FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I -- PHARMACEUTICS

Submitted by

Name: MANIVANNAN.D

REG.No.261610254

Under the Guidance of

Dr.V.KAMALAKKANNAN, M.Pharm, Ph.D,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTRAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU

MAY – 2018

FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN

A Dissertation submitted to

THE TAMIL NADU DR. M.G.R. MEDICAL UNIVERSITY,

CHENNAI - 600 032

In partial fulfilment of the award of the degree of

MASTER OF PHARMACY

IN

Branch-I – PHARMACEUTICS

Submitted by

Name: MANIVANNAN.D

REG.No.261610254

Under the Guidance of

Dr.V.KAMALAKKANNAN, M.Pharm, Ph.D,

DEPARTMENT OF PHARMACEUTICS

J.K.K. NATTRAJA COLLEGE OF PHARMACY

KUMARAPALAYAM – 638183

TAMILNADU

MAY – 2018

EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN''** submitted by student bearing **Reg.No-261610254** to "The Tamil Nadu Dr.M.G.R. Medical University, Chennai, for the partial fulfilment of the Degree of **MASTER OF PHARMACY** was evaluated by us during the examination held on……

Internal Examiner **External Examiner**

CERTIFICATE

This is to certify that the work embodied in this dissertation **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN''** Submitted to "The TamilNadu Dr.M.G.R.Medical University, Chennai, was carried out by **Reg.No-261610254** for the partial fulfilment of the degree of master of pharmacy in under direct supervision of **Dr.V.KAMALAKKANNAN. M.pharm,Ph.D.** Associate professor, Department of Pharmaceutics, J.K.K.Nattraja College of pharmacy, Komarapalayam, during the academic year 2017-2018.

Place : Kumarapalayam.
Date :

Dr. R.Sambathkumar, M.Pharm, Ph.D.,
Principal,
J.K.K. Nattraja College of Pharmacy,
Kumarapalayam- 638 183,
Tamilnadu.

CERTIFICATE

This is to certify that the work embodied in this dissertation entitled **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN''** Submitted to "The TamilNadu Dr.M.G.R.Medical University-Chennai, in partial fulfilment and requirement for the award of degree of **MASRT OF PHARMACY** is a bonafide work carried out by **Reg.No.-261610254** during the academic year 2017-2018, under the guidance and direct supervision in the department of pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

Dr.V.Kamalakkannan, M.pharm.,Ph.D.
Associate professor,
Department o Pharmaceutics,
J.K.K.Nattraja College of pharmacy,
Kumarapalayam-638183
Tamilnadu

Dr. R. Sambathkumar, M.Pharm, Ph.D.
Principal,
J.K.K.Nattraja College of Pharmacy
Kumarapalayam-638 183
Tamilnadu

Place : Kumarapalayam.

Date :

CERTIFICATE

This is to certify that the entitled **"FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN''** is a bonafide work done by **Reg.No-261610254** J.K.K.Nattraja College of Pharmacy part and fulfilment university rules and regulation for award of Master of pharmacy under my guidance and supervision during the academic year 2017-2018.

Dr.V.Kamalakkannan, M.pharm,Ph.D.
Associate professor,
Department of Pharmaceutics,
J.K.K.Nattraja College of pharmacy,
Kumarapalayam-638183
Tamilnadu

Dr.R.Sambathkumar, M.Pharm, Ph.D.
Principal,
J.K.K.Nattraja College of Pharmacy,
Kumarapalayam-638 183
Tamilnadu

Dr.S.Bhama, M.pharm, Ph.D,
Head of the Department,
J.K.K.Nattraja College of pharmacy,
Kumarapalayam-638183
Tamilnadu

DECLARATION

The work presented in this dissertation entitled**, "FORMULATION DESIGN, DEVELOPMENT AND *INVITRO* EVALUATION OF MOUTH DISSOLVING TABLETS OF ZOLMITRIPTAN''** was carried out by me, under the direct supervision of **Dr.V.KAMALAKKANNAN, M.Pharm.,Ph.D**. Associate professor , Department of Pharmaceutics, J.K.K.Nattraja College of pharmacy, Kumarapalayam.

I further declare that the work is original and has not been submitted in part or full for the award of any other degree or diploma in any other university.

Place: Kumarapalayam

Date: **Reg.No. 261610254**

ACKNOWLEDGEMENT

I am proud to dedicate my deep sense of gratitude to the founder, (Late) Thiru J.K.K. Nattraja Chettiar, providing us the historical institution to study.

My sincere thanks and respectful regards to our reverent Chairperson. Smt N.Sendamaraai. B.Com. Managing Director Mr.S.Omm sharravana, B.Com.,LLB., J.K.K.Nattraja Educational Institutions, Komarapalayam for their blessings, encouragement and support at all times.

It is most pleasant duty to thank our beloved Principal Dr. R.SAMBATHKUMAR, M.Pharm., Ph.D., J.K.K.Nattraja College of Pharmacy, Komarapalayam for ensuring all the facilities were made available to me for the smooth running of this project.

I express my whole hearted thanks to my guide Dr.V.KAMALAKKANNAN M.Pharm.,Ph.D Associate Professor , Department of Pharmaceutics, for suggesting solution to problems faced by me and providing indispensable guidance, tremendous encouragement at each and every step of this dissertation work. Without his critical advice and deep-rooted knowledge, this work would not have been a reality.

My sincere thanks to Dr.R.Shanmugasundaram, M.Pharm, Ph.D., Vice Principal and Professor and Head of the Department, Department of Pharmacology, Dr.Kalaiarasi. M.Pharm, Ph.D Assistant Professor, Department of Pharmacology, for their valuable suggestions during my project work.

