying or Lyophilization are exceptionally porous in nature and break down or disintegrate immediately when interacted with salivation. In this procedure, water is sublimated from product after solidifying. The active medication is disintegrated or scattered in a fluid arrangement of a transporter/polymer.. Most importantly, the material is solidified to bring it beneath its eutectic point. At that point essential drying is carried out to reduction the dampness to around 4% w/w of dry product. Ultimately, auxiliary drying is made to decrease the bound dampness to the obliged volume. The freeze drying procedure has showed enhanced retention and increment in bioavailability. However the utilization of this method is limited because of high cost of supplies and preparing. A significant confinement of the last measurements structure contains absence of physical safety in standard blister packs.

1.10.2 Tablet Moulding:

Molding process can be achieved by two procedures i.e. solvent method and heatmethod strategy. Solvent technique includes damping the powder mix utilizing aalcoholicsolvent and later on layering at squat weight in formed platters to structure a wet mass. The flush is then uprooted via drying in air. The products arranged by this procedure are less conservative than layered tablets and forces a permeable structure that quickens the disintegration. The hot molding procedure includes planning of a suspension that constitutes a medication, agar and sugar (e.g. mannitol or lactose). The mechanical quality of formed tablets is to be notified and thus binding operators are blended to give strength .Taste covering is an extra inconvenience in this technology . Contrasted with the Lyophilization strategy, tablets shaped by the molding system are less demanding to update for mechanical production.

1.10.3 Spray drying:

The products are fused by hydrolyzed and non hydrolyzedgelatins as supportive operators, mannitol as building specialists, SSG or croscarmellose sodium as breaking down and an acidic material (e.g. citrus extract) and/ or soluble base material (e.g. Na_2CO_3) to upgrade deterioration and crumbling. Tablet packed from the spray dried powder deteriorated inside 20 seconds when inundated in a fluid medium.

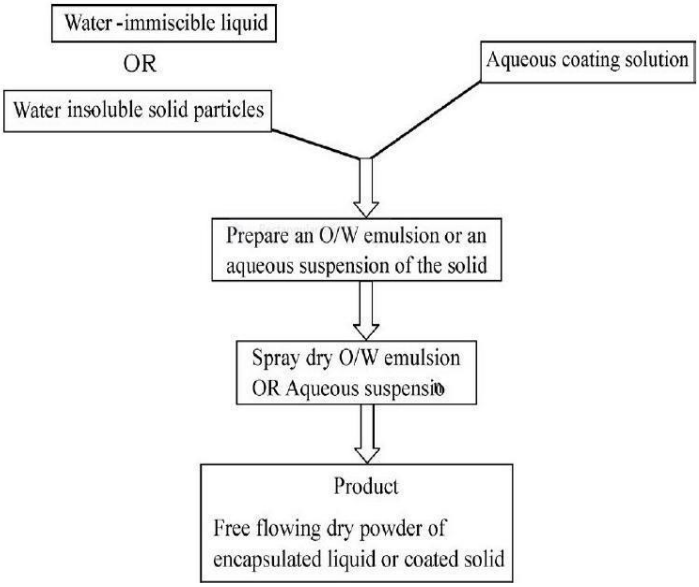


Figure 1.1 Flow chart of spray drying technique

1.10.4 Sublimation:

Latent solid ingredients are added with remaining additives and the mix was layered into tablet. Evacuation of unstable material by sublimation created a permeable structure. A strategy for creating quick dissolving tablet utilizing water as the pore structuring material has been depicted by Makino, et al.. The tablets break down in under 20 seconds and display sufficient mechanical quality. The way to quick breaking down for FDT's is the vicinity of a spongy structure in the tablet grid. Ordinary layered tablets that encompass profoundly water-dissolvable fixings regularly tumble to break up quickly in view of low porosity of the lattice. Thus to create permeable lattice, unpredictable fixings are utilized that are finally subjected to a methodology of sublimation.

1.10.5 Direct compression:

Traditional apparatus, usually accessible excipients and a few preparing steps are included in this method. Additionally high dosages can be obliged, last mass of tablet can undoubtedly surpass that of other generation methods. The deterioration and solubilisation of specifically compacted tablets relies on upon single or joined activity of disintegrants, solvent excipients and fizzy agents used. Large and hard tablets have breaking down time beyond that normally needed. . To guarantee a high deterioration rate, decision of appropriate sort and an ideal measure of disintegrants is important.

1.10.6 Mass extrusion:

The innovation includes moderating the active mix utilizing the vehicle amalgamate of water-solvent PEG and CH_3OH and succeeding evacuation of mitigate mass via extruder

or syringe to obtain a chamber of the product into even sections utilizing warmed blade sharp edge to structure tablet. The dried barrel can likewise be utilized to layer pellet for bitter medications and in this manner accomplishing taste concealing.

1.10.7 Cotton candy process:

Methodology is termed as it makes utilization of an interesting spinning system to deliver floss-like crystalline structure, which apes cotton candy. This methodology includes the arrangement of lattice of polysaccharides or saccharides by concurrent activity of instant liquefying and spinning. The framework shaped is somewhat recrystallized to obtain better stream chattels and compressibility. This candy floss grid is then processed and mixed with

API's and additives and consequently packed to FDT. It can suit large medication measurements and offers enhanced mechanical quality. Not with standing, high-handle temperature confines the utilization of this procedure.

1.10.8 Solid dispersion:

Strong scattering can be arranged by diverse technique taking into account the physical properties and warm dependability of the medication and the bearers.

Liquefying or combination technique:A physical mixture of a dynamic operators and a water-solvent transporter is warmed until it is dissolved. The melt is quickly set in ice shower under thorough mixing. The intertwined mass is then pummeled and sieved. Fast solidifying is attractive on the grounds that it brings about super immersion of medication as an aftereffect of capture of solute particles in the dissolvable grid by quickly hardening. The cementing methodology can be accomplished on stainless steel plates appended to a cooling framework to support quick warmth misfortune. Splash coagulating from an altered shower drier onto a chilly metal surface has likewise been utilized. Item from shower coagulating can be acquired in pellet structure without the need of a granulating step that may adjust crystalline alteration.

Dissolvable technique: Physical mixture of two strong segments is disintegrated in a typical dissolvable and afterward the dissolvable is typically uprooted by dissipation under decreased weight at different temperatures. The decision of dissolvable and its evacuation rate is basic to the nature of the scatterings. A mixture of dissolvable may likewise be utilized. Stop drying and shower drying can likewise accomplish the dissolvable evacuation. This technique is additionally called co-precipitation. Co precipitation is a perceived procedure for expanding the disintegration of inadequately watersoluble medications, for example, Ketoprofen, spironolactone, nifedipine, to subsequently enhance their bioavailability.

1.10.9 Wet granulation:

In wet granulation, granules are shaped by the expansion of a granulation fluid onto a powder bed which is affected by an impeller (in a High shear granulator, screws (in a twin screw granulator) or air (in a fluidized bed granulator). The unsettling bringing about the framework alongside the wetting of the parts inside the plan brings about the collection of the essential powder particles to create wet granules. The granulation fluid (liquid) contains a dissolvable which must be unpredictable so it can be evacuated by drying, and be non-dangerous. Common fluids incorporate water, ethanol and isopropanol either alone or in blend. The fluid arrangement can be either watery based or dissolvable based. Fluid arrangements have the upside of being more secure to manage than solvents. Water blended into the powders can shape bonds between powder particles that are sufficiently solid to bolt them together. Be that as it may, once the water dries, the powders may come apart. In this way, water may not be sufficiently solid to make and hold a bond. In such occasions, a fluid arrangement that incorporates a cover (pharmaceutical paste) is needed. Povidone, which is a polyvinyl pyrrolidone (PVP), is a standout amongst the most normally utilized pharmaceutical covers. PVP is disintegrated in water or dissolvable and added to the methodology. At the point when PVP and a dissolvable/water are blended with powders, PVP frames a security with the powders amid the methodology, and the dissolvable/water vanishes (dries). Once the dissolvable/water has been dried and the powders have framed an all the more thickly held mass, then the granulation is processed. This procedure brings about the arrangement of granules. The methodology can be exceptionally straightforward or extremely complex relying upon the attributes of the powders, the last target of tablet making, and the hardware that is accessible. In the conventional wet granulation technique the wet mass is constrained through a sifter to create wet granules which are in this way dried.