It is my privilege to express deepest sense of gratitude toward Dr.M. Senthilraja, M.Pharm., Ph.D., Professor and Head, Department of Pharmacognosy and Mrs.P.MeenaPrabha, M.Pharm. Assistant Professor, Department of Pharmacognosy for their valuable suggestions during my project work.

My sincere thanks to Dr.M.Vijayabaskaran, M.Pharm., Ph.D., Assistant Professor and head Department of Pharmaceutical chemistry Mrs.S.Gomathi, M.Pharm., Lecturer, Department of Pharmaceutical chemistry and for their valuable suggestions and inspiration.

My sincere thanks to Dr.N.Venkateswaramurthy, M.Pharm.,Ph.D Professor and Head, Department of Pharmacy Practice. Mrs.K.Krishnaveni, M.Pharm. Assistant Professor, Department of Pharmacy Practice, for their help during my project.

My sincere thanks to Dr.V.Sekar, M.Pharm., Ph.D., Professor and Head of The Department of analysis, and Dr.I.Caroline nimila,M.Pharm.,Ph.D., Assistant Professor, Department of Pharmaceutical Analysis for their valuable suggestions.

My sincere thanks to Dr.S.Bhama, M.Pharm.,Ph.D Associate Professor, Mr.R. Kanagasabai, B. Pharm. M.Tech., Assistant Professor, Mr.K.Jaganathan, M.Pharm., Assistant professor, Department of Pharmaceutics, Mr.C.Kannan M.Pharm., Assistant Professor, Department of Pharmaceutics for their valuable help during my project.

I greatly acknowledge the help rendered by Mrs.K.Rani, Office Superintendent, Mrs. V.Gandhimathi, M.A., M.L.I.S., Librarian, and Mrs.S.Jayakala, B.A., B.L.I.S., Asst. Librarian for their co-operation.

My special thanks to all the Technical and Non-Technical Staff Members of the institute for their precious assistance and help.

Last, but nevertheless, I am thankful to my lovable parents and all my friends for their co-operation, encouragement and help extended to me throughout my project work.

Reg.No.261610254

LIST OF FIGURES

IST OF TABLES

LIST OF ABBREVATIONS

API	:	Active Pharmaceutical Ingredient
BP	:	British Pharmacopeia
DCB	:	Double cone blender
DSC	:	Differential scanning calorimetry
DT	:	Disintegration time
FT-IR	:	Fourier Transform Infrared
FZ1 TO FZ9	:	Formulation of Zolmitriptan 1 to 9.
HLB	:	Hydrophilic- Lypohilic Balance
HME	:	Hot Melt EXtrusion
ICH	:	Interanational Conference on Harmonisation
JP	:	Japan Pharmacopeia
KT	:	Ketorolac Tromethamine
LHPC	:	Low substituted hydroxy propyl cellulose
LOD	:	Loss on drying
MCC	:	Microcrystalline cellulose
MOA	:	Monoamine Oxidase
NMT	:	Not more than
NSAID	:	Non Steroidal anti-inflammatory Drugs
ODDF	:	Orally disintegrating dosage form
ODT	:	Orally disintegrating tablets
PEG	:	Poly Ethylene Glycol
PhEur	:	European Pharmacopeia
PSA	:	Pressure sensitive adhesive

PVD	:	Peripheral vascular disease
PVDF	:	Poly vinylidene difluoride
RH	:	Relative Humidity
RPM	:	Revolutions per minute
RSD	:	Relative standard deviation
SEM	:	Scanning Electron Microscopy
TIA	:	Transient ischemic attack
TMISG	:	Thermo reversible in-situ mucoadhesive intranasal gel
USFDA	:	United States food and drug administration
USP	:	United States Pharmacopeia
WRS	:	World wide reference system
ZT	:	Zolmitriptan

CONTENTS

1. INTRODUCTION

1.1 Oral Drug delivery System

Sastry SV et al, 2000 A drug may be defined as an agent, intended for use in the diagnosis, mitigation, treatment cure or prevention of disease in man or in animals. Drugs are very rarely administered in the original pure state. They are converted into suitable formulation which is converted into suitable formulation which is called dosage forms. Every dosage form is a combination of the drug and other non drug components. The non drug components are known as additives are used to give a particular shape to the formulation to increase its stability and also to increase its palatability as well as to give more elegance to preparation.

1.2 Various pharmaceutical dosage forms

Dosage forms can be classified based on different route of administrations or based on the physical state

Route of administration	**Dosage forms**
Oral	Powders, Tablets, Capsules, Solutions,
Parentral	Solutions, Suspensions, Emulsions
Transdermal	Ointments, Creams, Powder, Pastes,
Rectal	Suppositories, Tablets, Ointments,
Urethral	Suppositories
Sublingual	Lozenges, Tablets
Intranasal	Solutions, Sprays, Inhalations.
Conjuctival	Ointments
Intra-occular	Solutions
Intra-respiratory	Aerosols

Table 1. Various route of administrations and respective dosage forms

Tablets

Tablets are solid dosage form each containing a unit dose of one or more medicaments. They are intended for oral administration. A tablet consists of active medicament along with excipients which are in powder form are compressed or pressed into solid dosage form.