LITERATURE REVIEW

Chapter 2

LITERATURE REVIEW

2.1 Research on direct compression method:

2.1.1 Ankur Sharma et al., prepared and tested FDT's of Aceclofenac. The fast dissolving tablets are formulated by using crospovidone, croscarmellose sodium, SSG and sodium lauryl sulphate as surfactant. It was reported that the formulation containing 6% croscarmellose sodium was found to give best results and the tablets exhibited higher rate of release.[2]

2.1.2 R ShireeshKiran et al., six formulations of aceclofenacFDT's were formulated by using SSG, Crospovidone and yellow starch potato. The formulated tablets were appraised for various parameters such as invitro, invivo and drug release and the data was compared. It was reported that the tablets containing yellow sweet potato starch showed the fastest disintegration, good and rapid dissolution efficiency.[40]

2.1.3 SudhirBhardwaj et al., formulated and evaluated the tablets of Aceclofenac. Various super disintegrants were used in different strengths. The formulated tablets were appraised for various parameters of tablets. It was reported that the formulation having the highest concentration of super disintegrant showed the 99% of drug release.[43]

2.1.4 Shobhitkumar et al., formulated and evaluated the mouth dispersible tablets of aceclofenac using crospovidone, SSG as super disintegrants. It was showed that the formulation containing 4%w/w concentration of crospovidone has shown 30 s disintegration time, 25 s wetting time and 79.34% in vitrorelease of drug in 25 min.[42]

2.1.5 Milind P wagh et al., prepared and tested fast dispersible tablets of aceclofenac using croscarmellose sodium, Crospovidone and SSG. Nine batches were prepared using various concentrations of super disintegrants, out of which the formulation consisting croscarmellose sodium showed outstanding diffusion time with the drug discharge in 30 min.[24]

2.1.6 Premamaria Thomas et al., formulated and evaluated aceclofenac mouth melt tablets by using Croscarmellose sodium and SSG. The formulated tablets were evaluated for both invitro and invivo parameters. It was reported that the selected super disintegrants showed enhanced dissolution, taste masking and better patient compliance.[27]

2.1.7 A.A.Srirwaikar et al., was formulated fast disintegrating tablets of Atenolol using croscarmellose sodium and SSG. Croscarmellose sodium was found to be best among the three superdisintegrants. At 8%w/w concentration level it showed the best disintegration time of 31±2 seconds and release of 98% of the drug in 10 minutes.[41]

2.1.8 ManivannanRangasamy et al., designed and evaluated FDT's of Terbutaline sulphate by incorporating superdisintegrats such as Explotab, Ac-di-sol, and Polyplasdone XL, by direct compression method. Out of 9, the formulation F9 (containing 5 %w/w conc. of polyplasdone XL) was considered to be the best formulation, which release up to 99.33% of the drug in 10 min.,and dispersion time 9 seconds.[23]

2.1.9 Radke R.S.et.al. were formulated ODTs of Baclofen using various superdisintegrants Ac-Di-Sol, crospovidone and SSG . Among the formulations F3 containing Ac-Di-Sol showed enhanced organoleptic assets and outstanding in-vitro disintegration time(28.6 sec.) and drug release (100.51%).[29]

2.1.10 H.S.Mahajan et.al., have worked on the mouth dissolved tablets of sumatriptan succinate were formulated using superdisintegrants SSG, carboxy methyl cellulose, sodium and treated agar by direct compression method. The tablet disintegrates invitro and in vivo within 10 to 16 second and 12 to 18 seconds respectively. Almost 90% of drug was release from all the formulations within 10 minutes.[21]

2.1.11 Shailesh Sharma et.al prepared FDT's of Promethazine Theoclate using Ac-Di-Sol, SSG and crospovidone in diverse concentration. The tablet containing Ac-Di-Sol showed better-quality organoleptic chattels together with exceptional breakdown time (52 sec.) and medicament discharge (72.57%).[39]

2.1.12 Sajal Kumar Jhaet.al. prepared mouth melt tablets of haloperidol using Ac-Di-Sol, SSG and crospovidone in different concentration as superdisintegrants. All the formulation showed breakdown time under 30 seconds and liberate greatest quantity of drug by 12 minutes.[35]

2.2 Research on granulation methods:

2.2.1 Anas Bahnassi et.al., formulated and evaluated fast dissolving tablets of aceclofenac. The prepared tablets were testedfor various parameters of tablet.s. It was concluded that all the formulations showed acceptable dissolution and drug release according to the specifications officially provided.[1]

2.2.2 Shaikhsiraj et.al. formulated and evaluated aceclofenac fast dissolving tablets by consuming super disintegrants such as SSG with polyplasdone x1-10. The formulated tablets were appraised for invitro and invivo parameters.[38]

2.2.3 S. Dharani et.al. formulated and evaluated five batches of aceclofenac oral dispersible tablets by wet granulation method by using polyvinyl pyrrolidone, SSG, microcrystalline cellulose, starch and saccharin sodium as a super disintegrants. The formulation were evaluated for invitro and invivo parameters. It was concluded that the formulation contain Croscarmellose Sodium and SSG in equal concentrations shown rapid disintegration and maximum percentage of drug release compared to other formulations.[8]

2.2.4 B.Selvaraj et al., formulated and evaluated fast dissolving tablets of Aceclofenac using wet granulation technique. Using croscarmellose sodium, SSG as super disintegrants. One of the formulations among the eight formulations showed excellent physicochemical parameters and *invitro* drug release profile than the other seven formulations and marketed sample.[37]

2.2.4 C MallikarjunaSetty et al.,developed and evaluated FDT's of Aceclofenac by wet granulation method by using various super disintigrants, diluents and binders. the prepared tablets were tested for different parameters such as hardness, friability, drug content with in the official limits. It was concluded that variables of formulation influence the performance of tablet.[22]

2.3 Research on solid dispersion technique:

2.3.1 M.Ratnaparkhi et al.,developed a formulation and evaluated FDT's ofAceclofenac tablets by using mannitol as water soluble carrier to improve the solubility of aceclofenac. It was reported that the prepared tablets showed release of drug in 30 min.[30]

2.3.2 Upendra kulkarni et al., developed fast dissolving tablets and evaluated them for various invitro and invivo parameters these tablets were prepared by using modified aeglemarmelosgum.It was reported that the tablets have enhanced solubility and dissolution and bioavailability.[45]

2.3.4 K. Gowthamarajan et al., formulated and evaluated Aceclofenac FDT'S by solid dispersion technique by using different ingredients such as Poly ethylene glycol- 6000, Gelatin Hydrolysate, Beta Cyclodextrin, Sodium laryl sulphate and Croscarmellose and compared the prepared formulations with marketed products. It was concluded that tablets which containing Aceclofenac and Croscarmellose was shown the higher percentage release and 90% more than marketed product.[12]

2.3.5 M.A.EL-Nabarawi et al., formulated and optimized FDT's of Aceclofenac by solid dispersion technique by using various carriers. It was concluded that the polymers which are used in this study has showed the great effect on solubility and dissolution of API and by acting as a pH modifier sodium bi carbonate controlled the microenvironment enhanced the intial drug dissolution and solubility.[25]

2.3.6 BachhavDevidas G et al., formulated and evaluated FTD's of Aceclofenac by using different carriers like PVP K-30, Poly ethylene glycol-6000, Mannitol and Lactose and they have studied the effect of carriers in case of solubility of API. It was concluded that the carriers poly ethylene glycol-6000 and PVP K-30 was enhanced the solubility of drug.[3]

2.3.7 KirojRajbanshi et al., developed formulations and evaluated FDT's of Aceclofenac by solid dispersion technique using various carriers and super disintegrants. Hydroxypropyl Beta Cyclodextrin (HPBCD), premix of Lactose and Maize Starch and Mannitol as carriers and Similarly, as superdisintegrant, Sodium Starch Glycolate ,Croscarmellose and Crospovidone was used. It was concluded that combination of carrier and superdisintegrant to solid dispersion of drug is very good approach to increase dissolution of ailing water soluble drugs.[15]

2.4 Research on sublimation technique:

2.4.1 Kalpesh Gaur et al., formulated and characterized FDT'S of Aceclofenac by sublimation method using two Superdisintegrants i.e., crospovidone, SSG with camphor as subliming agent.Among all formulations, the formulation having 8% crospovidone showed best results for the evaluation of all invitro and invivo parameters.[14]

2.4.2 Gandhi KR et al., formulated and evaluated mouth dissolving tablets of Aceclofenac using Polyplasdone XI 10 as Superdisintegrants by sublimation technique. Menthol is used as subliming agent. This work reported tablets with improved absorption and bioavailability.[10]

2.4.3 SumanthaMalakar et al., formulated and evaluated oral dispersable tablets of Aceclofenac by sublimation technique by using camphor. Cross linked poly vinyl pyrrolidone and SSG are used as super disintegrants. Formulation 6 out of all formulation proved to be the best formulation and is stable for 3 months.[44]

RESEARCH ENVISAGED

AND

PLAN OF WORK

Chapter 3

RESEARCH ENVISAGED AND PLAN OF WORK

3.1 Rationale of the study:

Oral route of administration is highly agreeable by the patients because of their administration, non-invasiveness and cost effectiveness. Butoral dosage forms are limited by first pass metabolism and gulping of tablets especially incase of paediatric and geriatrics. Fast dissolvingtablets ororaldispersible tablets are novel form of oral dosage systems. These are advantageous because these are rapidly dissolute within couple of seconds in saliva thus enhancing bioavailability in addition also avoids enterohepatic cycling.

Aceclofenac is NSAID analogue of Diclofenac. It is used as pain reliever and inflammation resulted from the Arthritis. Its how sits mode of action by inhibiting the cyclo-oxygen as which is used in synthesis of prostaglandins which causes pain and inflammation.

As Aceclofenac has poor aqueous solubility, it would be beneficial when it is formulated in the form of oral dispersible tablets so that its solubility can be enhanced leading to better absorption of medicament. This research focuses on the formulation of FDT's of dispersible tablets and comparative evaluation of all the techniques.

3.2 Aim:

Comparative Evaluation of FDT's of Aceclofenac by Different Techniques.

3.3 Objective:

- To develop Fast dissolving formulations ofAceclofenacbyvarious techniques
- To evaluate the developed tablets for different *in vitro* and *in vivo* factors
- To carry out comparative evaluation of the techniques used for formulation.

EXPERIMENTAL

Chapter 4

EXPERIMENTAL

Table 4.1 Materials used

S.No.	Chemical	Manufacturer
1.	Polyethylene glycol	Central Drug house (P) Ltd.
2.	Lactose	Loba chemicals Mumbai India
3.	SSG	Loba chemicals Mumbai India
4.	Sodium lauryl sulphate	Loba chemicals Mumbai India
5.	Microcrystalline cellulose	Loba chemicals Mumbai India
6.	Acetone	Central Drug house (P) Ltd.
7.	Methanol	Central Drug house (P) Ltd.
8.	Talc	Loba chemicals Mumbai India
9.	Magnesium stearate	sd fi NE-CHEM Ltd. Mumbai India
10.	Polyvinyl pyrrolidine	Loba chemicals Mumbai India

Table 4.2 Equipments used

S.No.	Equipments	Model/Source
1.	Tablet punching machine	Trover Pharmamach, Nakodar, India
2.	Sieves	Bhushan Engineering & Scientific Traders, Ambala Cantt., India
3.	Monsanto hardness tester	Popular Traders, Ambala Cantt., India
4.	Infrared red spectrophotometer	Rkin- Elmer, Corporation, USA
5.	pH meter	Systronics, Ahmedabad, India
6.	Dissolution test apparatus II	Microsil, Ambala Cantt., India
7.	Melting point apparatus	Popular Traders, Ambala Cantt., India
8.	Hot air oven	Navyug India Q5247, Ambala Cantt., India
9.	UV visible spectrophotometer	Shimadzu Ltd. Japan
10	Electronic balance (BL-22OH)	Shimadzu Co.Ltd. Japan

4.1 Preliminary investigation:

4.1.1. Physicochemical characterization and identification of Aceclofenac

4.1.1.1 Appearance:

Aceclofenac was observed for colour and appearance.

4.1.1.2 Melting point:

The melting point of the Aceclofenac was determined by capillary method. In this method capillary was taken (one end sealed) and from the open end Aceclofenac drug was filled at a height of 3mm from the closed end. Then capillary was introduced in to the melting point apparatus along with the thermometer in the apparatus then with the rise in the temperature, that range was noted down at which temperature drug material was started to melt and melts completely.

4.1.1.3 Infrared spectral analysis:

Infrared spectral analysis of Aceclofenac was carried out using IR spectrophotometer using small discs of drug with Potassium Bromide (KBr). The infrared spectrum obtained was compared with the spectrum obtained with Aceclofenac working standard.

4.1.1.4. Estimation of Aceclofenac drug using Ultraviolet (UV) visible spectrophotometer:

A. Preparation of standard plot of Aceclofenac in methanol:

- Preparation of stock solution in methanol:50 mg of Aceclofenac was weighed and dissolved in 10 ml methanol in a 50 ml volumetric flask and the contents were dissolved and the volume was adjusted to 50 ml by using methanol. From this 10 ml of solution transferred into 100 ml volumetric flask and volume adjusted by using methanol. This is known as the stock solution of drug in methanol.
- Determination of the maximum wavelength: From the stock solution 10ml of sample was taken out and filled in to the cuvette of the UV apparatus. Maximum wavelength was checked from the range of 200-400nm.the maximum wavelength was found to be 275nm.
- Validation of assay method of Aceclofenac in methanol:From the stock solution 2µg/ml, 4µg/ml, 6µg/ml, 8µg/ml, 10µg/ml, 12µg/ml, 14µg/ml were prepared using methanol. Then their absorbance was noted down at the wavelength 275nm.

B. Preparation of standard plot of Aceclofenac in Acid Buffer (pH 1.2):

- *Preparation of buffer*:50ml of 0.2M potassium chloride transferred into a 1000ml volumetric flask and added the specified volume of 0.2M HCl, added water up to 1000ml.
- *Determination of the maximum wavelength*: 100 mg of Aceclofenac transferred into a 100 ml of volumetric flask and dissolved in 10 ml of methanol and make up the volume with pH 1.2 buffer solution. From this solution 10 ml was taken in a 100 ml of volumetric flask and make up the volume with pH 1.2 buffer solution to get concentration 100µg/ml. this is known as stock solution. From this solution aliquots 1ml, 2ml, 3ml, 4ml, and 5ml were pipetted out into a 50ml volumetric flasks and make up the volume up to the mark with pH 1.2 buffer solution. From the 50ml flasks sample was taken out and filled in to the cuvette of the UV apparatus. Maximum wavelength was checked from the range of 200-400nm.the highest wavelength was measured out to be 272.4nm.
- *Validation of assay method of Aceclofenac in Acid Buffer (pH 1.2):* From the stock solution aliquots 2ml, 4ml, 6ml, 8ml, and 10ml were pipetted out into a 50ml volumetric flask and make up the volume up to the mark with pH 1.2 buffer solution. Then their absorbance noted down at the wavelength 272.4nm.[28]

C. Preparation of standard plot of Aceclofenac in Phosphate Buffer (pH 7.5):

- *Preparation of buffer*:6.8gm of potassium di hydrogen ortho phosphate and 1.56gm of sodium hydroxide were weighed and transferred into a 1000ml volumetric flask and dissolved in distilled water and volume adjusted up to the mark.
- *Determination of the maximum wavelength*: 100 mg of Aceclofenac transferred into a 100 ml of volumetric flask and dissolved in 10 ml of methanol and make up the volume with pH 7.5 buffer solution. From this solution 10 ml was taken in a 100 ml of volumetric flask and make up the volume with pH 7.5 buffer solution to get concentration 100µg/ml. this is known as stock solution. From this solution aliquots 1ml, 2ml, 3ml, 4ml, and 5ml were pipetted out into a 50ml volumetric flasks and make up the volume up to the mark with pH 7.5 buffer solution. From the 50ml flasks sample was taken out and filled in to the cuvette of the UV apparatus. Maximum wavelength was checked from the range of 200-400nm.the highest wavelength was measured out to be 274nm.
- *Validation of assay method of Aceclofenac in Phosphate Buffer (pH 7.5):*From the stock solution aliquots 2ml, 4ml, 6ml, 8ml, and 10ml were pipetted out into a 50ml

volumetric flasks and make up the volume up to the mark with pH 7.5 buffer solution. Then their absorbance noted down at the wavelength 274nm.[28]

D. Preparation of standard plot of Aceclofenac in Phosphate Buffer (pH 6.8):

- *Preparation of buffer:*28.80gm of disodium hydrogen phosphate and 11.45gm of potassium di hydrogen phosphate were weighed and transferred into a 1000ml volumetric flask and dissolved in distilled water and volume adjusted up to the mark.
- *Determination of the maximum wavelength*: 100 mg of Aceclofenac transferred into a 100 ml of volumetric flask and dissolved in 10 ml of methanol and make up the volume with pH 6.8 buffer solution. From this solution 10 ml was taken in a 100 ml of volumetric flask and make up the volume with pH 6.8 buffer solution to get concentration 100µg/ml. this is known as stock solution. From this solution aliquots 1ml, 2ml, 3ml, 4ml, and 5ml were pipetted out into a 50ml volumetric flasks and make up the volume up to the mark with pH 6.8 buffer solution. From the 50ml flasks sample was taken out and filled in to the cuvette of the UV apparatus. Maximum wavelength was checked from the range of 200-400nm.the highest wavelength was measured out to be 273.2nm.
- Validation of assay method of Aceclofenac in Phosphate Buffer (pH 7.5):From the stock solution aliquots 5µg/ml, 10µg/ml, 15µg/ml, 20µg/ml, 25µg/ml, 30µg/ml were prepared Then their absorbance noted down at the wavelength 273.2nm.[28]

4.2. Physical compatibility study of the Aceclofenac with various excipients:

The samples as shown in the table.Were exposed to condition of 40^0C/75% RH (open/closed) in glass vials sealed with aluminium foil for a period of one month. The glass vials which were punctured from top of foil were called open glass vials, whereas glass vials kept as such were recorded. These samples were then periodically examined against a control sample.

Table 4.3 Physical compatibility study of Aceclofenac with various excipients

S.No	Composition	Proportion	Final weight
1.	Drug(Aceclofenac)	-	100mg
2.	Drug: Microcrystalline cellulose	1:1	100mg
3.	Drug: Sodium starch glycolate	1:1	100mg
4.	Drug: Sodium laryl sulphate	1:1	100mg
5.	Drug: Magnesium stearate	1:1	100mg
6.	Drug: Talc	1:1	100mg
7.	Drug: Lactose monohydrate	1:1	100mg
8.	Drug: Poly ethylene glycol-6000	1:1	100mg

4.3. Formulation development

4.3.1. Preparation of different formulation series of Aceclofenac by Direct compression method

Different batches of tablets were prepared by direct pressure strategy. Drug, diluent, superdisintegrants, surfactant and sweetener were passed however sieve # 40 and magnesium stearate and talc were gone through # 80sieve. Obliged amount of medication, and surfactant was blended first than different excipients were blended completely. The powder was compacted utilizing direct compression process. The formula of different batches is indicated in table.[2]

Table 4.4 Formula used for Formulations of Aceclofenac by direct compression

Ingredients	Batches coded Quantity (mg)		
	F1	F2	F3
Aceclofenac	100	100	100
Sodium starch glycolate	55	66	77
Microcrystalline cellulose	50	50	50
Talc	10	10	10
Magnesium stearate	5	5	5
Sodium lauryl sulphate	5	5	5
Lactose monohydrate	325	314	303
Total	550	550	550

4.3.2. Preparation of different formulation series of Aceclofenac by Solid dispersion method

Preparation of solid dispersion with carrier by melting solvent method: It has discovered that 5-10 % w/w of fluid compound could be consolidated in PEG 6000 without huge loss of its strong properties. Thus it is conceivable to plan solid dispersion by first dissolving drug in a suitable solvent and after that the arrangement is consolidated straightforwardly into the melt of PEG (70^{0} C) without evacuating the fluid solvent. To this solid dispersion accurately weighed remaining ingredients was added and mixed thoroughly and passed by sieve # 40 and compressed for tablets.[30]

Table 4.5 Formula used for Formulations of Aceclofenac by Solid dispersion technique

Ingredients	Batches coded Quantity (mg)		
	F1	F2	F3
Aceclofenac	100	100	100
Poly ethylene glycol-6000	0	100	200
Sodium starch glycolate	52	54	56
Microcrystalline cellulose	50	50	50
Talc	10	10	10
Magnesium stearate	5	5	5
Sodium lauryl sulphate	5	5	5
Lactose monohydrate	328	226	124
Total	550	550	550

4.3.3. Preparation of different formulation series of Aceclofenac by Wet granulation method

Tablets containing 100mg of API are prepared by wet granulation technique by using 10%w/v PVP as a binder. The accurately weighed all ingredients were mixed and triturated gentle by adding binder solution. The obtained granules were dried at 60^0 C for complete drying and the dried powder was mixed with magnesium stearate and talc and blended. Then the powder compressed in to tablets.[38]

Table 4.6 Formula used for Formulations of Aceclofenac by Wet granulation method

Ingredients	Batches coded Quantity (mg)		
	F1	F2	F3
Aceclofenac	100	100	100
Sodium starch glycolate	52	54	56
Microcrystalline cellulose	50	50	50
Talc	10	10	10
Magnesium stearate	5	5	5
Sodium lauryl sulphate	5	5	5
Lactose monohydrate	328	326	324
Total	550	550	550

4.4. Evaluation of Aceclofenac FDT's

The prepared FDT's are evaluated for various official specifications

4.4.1. Hardness

The crushing strength of tablets (hardness) was measured using Monsanto hardness tester. The force required to crush the tablet was measured in Kg/cm^2.