1.3 Various types of tablets

1.3.1 Oral Tablets for Ingestion:

1. Compressed tablets
2. Multiple compressed tablets
3. Layered tablets
4. Compression-coated tablets
5. Repeat-action tablets
6. Delayed-action and enteric-coated tablets
7. Sugar and chocolate-coated tablets
8. Film coated tablets
9. Chewable tablets

1.3.2 Tablets Used in the Oral Cavity:

1. Buccal tablets
2. Sublingual tablets
3. Troches and lozenges
4. Dental cones

1.3.3 Tablets Administered by Other Routes:

1. Implantation tablets
2. Vaginal tablets

1.3.4 Tablets Used to Prepare Solutions:

1. Effervescent tablets
2. Dispensing tablets
3. Hypodermic tablets
4. Tablet triturates

1.4 Orally Disintegrating Tablets

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (To accommodate various types of drug candidates) and most

importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. A vast variety of pharmaceutical research is directed at developing new dosage forms for oral administration. Most of these efforts have focused on either formulating novel drug delivery systems or increasing the patient compliance. Among the dosage forms developed for facilitating ease of medication, the orally disintegrating systems have been the favourite of product development scientists. In similar fashion the oral cavity is highly acceptable by patients, the mucosa is relatively permeable with rich blood supply and virtual lack of langerhans cells makes oral mucosa tolerant to potential allergens**.**

1.5 Overview of Oral Mucosa

The oral cavity comprises Journal the lips, cheek, tongue, hard palate, soft palate and floor of the mouth (Fig. 1). The lining of the oral cavity is referred to as the oral mucosa, and includes the buccal, sublingual, gingival, palatal and labial mucosa. The buccal, sublingual and mucosal tissues at the ventral surface of the tongue account for about 60% of the oral mucosal surface area. The top quarter to one-third of the oral mucosa is made up of closely compacted epithelial cells.

The primary function of the oral epithelium is to protect the underlying tissue against potential harmful agents in the oral environment and from fluid loss. Beneath the epithelium are the basement membranes, lamina propia and submucosa. The oral mucosa also contains many sensory receptors including the taste receptors of the tongue. Three types of oral mucosa can be found in the oral cavity; the lining mucosa is found in the outer oral vestibule (the buccal mucosa) and the sublingual region (floor of the mouth) (Fig. 1). The specialized mucosa is found on the dorsal surface of tongue, while the masticatory mucosa is found on the hard palate (the upper surface

of the mouth) and the gingival (gums).

The lining mucosa comprises approximately 60%, the masticatory mucosa approximately 25%, and the specialized mucosa approximately 15% of the total surface area of the oral mucosal lining in an adult human. The masticatory mucosa is located in the regions particularly susceptible to the stress and strains resulting from masticatory activity. The superficial cells of the masticatory mucosa are keratinized, and a thick lamina propia tightly binds the mucosa to the underlying periosteum. Lining mucosa on the other hand is not nearly as subject to masticatory loads and consequently, has a non-keratinized epithelium, which sits on a thin and elastic lamina propia and a sub mucosa.(Fig. 2) The mucosa of the dorsum of the tongue is a specialized gustatory mucosa, which has well papillated surfaces which are both keratinized and some non-keratinized .Depicted the advantages and disadvantages associated with utilizing the oral mucosa as a drug delivery site.

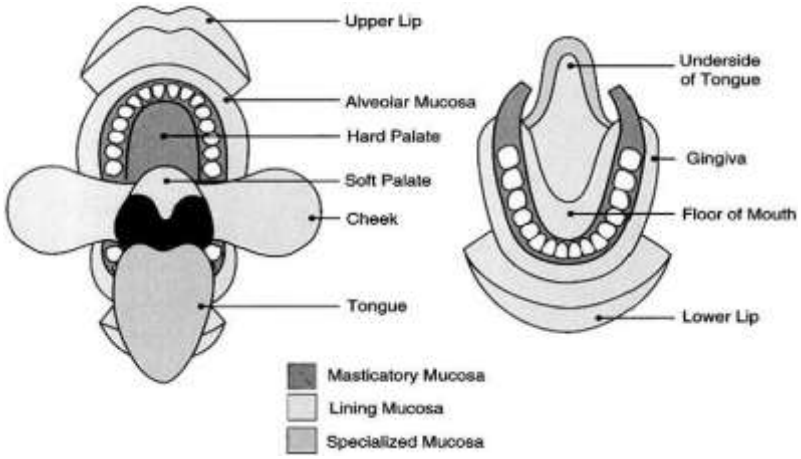


Figure 1: Schematic representation of the different linings of mucosa in mouth.

1.6 ORALLY DISINTEGRATING DOSAGE FORMS

The concept of orally disintegrating dosage forms has emerged from the desire to provide patients with more conventional means of taking their medication. Interestingly, the demand for ODDFs has enormously increased during the last decade, particularly for geriatric and paediatric patients who experience difficulty in

swallowing conventional tablets and capsules. Hence, they do not comply with prescription, which results in high incidence of ineffective therapy

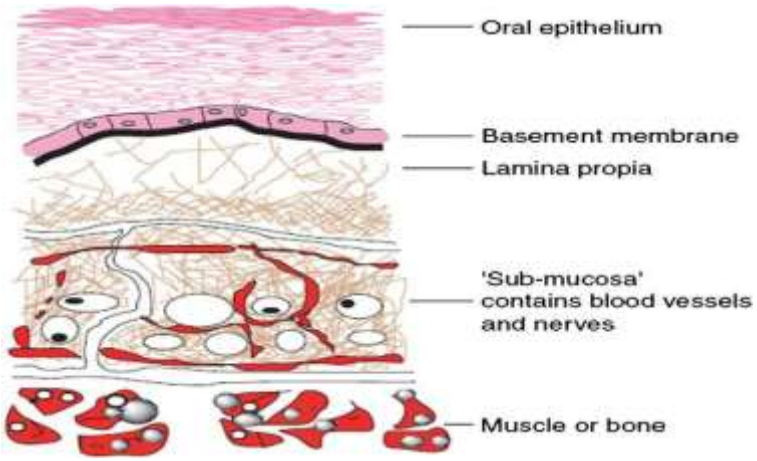


Figure 2: Schematic diagram of buccal mucosa

Advantages of ODTs (Priyanka Nagar et al, 2011)

1. ODT can be administer to the patients who cannot swallow tablets/cap, such as the elderly, stroke victims, bedridden patients, patients with esophageal problems & patients who refuse to swallow such as paediatric, geriatric & psychiatric patients and thus improves patient compliance.
2. It contain the certain studies which concluded increased bioavailability and proved rapid absorption of drugs through pregastric absorption of drugs from mouth, pharynx & oesophagus as saliva passes down.
3. ODT is most convenient for disabled, bedridden patients, travellers and busy people, who do not always have access to water.
4. Good mouth feel property of ODT helps to change the perception of medication. As bitter pill particularly in paediatric patients.
5. The risk of chocking or suffocation during oral administration of conventional formulations due to physical obstruction is avoided, thus providing improved safety.