4.4.2. Friability

The friability of a sample of 10 tablets was measured using a Roche Friabilator. 10 pre-weighed tablets were rotated at 25rpm for 4minutes. The tablets then reweighed after removal of fines and the %of weight loss was calculated using formula:

$$\%Friability=(W_i-W_f)\times100\div W_i$$

Where W_i= initial weight of tablets

W_f= final weight of tablets

4.4.3. Weight variation

10 tablets of each batch were selected at a random and average weight was calculated. The individual tablets were weighed and the weight was compared with an average weight.

4.4.4. Wetting time

The wetting time of tablets was evaluated by the use of a piece of double folded tissue paper placed in a petri dish containing 6ml of water. A pre-weighed tablet was placed on this paper and the time for complete wetting of tablet was noted as wetting time.

4.4.5. In vitro dispersion time

The tablet was added to 10ml of water and time required for complete dispersion was measured. Two tablets from each formulation batches were randomly selected and in vitro dispersion time was performed.

4.4.6. In vitro dissolution study of tablets

The in-vitro study of tablets was carried out using USP II dissolution apparatus (paddle method). The in-vitro dissolution Medias used was phosphate buffers 6.8pH and 7.5pH. The FDT of formulation batch was dropped in to 900ml of dissolution media maintained at a temperature of 37 ± 0.5^0 C and stirred at a specified rpm i.e. 50rpm. 5ml of aliquots of dissolution medium were withdrawn at a time interval of 5, 10, 15, 20, 25, 30 minutes which was replaced with 10ml of fresh dissolution medium. The samples withdrawn were filtered and diluted and assayed at 275nm using UV- visible double beam spectrophotometer.

RESULT AND DISCUSSION

Chapter 5

RESULT AND DISCUSSION

5.1. Pre formulation study (identification and characterization of Aceclofenac)

5.1.1. Appearance:

A white, crystalline powder.

5.1.2. Melting point:

The temperature at which the drug melts was found to be 149-153^{0}C which is as per the specifications in the certificate of analysis issued by the manufacturer.

5.1.3. IR Spectra of Aceclofenac:

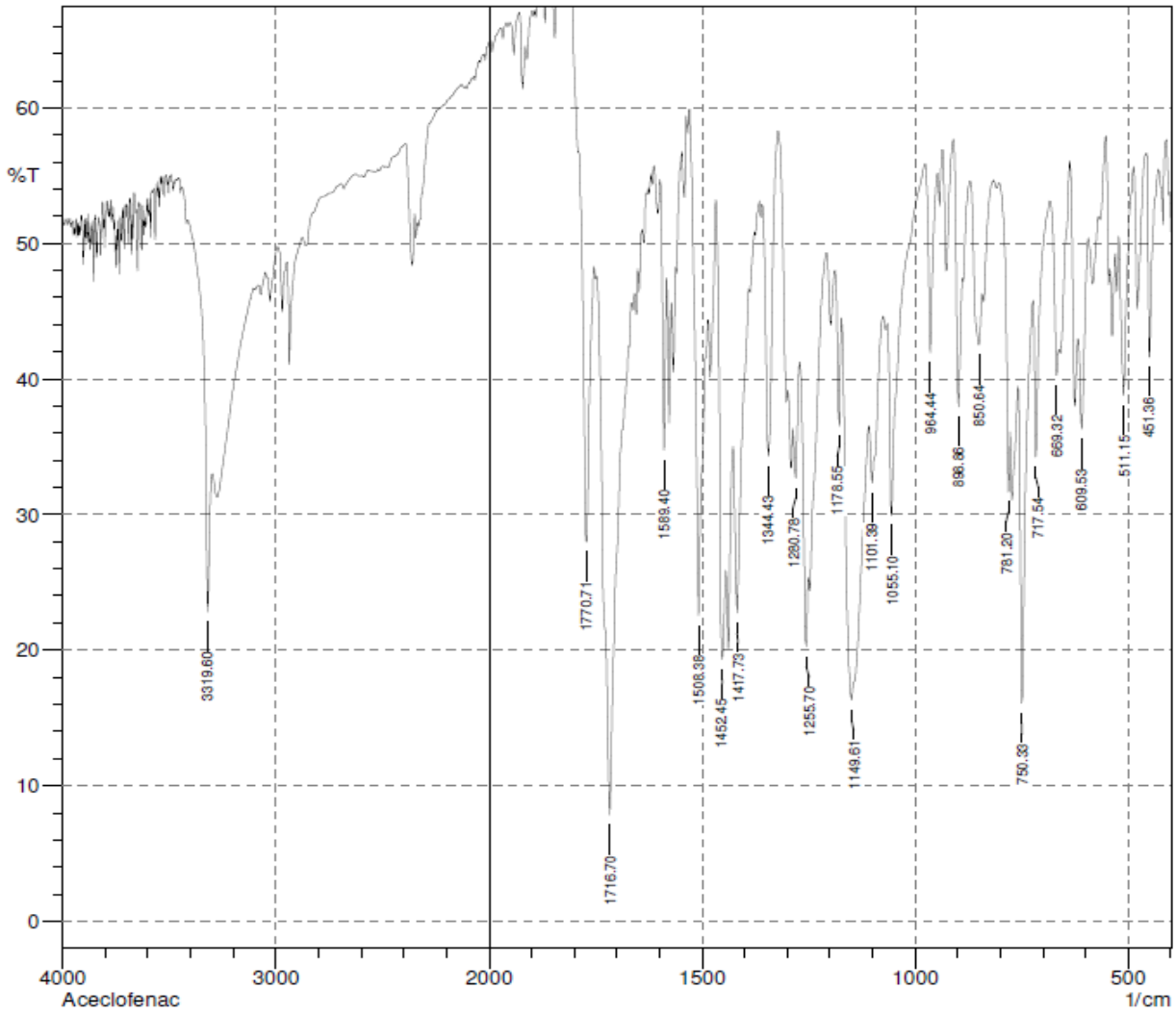


Figure 5.1 IR spectra of Aceclofenac

5.1.4. Concentration and absorbance values for standard calibration curve of Aceclofenac in methanol at λ_{max}= 275nm.

Table 5.1 Absorbance data for UV identification of Aceclofenac in methanol

Concentration(mg/ml)	Absorbance(nm)
2	0.097
4	0.247
6	0.366
8	0.506
10	0.622
12	0.771
14	0.892

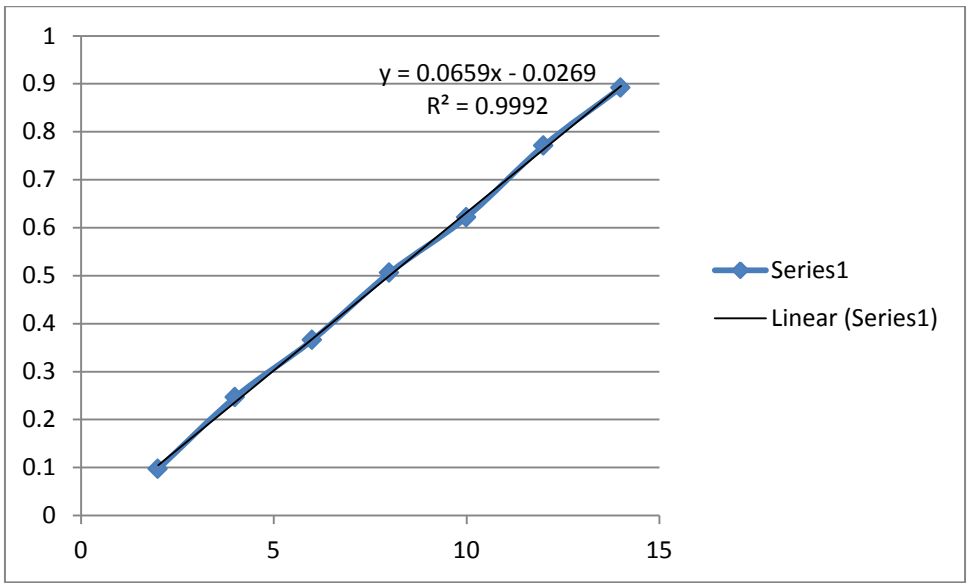


Figure 5.2 Calibration curve of Aceclofenac in methanol

5.1.5. Concentration and absorbance values for standard calibration curve of Aceclofenac in Acid Buffer (pH 1.2):atλ_{max}= 272.4nm.

Table 5.2 Absorbance data for UV identification of Aceclofenac in Acid Buffer (pH 1.2)

Concentration(mg/ml)	Absorbance(nm)
2	0.052
4	0.107
6	0.146
8	0.180
10	0.224

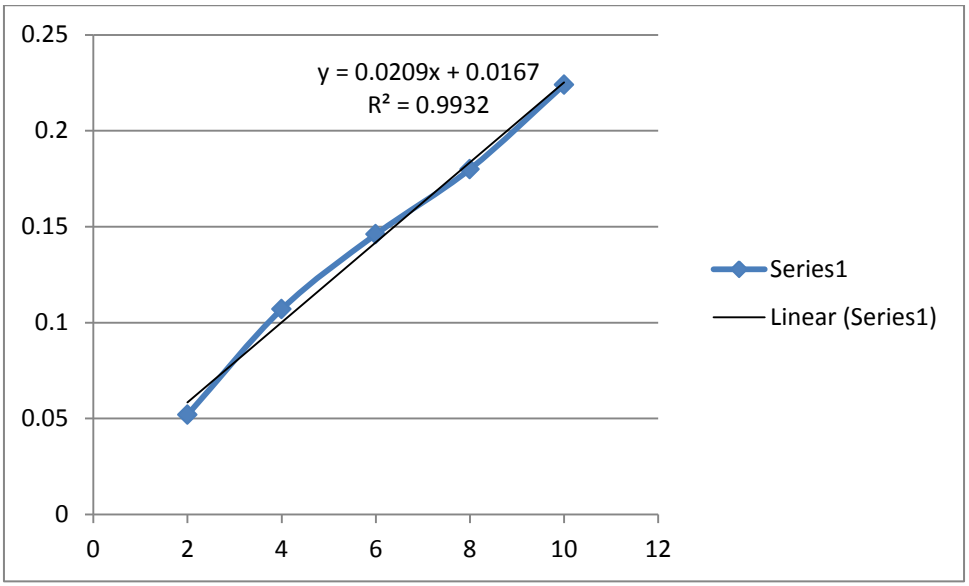


Figure 5.3 Calibration curve of Aceclofenac in Acid Buffer (pH 1.2)

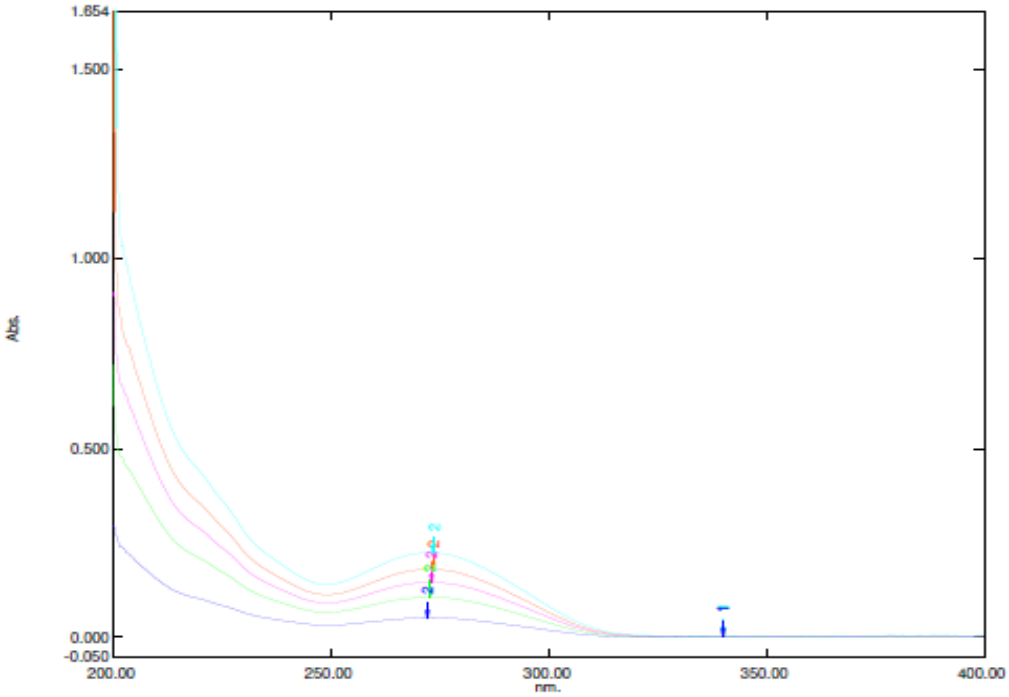


Figure 5.4 UV spectrum of Aceclofenac in Acid Buffer (pH 1.2)

5.1.6. Concentration and absorbance values for standard calibration curve of Aceclofenac in Phosphate Buffer (pH 7.5) at λ_{max}= 274nm.

Table 5.3 Absorbance data for UV identification of Aceclofenac in Phosphate Buffer (pH 7.5)

Concentration(mg/ml)	Absorbance(nm)
2	0.187
4	0.312
6	0.478
8	0.627
10	0.767

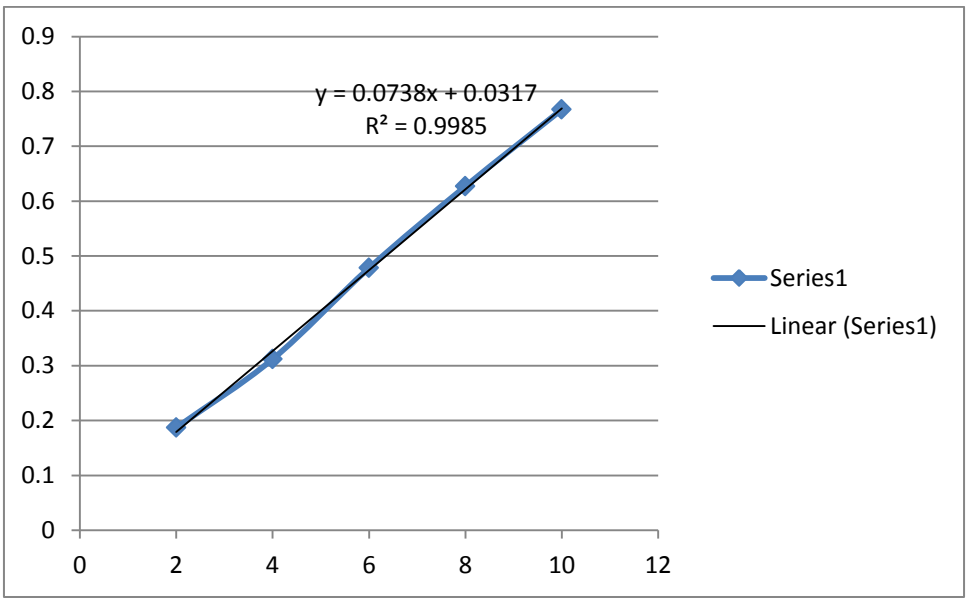


Figure 5.5 Calibration curve of Aceclofenac in Phosphate Buffer (pH 7.5)

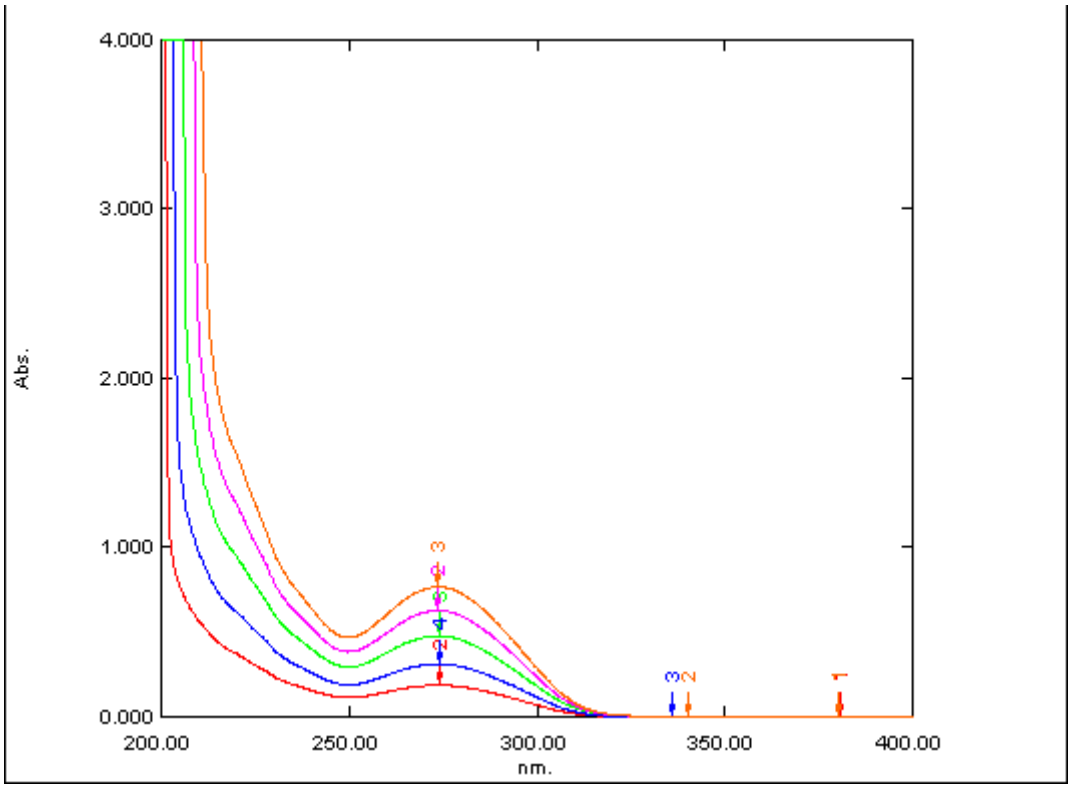


Figure 5.6 UV spectrum of Aceclofenac in Phosphate Buffer (pH 7.5)

5.1.7. Concentration and absorbance values for standard calibration curve of Aceclofenac in Phosphate Buffer (pH 6.8) at λ_{max}= 274nm.