6. ODT opened new business opportunity like product differentiation, product promotion, patent extension and life cycle management.
7. Suitable during travelling where water may not be available.
8. No specific packaging required can be packaged in push through blisters.
9. Conventional manufacturing equipment.
10. Cost effective.
11. Good chemical stability as conventional oral solid dosage form.
12. New business opportunity like product differentiation, product promotion, patent extension and life style management.
13. Allow high drug loading.
14. Provides rapid drug delivery from dosage forms.
15. Provide advantage of liquid medication in form of solid preparation.
16. Rapid drug therapy intervention.
17. No chewing needed.
19. Adaptable and amenable to existing processing and packaging machinery.
20. Rapid onset of action.

Disadvantages of ODTs

1. ODT is hygroscopic in nature so must be keep in dry place.
2. Some time it possesses mouth feeling.
3. It is also shows the fragile, effervescence granules property.
4. ODT requires special packaging for properly stabilization & safety of stable product.

Formulation aspect of ODT's (JaysukhHirani J et al, 2009)

Important ingredients that are used in the formulation of ODTs should allow quick release of the drug, resulting in faster dissolution. This includes both the

pharmacologically active ingredients (drug) and the excipients (additives).

A. Selection of drug candidate: Several factors may be considered while selecting an appropriate drug candidate for development of orally disintegrating tablets. The ultimate characteristics of a drug for dissolution in mouth and pregastric absorption from fast dissolving tablets include

1. Free from bitter taste
2. Dose lower than 20mg
3. Small to moderate molecular weight
4. Good solubility in water and saliva
5. Partially unionized at oral cavity pH
6. Ability to diffuse and partition in to the epithelium of upper GIT(log >1,or preferably>2)
7. Ability to permeate oral mucosal tissue.

There are no particular limitations as long as it is a substance which is used as a pharmaceutical active ingredient. Researchers have formulated ODT for various categories of drugs used for therapy in which rapid peak plasma concentration is required to achieve the desired pharmacological response. These include neuroleptics, cardiovascular agents, analgesics, anti-allergic, anti-epileptics, anxiolytics, sedatives, hypnotics, diuretics, anti-parkinsonism agents, anti-bacterial agents and drugs used for erectile dysfunction

In contrast, the following characteristics may render unsuitable for delivery as an orally disintegrating tablet:-

1. Short half-life and frequent dosing.
2. Very bitter or otherwise unacceptable taste because taste masking cannot be successfully achieved.

3. Require controlled or sustained release.
4. Combination with anticholinergics.

Techniques in preparation of orally disintegrating drug delivery system (RakeshPahwa et al., 2010)

The various technologies are developed for the preparation ofOrally DisintegratingDrugDelivery Systemthat are:

- Freeze drying
- Spray drying
- Molding
- Phase transition process
- Melt granulation
- Sublimation
- Mass Extrusion
- Cotton Candy Process
- Directcompression

Freeze drying

Lyophilization means drying at low temperature under condition that involves the removal of water by sublimation. Drugging water soluble matrix which is then freeze dried to give highly porous structure. The tablets prepared by Lyophilization disintegrate rapidly in less than 5 seconds due to quick penetrate on of saliva in pores when placed in the oral cavity. Lyophilization is useful for heat sensitive drugs i.e., thermo-labile substances.

Ahmed et al., 2006 prepared lyophilized tablet using freeze drying technique. The lyophilized tablet prepared by dispersing drug Ketoprofen in aqueous solution of

highly water soluble carrier consisting of gelatin, glycine and sorbitol in blister packs and then subjected to Lyophilization in blister packs. It was found that the increase in solubility of ketoprofen from lyophilized tablet matrix was nearly three times greater than solubility of the plain drug which was duet super saturation generated by amorphous form of drug.

Spray drying

Spray drying can produce highly porous and fine powders that dissolve rapidly. This technique is based on a particulate support matrix, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets. The formulations are incorporated by hydrolyzed and non hydrolyzed gelatine as supporting agents, mannitol as bulking agent, sodium starch glycolate or cross carmellose sodium as disintegrating and an acidic material (e.g. citric acid) and / or alkali material (e.g. sodium bicarbonate) to enhance disintegration and dissolution. Tablet compressed from the spray dried powder disintegrated within 20 seconds when immersed in an aqueous medium.

Allen et al., 2011 used as pray drying technique to prepare fast dissolving tablets. Thetabletsmadefromthis technology are claimed to disintegrate within 20 seconds.

Direct compression

This is most popular technique because of its easy implementation and cost-effectiveness. The basic principle involves addition of disintegrants and/or water soluble excipients and/or effervescent agents. Super disintegrates in optimum concentration (about2-5%) are mostly used so as to achieve rapid disintegration along with the good mouth feel. **(RakeshPahwa et al, 2011)**

Bi et al. 1996 examined the disintegrant property of mixture of microcrystalline cellulose and low substituted hydroxypropyl cellulose (MCC: L-HPC) for orally disintegrating tablet and found that shortest disintegration time was observed in the range of ratio of MCC: L-HPC (8:2 to 9:1).