Table 5.4 Absorbance data for UV identification of Aceclofenac in Phosphate Buffer (pH 6.8)

Concentration(µg/ml)	Absorbance(nm)
5	0.141
10	0.235
15	0.359
20	0.469
25	0.641
30	0.691

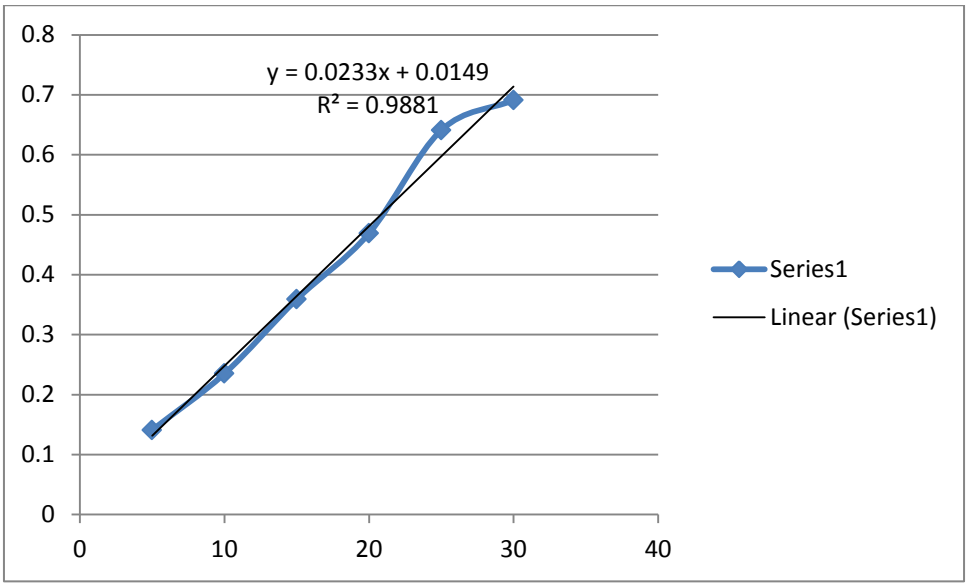


Figure 5.7 Calibration curve of Aceclofenac in Phosphate Buffer (pH 6.8)

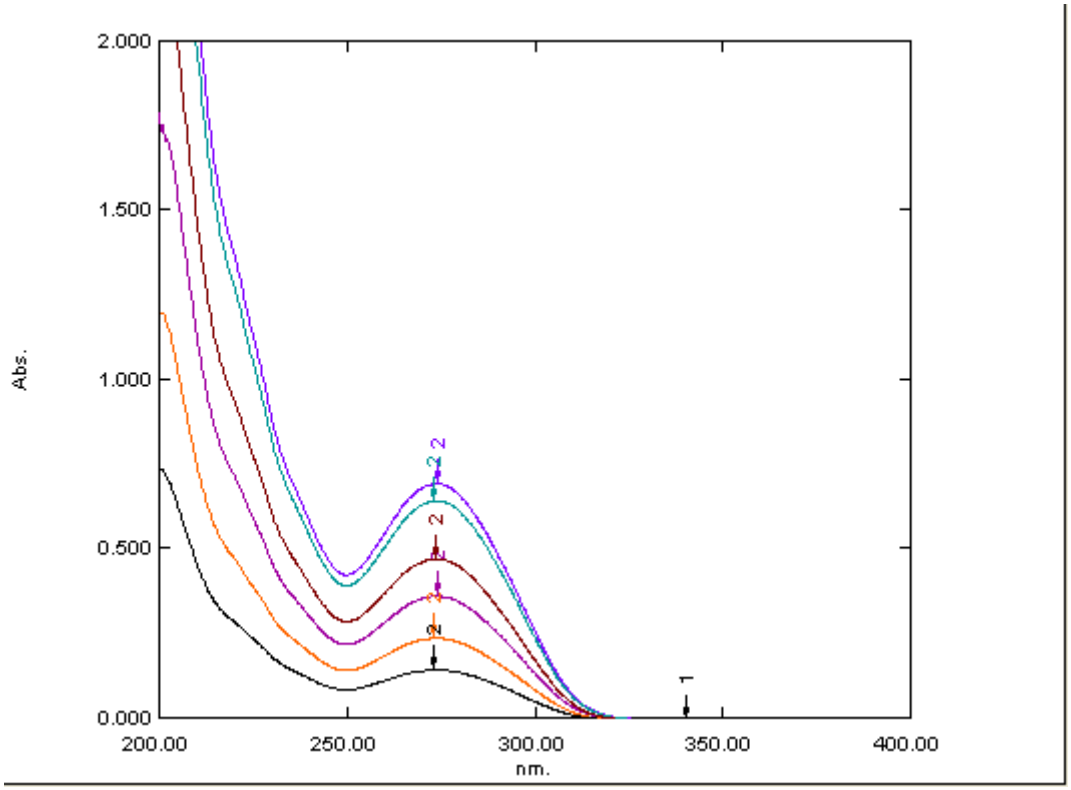


Figure 5.8 UV spectrum of Aceclofenac in Phosphate Buffer (pH 6.8)

5.2. Physical compatibility study of theAceclofenac with different excipients

The physical compatibility study was designed to determine the interaction of Aceclofenac with various excipients proposed to be used in the formulation. Aceclofenac along with the physical mixture of Aceclofenac with various excipients were kept at different environmental conditions for physical compatibility studies as shown in table. A comparison of the initial sample, control sample and samples kept at different environmental conditions for physical change was made periodically at different time. The Aceclofenac was found to be physical compatible with all the excipients has no colour changes or lump formation occurred in samples kept at different environmental conditions with respect to initial and control samples.

Table 5.5 Physical compatibility study of theAceclofenac with different excipients

S.NO	Composition	Ratio (w/w)	Final weight (mg)	Initial	Control(weeks)			40^0C,75%RH open(weeks)				
					1	2	3	4	1	2	3	4
1	Drug(Aceclofenac)	-	100mg	White colour	√	√	√	√	√	√	√	√
2	Drug: Microcrystalline cellulose	1:1	100mg	White colour	√	√	√	√	√	√	√	√
3	Drug: Sodium starch glycolate	1:1	100mg	White colour	√	√	√	√	√	√	√	√
4	Drug: Sodium laryl sulphate	1:1	100mg	White colour	√	√	√	√	√	√	√	√
5	Drug: Magnesium stearate	1:1	100mg	White colour	√	√	√	√	√	√	√	√
6	Drug: Talc√√	1:1	100mg	White colour	√	√	√	√	√	√	√	√
7	Drug: Lactose monohydrate	1:1	100mg	White colour	√	√	√	√	√	√	√	√
8	Drug: Poly ethylene glycol-6000	1:1	100mg	White colour	√	√	√	√	√	√	√	√

√: Refers to the same as original. RH:- stands for relative humidity

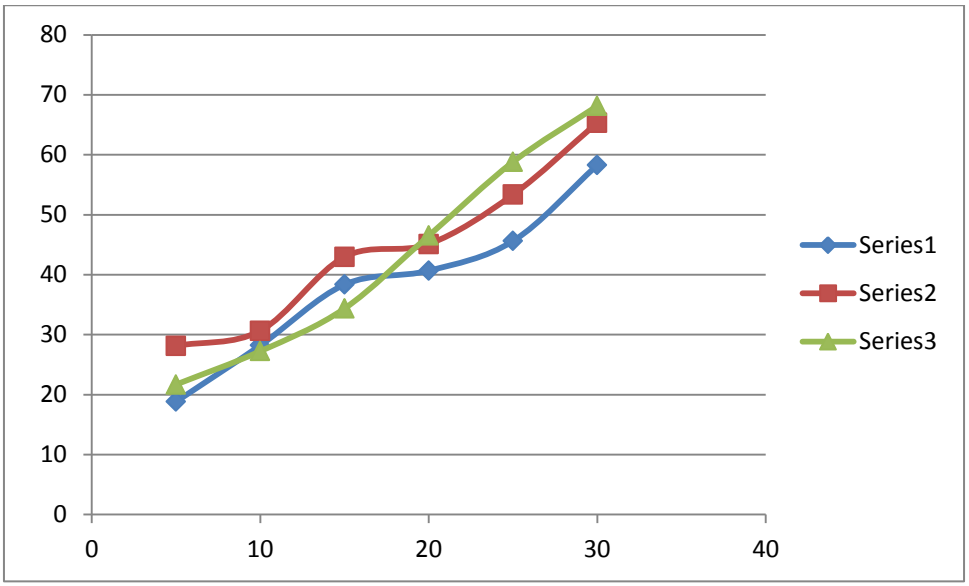
5.3. Results of formulation series of Aceclofenac by different methods

Table 5.6 Results of formulation series of Aceclofenac by direct compression method

Parameters	Formulations		
	F1	F2	F3
Hardness(kg/cm^2)	3.52	3.54	3.56
Friability(%)	0.857	0.556	0.723
Weight variation	Pass	Pass	Pass
Wetting time(sec)	193	181	165
In vitro dispersion time(sec)	137	122	118

Table 5.7 Cumulative percentage of Aceclofenac release from formulated tablets

No	Time (min)	F1	F2	F3
1	5	18.82	28.14	21.68
2	10	28.21	30.65	27.24
3	15	38.35	42.97	34.36
4	20	40.66	45.11	46.51
5	25	45.61	53.35	58.81
6	30	58.27	65.34	68.14



Series1- (F1), Series2-(F2), Series3-(F3).

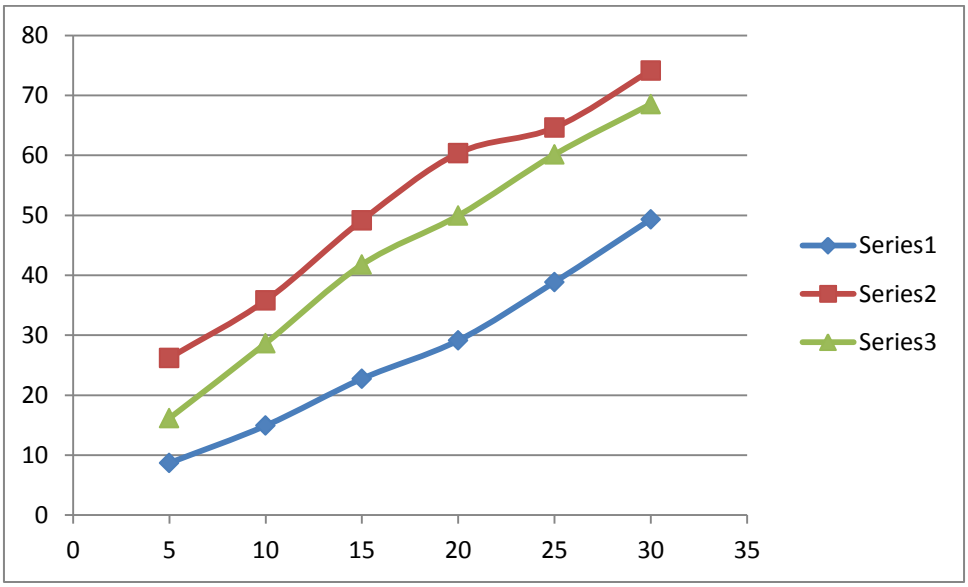
Figure 5.9 Comparison of cumulative %release of different formulation prepared by direct compression method.

Table 5.8 Results of formulation series of Aceclofenac by solid dispersion technique

Parameters	**Formulations**		
	F1	**F2**	**F3**
Hardness(kg/cm^2)	3.22	3.18	3.12
Friability(%)	0.551	0.632	0.618
Weight variation	Pass	Pass	Pass
Wetting time(sec)	154	93	117
In vitro dispersion time(sec)	103.7	78.9	84.4

Table 5.9 Cumulative percentage of Aceclofenac release from formulated tablets

No	Time (min)	F1	F2	F3
1	5	8.70	26.22	16.15
2	10	14.92	35.8	28.64
3	15	22.74	49.17	41.77
4	20	29.12	60.36	49.94
5	25	38.86	64.61	60.12
6	30	49.33	74.14	68.54



Series1- (F1), Series2-(F2), Series3-(F3).

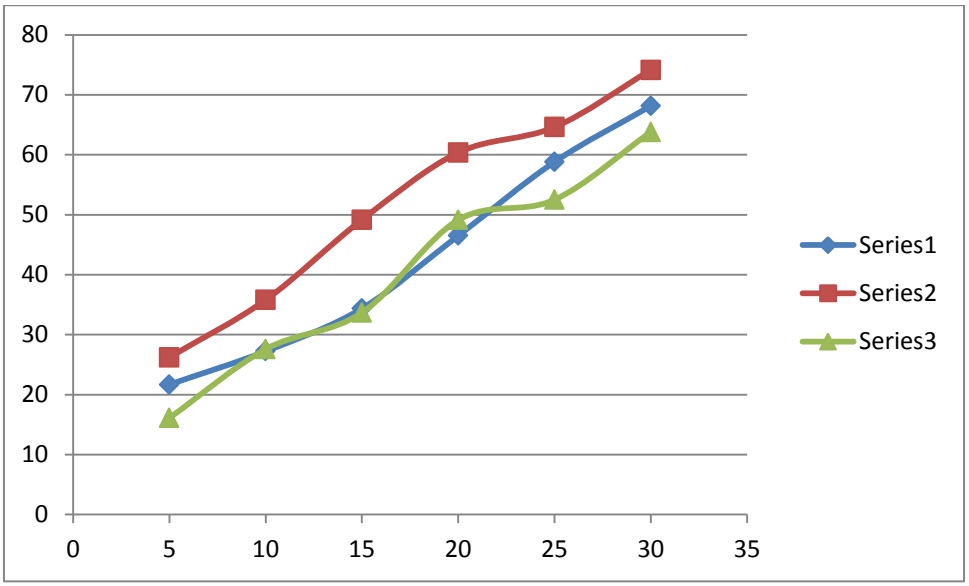
Figure 5.10 Comparison of cumulative %release of different formulation prepared by solid dispersion technique.

Table 5.10 Results of formulation series of Aceclofenac by Wet granulation method

Parameters	**Formulations**		
	F1	**F2**	**F3**
Hardness((kg/cm^2)	4.1	4.5	4.7
Friability(%)	0.447	0.683	0.722
Weight variation	Pass	Pass	Pass
Wetting time(sec)	145	159	147
In vitro dispersion time(sec)	123	138	148

Table 5.11:Cumulative percentage of Aceclofenac release from formulated tablets

No	**Time (min)**	**F1**	**F2**	**F3**
1	5	16.11	13.83	11.59
2	10	27.58	23.37	20.82
3	15	33.67	30.77	25.91
4	20	49.13	34.93	31.77
5	25	52.5	46.06	45.87
6	30	63.8	59.5	57.1



Series1- (F2), Series2-(F1), Series3-(F3).

Figure 5.11Comparison of cumulative %release of different formulation prepared by wet granulation technique.

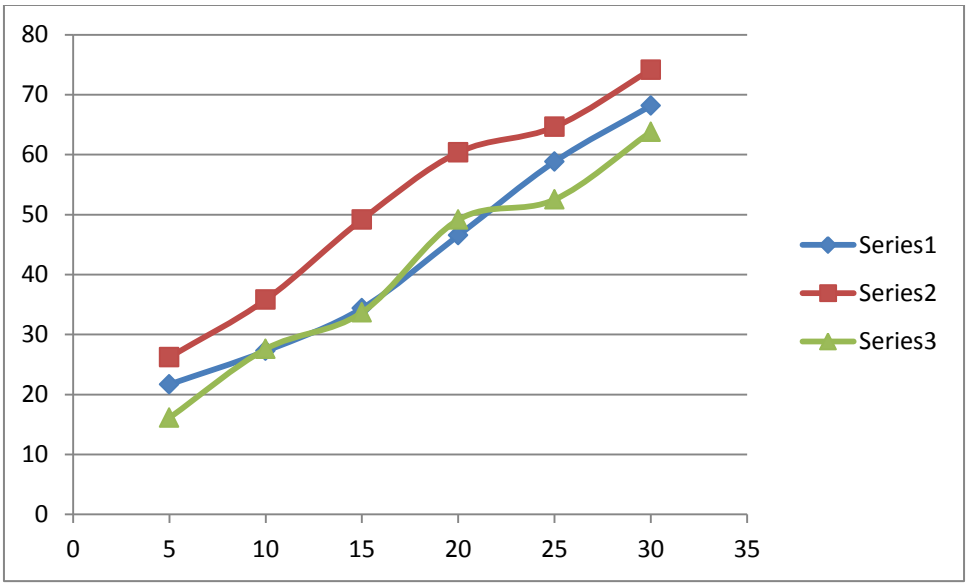


Figure 5.12 Comparison of % release of three preparation techniques

Series1- Direct compression (F3), Series2-solid dispersion (F2), Series3-wet granulation (F1).

SUMMARY AND CONCLUSION

Chapter 6

SUMMARY AND CONCLUSION

Oral dosage forms are limited by first pass metabolism and gulping of tablets especially in case of pediatric and geriatrics. Fast dissolving tablets or oral dispersible tablets are novel form of oral dosage systems which disintegrates in couple of seconds so that the proportion of drug that reaches the systemic circulation is increased. Aceclofenac is poorly aqueous soluble, so it can be formulated as oral dispersible tablets, which enhances its dissolvability and ultimately its bioavailability is increased.

The Main objective of the study was to develop, optimize, evaluate and compare the percentage release of drug Aceclofenac FDT's prepared by different techniques such as direct compression, Solid dispersion and Wet granulation. The sample of pure drug (Aceclofenac) was identified and characterized as per requirements of certificate of analysis (COA) issued by the manufacturer. The identification of Aceclofenac was confirmed by melting point and IR spectra. The solubility of Aceclofenac in various dissolution media and solvent meets the specification as per requirements of certificate of analysis (COA).

The present investigation done to select an optimum formulation which is showing good percentage release of drug than other techniques and comparison of the techniques about their drug release profile. After compression of powder blend, the tablets were evaluated for various parameters i.e. hardness, friability, wetting time, weight variation, disintegration time and in-vitro dissolution.

The effect of concentration and type of superdisintigrants on in- vitro drug release used in formulations of fast dissolving tablets was also investigated. the higher in-vitro drug release results of FDT's showed that batch formulated containing PEG-6000 (1:1 ratio) formulated by solid dispersion technique and lower % of drug release in found to be in wet granulation technique.