Gillis et al. prepared a fast-dissolving tablet of Galanth amine hydrobromide which comprise of diluent which is a spray dried mixture of lactose monohydrate and micro crystalline cellulose in the ratio of 75:25,a cross linked polymeric disintegrant such as cros povidone and a direct compression process was used for preparation of fast dissolving tablets.

Gattanietal. Prepared Ondansetron mouth dissolving tablet using treatedagar as a super disintegrating agent and found that tablets with treatedagar powder had disintegration rate comparable to other super disintegrants.

Zolmitriptan is an anti-migraine drug. It is widely used for the acute treatment of migraines with or without aura.The bioavailability of Zolmitriptan is about 40% via oral dosage forms & its problem arises from its low water solubility and dissolution rate. Oral Zolmitriptan administration is characterized by slow absorption. Zolmitriptan is available in the market as a tablet, conventional dosage form. But this

formulation suffers from the bioavailability problem. Among numerous ways of enhancing drug dissolution, orally disintegrating tablets are one of the promising techniques to overcome the solubility problem of zolmitriptan. The present study is focused on the development of zolmitriptan ODT tablets for improved bioavailability.

Patient counseling points for ODT

Reddy L. H et al 2002 as pharmacist are ideal person to become familiar with recent technology advancement in novel dosage form, thus have opportunity to counsel the patient for effective treatment. Educating the patients about ODT can avoid any confusion and misunderstanding of this dosage form.

Counselling points to the patients include:

· Patients may mistake ODT for effervescent tablets, pharmacist need to be clearly told about the different between them. The cima technologies orosolv and durasolv use slight effervescence, patients may experience a pleasant tingling effect on the tongue.

· ODT need to be handled carefully because some of ODT developed may not have sufficient mechanical strength.

· Patients with dryness of mouth or with siogrens syndrome or who taking anticholengic drugs may not be suitable population for administering ODT.Although no water is needed to allow the drug to dispense quickly and efficiently but most technologies of ODT utilizes the body own salivation but decreased volume of saliva may slow down dissolution/ disintegration/ bioavailability of the product.

· Although chewable tablets have been in the market for long time, patients need to be counseled properly the difference between chewable and ODT tablets.ODT can be used easily in children who have lost their primary teeth but do not have full use of their permanent teeth and also for geriatric patients who have lost their teeth permanently.

· With the pharmacist counseling, intervention and assistance all of these patients who taking ODT could be more properly treated with greater convenience.

Industrial Applications

(Kumar et al., 2012, Beri and Sacher, 2013) Industrial applications include the following:

- To develop an orally disintegrating dosage forms and to work with existing disintegrants
- To further improvise upon the existing technology of ODTs
- To optimize the blend of disintegrants or excipients to achieve ODTs
- To select and develop proper packaging material and system for enhanced stability of the product and also develop a cost-effective product
- To arrive at various taste-masking agents and prepare palatable dosage forms thereby increasing patient compliance
- To develop disintegrants from different polymers which are used as coating materials by certain modifications and use them for formulating ODTs

Future Prospects

These dosage forms may be suitable for the oral delivery of drugs such as protein and peptide-based therapeutics that have limited bioavailability when administered by conventional tablets. These products usually degrade rapidly in the stomach. Should next generation drugs be predominantly protein or peptide based, tablets may no longer be the dominant format for dosing such moieties. Injections generally are not favoured for use by patients unless facilitated by sophisticated auto-injectors. Inhalation is one good alternative system to deliver these drugs, but the increased research into biopharmaceuticals so far has generated predominantly

chemical entities with low molecular weights.

Challenges and Limitations for ODTs

(**Velmurugan S, Vinushitha S et al 2010)** Drugs with relatively larger doses are difficult to formulate into ODTs e.g. antibiotics like ciprofloxacin with adult dose tablet containing about 500 mg of the drug. The application for technologies used for ODTs is limited by the amount of drug into each unit dose. The drug dose must be lower than 400mg for insoluble drugs and 60mg for soluble drugs. However Flashdose technology can accommodate larger drug doses and offers improved mechanical strength. Orasolv® technology can accommodate a wide range of active pharmaceutical ingredient from 1 mg to 500 mg

• Mechanical strength - ODTs are made of porous or soft molded matrices in order to allow its disintegration in mouth. This makes tablet friable and handling becomes difficult. Orodispersible tablets with highly porous structure and good mechanical strength have been developed by sublimation method. Also Durasolv® has much higher mechanical strength than Orasolv due to the use of higher compaction pressures during compression.

• Palatability - ODTs are intended to be dissolved in mouth. Most of the drugs have bitter taste. Bitter taste can be masked with enough sweetener and flavors. Specifically, methods of taste masking include lipophilic vehicles, coating with polymers, carbohydrates, lipids or proteins complexation with cyclodextrins or ion-exchange resins, formation of salts, use of salting out layers and solid dispersions [55]. OraQuick utilizes its own patented taste masking technology i.e. MicroMask®. In MicroMask® technology, taste-masking process is done by incorporating drug into matrix microsphere.

• Drugs in form of ODTs are hygroscopic in nature and hence need to be protected

from humidity. To overcome humidity problem special working facilities can be designed by simple methods and special air-conditioning systems can be set up. Size of tablet 7 and 8 mm are easy to swallow while tablets of size 8mm are easy to handle. Hence, tablet sizes which are both easy to handle and swallow are difficult to achieve. For the patient compliance, to make the swallowing easier, round shape punches having optimum dimensions can be used.

• Drug candidates should be stable both in water and in saliva, should not ionize at oral cavity pH and should be able to permeate oral mucosal tissue to diffuse and partition in upper GI epithelium (logP > 1, or preferably > 2, not have short half-life). To optimize solubility problem of the active pharmaceutical ingredient some solid buffers and surfactants can also be chosen.

Conclusion

(Aurora J, Pathak V et al 2005) Orally disintegrating tablets have better patient acceptance and compliance and may offer improved biopharmaceutical properties, improved efficacy, and better safety compared with conventional oral dosage forms. Prescription ODT products initially were developed to overcome the difficulty in swallowing conventional tablets among pediatric, geriatric, and psychiatric patients with dysphagia. Today, ODTs are more widely available as OTC products for the treatment of allergies, cold, and flu symptoms. The target population has expanded to those who want convenient dosing anywhere, anytime, without water. The potential for such dosage forms is promising because of the availability of new technologies combined with strong market acceptance and patient demand. By paying close attention to advances in technologies, With continued development of new pharmaceutical excipients, one can expect the emergence of more novel technologies for ODTs in the days to come.

2. LITERATURE REVIEW

2.1 Orally Disintegrating Tablets

Priyanka Nagar et al., 2011 oral delivery which is currently the gold standard in the pharmaceutical industry, where it is regarded as the safest, most convenient and most economical method of drug delivery having the highest patient compliance. Formulation of a convenient dosage form for oral administration, by considering swallowing difficulty especially in case of geriatric and paediatric patient leads to poor patient compliance. To troubleshoot such problems a new dosage form known as orally disintegrating tablet (ODT), has been developed which rapidly disintegrate & dissolve in saliva and then easily swallowed without need of water which is a major benefit over conventional dosage form. In addition, patients suffering from dysphasia, motion sickness, repeated emesis and mental disorders prefer such preparation because they cannot swallow large quantity of water. Further, drugs exhibiting satisfactory absorption from the oral mucosa or intended for immediate pharmacological action can be advantageously formulated in such type of dosage form. The popularity and usefulness of the formulation resulted in development of several ODT technologies for preparation. The current article is focused on ideal characteristics, advantages and disadvantages, formulation aspects, formulation technologies, evaluation of products and future potential. Various marketed preparations along with numerous scientific advancements made so far in this avenue have also been discussed.

Manoj Ashok Wagh et al., 2010 conventional preparation methods are spray drying, freeze drying, direct compression, Moulding, and sublimation while new technologies have been developed for the production of oro-dispersible tablets.

2.2 Various Manufacturing technologies for ODT

2.2.1 Spray Drying

Allen L Vetal., 2001 used a spray drying technique to prepare fast dissolving tablets. The tablets made from this technology are claimed to disintegrate within 20 seconds, which is prepared by spray drying an aqueous composition containing support matrix and other components to form a highly porous and fine powder. This then mixed with active ingredients and compressed into tablets.

2.2.2 Flash Tab Technology

Dinkar Sharma et al., 2012 taste-Masked orally disintegrating tablets of paracetamol were prepared by Flash Tab Technology. Taste masked granules of paracetamol were prepared by coating the granules of the drug using a pH -sensitive polymer Eudragit EPO in a fluidized bed coater and the coated granules were evaluated. Wet granulation technique was used for the preparation of the tablets using crospovidone and hydroxypropyl cellulose as disintegrants. Disintegration time of the tablets was found to be 27 sec and almost 100% drug released in 30 minutes.

2.2.3 Solid Dispersion Method

Alshehri SM et al, 2015 to enhance the solubility as well as to mask the intensely bitter taste of the poorly soluble drug, Mefenamic acid (MA). The taste masking and solubility of the drug was improved by using Eudragit® EPO in different ratios via hot melt extrusion (HME), solid dispersion technology. Differential scanning calorimetry (DSC) studies demonstrated that MA and E PO were completely miscible up to 40% drug loads. Powder X-ray diffraction analysis indicated that MA was converted to its amorphous phase in all of the formulations. Additionally, FT-IR analysis indicated hydrogen bonding between the drug and the carrier up to 25% of drug loading. SEM images indicated aggregation of MA at over 30% of drug loading. Based on the FT-

IR, SEM and dissolution results for the extrudates, two optimized formulations (20% and 25% drug loads) were selected to formulate the orallydisintegratingtablets (ODTs). ODTs were successfully prepared with excellent friability and rapid disintegration time in addition to having the desired taste-masking effect.

2.2.4 Molding

Tablets prepared by this method are solid dispersions. Moulded tablets offer improved taste due to water- soluble sugars present in dispersion matrix. Different moulding techniques can be used to prepare mouth-dissolving tablets:

a. **Compression molding:** The manufacturing process involves moistening the powder blend with a hydro- alcoholic solvent followed by compressing into mould plates to form a wetted mass which is then air dried to remove the solvent. Such tablets are less compact than compressed tablets and possess a porous structure that has tens dissolution.

b.**Heatmolding:** Amolten matrix in which drug is dissolved or dispersed can be directly moulded in to oro-dispersible tablets. The tablets prepared using heat moulding process involves settling of molten mass that contain a dispersed or dissolved drug. In this process, the suspension or solution of drug, a garland sugar is prepared and then poured into the blister packaging. The agar solution is then solidified at room temperature to form a jelly and dried at 30°C under the vacuum. Developed orally disintegrating tablets was found to improve the mouth feel due to the presence of the water soluble sugars.

c.**Novacuum lyophilization:** This process involves evaporation of solvent from a drug solution or suspension at a standard pressure.

Molded tablets had less mechanical strength. Drug can be present as micro particles or discrete particles dispersed in the matrix. However, addingsucrose, acacia or

polyvinyl pyrrolidone can increase mechanical strength. They possess highly porous structure which is supposed to increase their disintegration and dissolution rates.