REFERENCES

Chapter 7

REFERENCES

1) Anas, B., Diana, Z., 2012.Formulation and Evaluation of Aceclofenac Fast Dissolving Tablets using Foam Granulation Technique. Indo Global J. Pharm. Sci. 2(4), 342-347.
2) Ankur, S., Abhishek, J., 2011.Formulation and evaluation of aceclofenac fast dissolving tablets. Int. J. of Pharm. Life Sci. 2 (4), 681-686.
3) BachhavDevidas, G. PhatangareKundan. E.,2012. Study the effect of various carriers on the solubility of Aceclofnac. Pharmacophore.3 (3), 186-188.
4) Bhowmik, D., Chiranjib, B., Chandira, P. K., 2009. Fast Dissolving Tablet: An Overview. J. Chem. Pharm. Res. 1(1), 163-177.
5) Bi, Y., Sunada, H., Yonezawa, Y., Danjo, K., Lido, K., 1996. Preparation and evaluation of compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull. 44(11), 2121-2127.
6) Bradoo, R.,. 2001. Fast Dissolving Drug Delivery Systems. J. Am. Med. Assoc. 4 (10), 27-31. Chang, R., Guo, X., Burnside, B. A., Couch, R., 2000. Fast-dissolving tablets, Pharm. Tech. 24(6), 52-58.
7) Cousin, G., Etienne, B., Edouard, G., 1995. Rapidly Disintegrable Multiparticular Tablets. US patent 5,464,632.
8) Dharani, S., Ramesh, K. K., Elango, K., Hemalatha, S., Stephen, P., 2013. Formulation and Evaluation of AceclofenacOrodispersibleTablets.Int.J. Pharm. Sci. Res. 4(1).32-40.
9) Dong, Y., Kulkarni, R., Behme, R. J., Kotiyan, P. N., 2007.Effect of the melt granulation technique on the dissolution characteristics of griseofulvin. Int. J. Pharm. 329 (1-2), 72-80. Pharmaeuropa., 1998. European Directorate for quality of Medicines 10(4), 547.
10) Gandhi, K. R., Gandhi, B. R., Behera, A. L., Godhave, M. V., Gaikwad, D. D., Formulation and evaluation of Aceclofenac Mouth Dissolving Tablets by using Polyplasdone XI 10 as Super Disintegrant and Sublimation technique. Int. J. Pharm. Chem. Sci., 13-19.
11) Garg, S., Goldman, D., Krumme, M., Rohan, L. C., Smoot, S., Friend, D. R., 2010. Advances in development, scale-up and manufacturing of microbicide gels, films, and tablets.Antiviral Res. 88, S19-S29.

12) Gowthamarajan, K. Sachin Kumar, S., 2010. Dissolution Enhancement of Poorly Soluble
13) Aceclofenac by Solid Dispersion Technique and Its Comparison with Marketed Formulations.Int.J. PharmTech Res. 2(4), 2347-2356.
14) Heinemann, H., Rothe, W., 1975. Preparation of Porous Tablets. US patent No.US3885026. http://www.fda.gov/cder/dsm/DRG/drg00201.
15) Kalpesh, G., Lalit, K. T., Kori, M. L., Sharma, C. S., Nema, R. K., 2011. Formulation and Characterization of Fast Disintegrating tablets of Aceclofenac by using Sublimation method.Int. J. Pharm. Sci. Drug Res. 3(1), 19-22.
16) Kiroj, R. Rajiv, B., 2014. Dissolution enhancement of aceclofenac tablet by solid dispersion technique.Int J Pharm Pharm Sci. 5(4), 127-138.
17) Knitsch K.W., Hagen, A., Munz, E., Determann, H., 1979.Production of Porous Tablets. US patent No., US 4134943.
18) Koizumi, I. K., 1997. New method of preparing highly porous rapidly saliva soluble tablets by Sublimation technique. Int. J. Pharm.152, 127-131.
19) Kuchekar, B. S., Atul, B., Mahajan, C. H. S., 2003. Mouth dissolving Tablets: A novel drug delivery system. Pharm.Times 35, 7-9.
20) Lindgren, S., Janzon, L., 1991.Prevalence of swallowing complaints and clinical findings among 50-79- year-old men and women in an urban population. Dysphagia 6, 187–192.
21) Machalson, J., 1983. Rapidly Disintegrating Tablets Composition and Method. US patent 4,414,193.
22) Mahajan, H. S., Kuchkar, B. S., Badhan, B. S., 2004. Mouth dissolving tablets of sumatriptan succinate. Indian J. Pharm. Sci.3, 238 – 240.
23) MallikarjunaSetty, C. Muthadi, R., 2011. Effect of tablet processing and formulation factors on disintegration and dissolution of aceclofenac tablets.Int.J. Pharm.sci.nano tech. 3(4), 1240-1252.
24) Manivannam, R., Balasubramaniam, A., Senthilkumar, R., 2009. Design and evaluation of the fast dissolving tablets of Terbutaline Sulphate. Asian J. Pharm. 6, 215-217.
25) Milind, P. W., Chetan, P. Y., 2010. Formulation and Evaluation of Fast Dispersible tablets of Aceclofenac using different superdisintegrant. Int. J. Pharm. Pharm.Sci. 2(1).58-65.
26) Nabarawi, M.A. EL. Miligi, M.F. EL., 2012. Optimization of class II BCS drug using solid dispersion technique.*Int J Pharm PharmSci.4(5), 554-571.*
27) Prajapati, B. G., Ratnaker N., 2009. A review on recent patents on fast dissolving drug

delivery system. Int. J. Pharm. Tech. Res. 1(3), 790-798.

28) Prema, M. T., Ajmi, P. A., 2013. Forulation and Evaluation of Melt in Mouth Tablets of Aceclofenac.Int.J. Res. Pharm. Nano Sci. 2(1), 130- 134.

29) Praveen, B. Muralidharrao, R., 2011. Formulation and characterization of Aceclofenac loaded bovine serum albumin microspheres. Int.J. Pharm.Bio.Sci. 2(2), 37-53.

30) Radke, R. S., Jadhav, J.K., Chajeed, M. R., 2009. Formulation and evaluation of orodispersible tablets of Baclofen. Int. J. Chem Tech Res. 6, 517-521.

31) Ratnaparkhi, M., Dhomse, R., 2012. Formulation and Evaluation of Fast Dissolving Tablets prepared by Solid Dispersion Method. Int. J. Pharm. Chem. Biol. Sci. 2(3), 325-334.

32) Raymond, C. R., Paul, J. S., Marian, E. Quinn., Hand book of pharmaceutical Excipients, 6thed. Pharmaceutical press.

33) Reddy, L. H., Ghosh, B., Rajneesh., 2002. Fast dissolving drug delivery systems: A review of the literature. Indian J. Pharm. Sci. 64(4), 331-336.

34) Roser, B. J., Blair, J., 1998. Rapidly Soluble Oral Dosage Forms, Method of Making same and Compositions Thereof. US patent No., US 5762961.

35) Saini, S., Nanda, A., Hooda, M., Komal., 2011. Fast dissolving films (fdf): innovative drug delivery system. Pharmacol.online 2, 919-928.

36) Sajal, K. J., Vijayalaxmi.,Roopa, K., Divakar, G., 2008. Formulation and evaluation of mouth melts tablets of Haloperidol. Asian J. Pharm. 9, 255-260.

37) Seager, H., 1998. Drug delivery products and the Zydis Fast dissolving dosage form. J Pharm. Pharmacol. 50, 375-382.

38) Selvaraj, B., Malarvizhi.,Shanmugapandiyan, P., Nappina, G. M., 2011. Formulation and Evaluation of Fast Dispersible Tablets of Aceclofenac.Int, J. Formulation Res. 2(3), 210-217.

39) Shaikh, S., Sayyed, N., Gomase, P., Shaik, A., Quazi, M., Formulation and Evaluation of Aceclofenac of fast Dissolving Tablets.Int. J. Pharm. 2(1).71-78.

40) Shailesh, S., Gupta, G. D., 2009.Formulation and characterization of fast dissolving tablets of Promethazine theoclate. Asian J. Pharm 1, 70-72.

41) Shireesh, K. R., Vishnu, P. 2011. Influence of various super disintegrating agents on the aceclofenac fast dissolving tablets. Res. J. Pharm. Biol. Chem. Sci. 2(2), 99-105.

42) Shirwaikar, A. A., Ramesh, R., 2004. Fast disintegrating tablets of Atenolol by dry granulation method, Indian J. Pharm. Sci. 6, 422-426.

43) Shobhit, K. A., Satish, K. G., 2013. In Vitro Determination of Aceclofenac Mouth

Dissolving Tablets.Polim. Med. 43 (4), 227–229.

44) Sudhir, B., Vinay, J., 2010. Formulation and evaluation of fast dissolving tablet of aceclofenac, Int. J. Drug Deliv. 2, 93-97.

45) Sumanta, M., Ashok, K. P., Suresh, V., Kulkarni., Someshwara, R. B., Amit, S. Y., 2010. Design and Evaluation of the Fast Dissolving Tablets of Aceclofenac by sublimation Technique, Res. J. Pharm. Dosage Forms Tech. 2(3), 233-236.

46) Upendra, K.,Raghavendrarao, N. G., 2011. Design and Developement of Aceclofenac fast Dissolving tablets by Amorphous Solid Dispersion technique using Modified AegleMarmelos gum. Int. J. Pharm. Res. Develop. 3(6), 201-210.

47) Virely, P., Yarhood, R., 1989. zydis – a novel fast dissolving dosage form. Manufact.Chemist.2, 37 -38.

48) Watanabe, Y., Koizumi, K., Zama, Y., Kiriyama, M., Mastumoto, Y., Mastumoto, M., 1995.New compressed tablet rapidly disintegrating in saliva in the mouth using crystalline cellulose and a disintegrant. Biol. Pharm. Bull 18(9), 1308-1310.

49) Watanabe, Y., Ishikawa, T., Yotoguchi, N., Mastumoto, M., 2010. Preparation and evaluation of rapidly disintegrating in salive containing bitter taste masked granules by direct-compression method. Chem. Pharm. Bull. 47(10), 1451.

50) Wayne, C., Dipan, R., Ann, D., 2006. Selecting superdisintegrants for orally Disintegrating Tablet Formulations.Pharm.Tech. 30, 28-33