2.2.5 Phase transition process

The combination of low and high melting point sugar alcohols, as well as a phase transition in the manufacturing process, is important form a king orally disintegrating tablets without any special apparatus. Here, tablet produced by compressing the powder containing two sugar alcohols of high and low melting point and subsequently heating at temperature between their two melting points. Orally disintegrating tablets were produced by compressing powder containing erythritol (melting point: 122°C) and xylitol (melting point: 93-95°C), and then heating at about 93°C for 15 min. After heating, the median pore size of the tablets was increased and tablet hardness was also increased. The increase of tablet hardness with heating and storage did not depend on the crystal state of the lower melting point sugar alcohol.

2.2.6 Melt granulation

Abdelbary et al., 2014 preparedorally disintegrating tablet by incorporating a hydrophilic waxy binder PEG 6- stearate (Superpolystate®) in the formulation. It has melting point of 33-37°C and HLB value of 9. It acts as a binder and increases the physical resistance of tablet. It helps for fast disintegration of tablet when place in mouth and leaving no residue in oral cavity.

Perissuttietal., 2003developedthe orally disintegrating tablets of Carbamazepine by melt granulation technique. The granules were prepared by using poly ethylene glycol (PEG-4000) as a melting binder and lactose monohydrate as hydrophilic filler without using solvents or water. The dissolution profiles of granules containing Crospovidone as an intra-granulating agent were found to be super imposable to

those prepared without it. Also, the extra granular addition of a small amount of Crospovidone gave rise to a further increase in disintegration rate and dissolution performances.

2.2.7Sublimation

(Shinde et al., 2010) This technique is based on the use of volatile ingredients (e.g. camphor, ammonium bicarbonate, naphthalene, urea, urethane, etc.) to other tablet excipients and the mixture is then compressed into tablets. Entrapped volatile material is then removed via sublimation, which leads to formation of a porous structure. These compressed tablets which have high porosity (approximately30%) rapidly dissolved within 15seconds in saliva. Several solvents like cyclohexane, benzene etc. can also be used as pore forming agents. Orodispersible tablets with highly porous structure and good mechanical strength have been developed by this method.

Koizumi et al, 1997 prepared highly porous compressed tablets. They used mannitol as a tablet matrix material while camphor as subliming agent. Camphor was removed by subliming in vacuum at 80°C for 30 minutes to develop pores in the tablets.

Makino et al., 1998 described a method of producing a fast dissolving tablet using water as a pore forming material. They used a mixture containing active ingredient and carbohydrates (glucose, mannitol, xylitol etc.) which then moistened with water (1-3%w/w) and compressed into tablets. Then water was removed, yielding highly porous tablet.

2.2.8 Mass Extrusion

In this technique, a blend of active drug and other ingredients is softened using solvent mixture of water soluble polyethylene glycol, using methanol and then softened mass is extruded through the extruder or syringe to get a cylinder of product, which is finally cut into even segments with the help of heated blades to get tablets.

The dried cylinder can be used to coat the granules of bitter tasting drugs and thereby masked their bitter taste.

2.2.9 Cotton Candy Process

This process utilizes unique spinning mechanism to produce floss-like crystalline structure. Cotton candy process involves formation of matrix of polysaccharides or saccharides by simultaneous action of flash melting and spinning. The matrix formed is partially recrystallized to improve flow property and compressibility. This candy floss matrix is then milled and blended with active ingredients and excipients and subsequently compressed to orally disintegrating tablet. This process can accommodate larger drug doses and offers improved mechanical strength. However, high- process temperature limits the use ofthis process.

2.2.10 Direct Compression:

(Battu s ket al, 2007) formulation of directly compressible rapidly disintegrating tablets of fenoverine with sufficient mechanical integrity, content uniformity, and acceptable palatability to assist patients of any age group for easy administration was carried out. Effect of varying concentrations of different superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate on disintegration time was studied. In which crospovidone shows superior disintegration in the formulation.

Farshid A et al, 2014 Zolmitriptan tablets were prepared by direct compression method and sublimation method by using Menthol and Camphor as subliming agent and their pre and post compression parameters were determined. The dissolution studies were performed at 37°C±5°C and at 50 rpm in pH 6.8 phosphate buffer. In this study formulation with insoluble diluents and disintegrants were found to be better

than tablets containing soluble diluents and disintegrants. By sublimation method, menthol was found better than camphor in disintegration and drug release

HazeePeera N et al, 2013 orally disintegrating tablets of Zolmitriptan prepared by direct compression and using Supertab11SD, Avicel PH 102, Crospovidone, Ac-Di-Sol, Sodium starch glycolate, Aspartame, Magnesium stearate were prepared and evaluated for the pre compression parameters such as bulk density, compressibility, angle of repose etc. The prepared batches of tablets were evaluated for hardness, weight variation, friability, disintegration time and in-vitro dissolution profile and found satisfactory. Among the three groups, F9 Formulation as the best formulation and showed maximum dissolution rate with drug release.

El-Setouhy DA et al, 2015 formulation of sublingual tablets of Zolmitriptan using novel surfactant binder with limited permeability poses a great challenge due to their poor absorption. In this study, bioenhanced sublingual tablets (BESTs) of zolmitriptan were prepared using novel surfactant binder (Pluronic® p123/Syloid® mixture) to enhance tablet disintegration and dissolution. Microencapsulated polysorbate 80 (Sepitrap™ 80) were included in the composition of BESTs to enhance the drug transport through the sublingual mucosa. Tablets were evaluated for in vitro/in vivo disintegration, in vitro dissolution and ex vivo permeation. Solubility studies confirmed that phosphate buffer; pH 6.8 could be used as dissolution medium for sublingual tablets of zolmitriptan. BEST-5 containing Pluronic® p123/Syloid® mixture and Sepitrap™ 80 exhibited the shortest in vitro/in vivo disintegration times (<30s), the highest dissolution at early time dissolution points and the highest enhancement of drug transport through mucosal membrane. The in vivo pharmacokinetic study using human volunteers showed a significant increase in the rate and extent of sublingual absorption with less variations of T_{max} after sublingual

administration of both BEST-5 and Zomig-ZMT ODT. Our results proposed that Pluronic® p123/Syloid® mixture and Sepitrap™ 80 could be promising for the development of sublingual tablets for rapid onset of action of drugs with limited permeability.

(Ademir Barianni Rodero et al, 2009) in most of the ODT formulation of Zolmitriptan, Asparatame is used as sweetener. Considering the side effects of Asparatame, sucralose can be considered as the sweetener which shows equal potential. Sucralose is a non-nutritive artificial sweetener, 600 times sweeter than sucrose, and is very stable at high temperatures, among other characteristics.

2.3 Various drug delivery systems used in Zolmitriptan formulation

2.3.1 Combinational therapy using Triptans and NSAID.

(Kumar A et al., 2015) combinational formulation of Triptans and NSAID may provide a quicker and longer duration of relief from the subsequent pain during the attack. In this study, formulation of Zolmitriptan (ZT) & ketorolac tromethamine (KT) loaded thermo reversible in-situ mucoadhesive intranasal gel (TMISG) formulation which gels at the nasal mucosal temperature and contains a bioadhesive polymer (Xyloglucan) that lengthens the residence time will enhance the bioavailability of the combinational drugs. This study uses Box-Behnken design for the first time to develop, optimize the TMISG and assess factors affecting the critical quality attributes. Histopathological study of the nasal mucosa suggested that the formulation was safe for nasal administration. The statistical difference in absolute bioavailability between oral and intranasal route suggested that intranasal route had almost 21% increases in bioavailability for ZT and for KT there was 16% increase over oral formulations. Optimized formulation would help mitigate migraine associated symptoms much better over the currently available formulations.

Subedi RK et al., 2011 the effects of different formulation variables including pressure sensitive adhesive (PSA), thickness of the matrix, solvent system, inclusion of crystallization inhibitor, loading amount of drug and enhancers on the transdermal absorption of zolmitriptan were investigated. Acrylic adhesive with hydroxyl functional group provided good adhesion force and high flux of zolmitriptan. Pseudopolymorphs of zolmitriptan were found to possess different solid-state properties that affected the permeation rate. Polyoxyethylene alkyl ethers significantly increased the permeation of zolmitriptan through hairless mouse skin. However, these enhancers induced crystallization of zolmitriptan. Kollidon(®) 30 delayed the crystallization without altering the permeation profile of zolmitriptan. Stability studies suggested that terpenes did not induce crystallization of zolmitriptan in the patch and stable formulations could be produced by using cineole and limonene, or their combination.

Subedi RK et al., 2011 transdermal patch for Zolmitriptan have determined it's*in vivo* absorption using the rabbit skin. Solvent evaporation technique prepared zolmitriptan patch was settled in two-chamber diffusion cell combined with excised rabbit abdomen skin for permeation study. A sufficient cumulative penetration amount of Zolmitriptan (258.5 ± 26.9 μg/cm^2 in 24 h) was achieved by the formulation of 4% Zolmitriptan, 10% Azone, and adhesive of DURO-TAK® 87-4098. Pharmacokinetic parameters were determined via I.V and transdermal administrations using animal model of rabbit. The results revealed that the absolute bioavailability was about 63%. Zolmitriptan could be detected with drug level of 88 ± 51 mg/mL after transdermal administration of 15 min. The in vivo absorption curve obtained by de convolution approach using WinNonlin® program was correlated well with the in vitro permeation curve, the correlation coefficient R is

0.84, and the result indicated that in vitro skin permeation experiments were useful to predict the in vivo performance. In addition, little skin irritation was found in the irritation study. As a conclusion, the optimized zolmitriptan transdermal patches could effectively deliver adequate drug into systemic circulation in short time without producing any irritation phenomenon and worth to be developed.

The present study is aimed to develop a optimized ODT of Zolmitriptan 5mg by simple manufacturing process and with reduced number of excipients.

3. AIM &OBJECTIVE

Difficulty in swallowing (dysphagia) is a common problem of all age groups, especially the elderly and pediatrics, because of physiological changes associated with those groups. Other categories that experience problems in using conventional oral dosage forms include the mentally ill, uncooperative and patients suffering from nausea, motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to non-availability of water. These problems led to the development of a novel type of solid oral dosage form called orodispersible tablet, which disintegrates/dissolves rapidly in saliva without the need of drinking water.

The benefits in terms of patient compliance, rapid onset of action, increased bioavailability and good stability make these tablets popular as a dosage form of choice in the current market. Some drugs are in such cases bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

The basic approach used in the development of the ODTs is the use of superdisintegrants. Many approaches have been developed to manufacture ODTs. These include vacuum drying direct compression, lyophilization and molding. The direct compression method is inexpensive and convenient for producing tablets of sufficient mechanical strength.

Zolmitriptan are the new serotogenic agonist with excellent oral bioavailability exhibiting a potent symptomatic antimigraine effect. Zolmitriptan is a selectiveagonist of 5-HT1 B/D receptors.

In the present study, orodispersible tablets of Zolmitriptan are designed by using polymers namely Pharmabusrst, Pearlitol Flash and Panexcea ODT. Effervescent substances like citric acid and sodium stearyl fumarate.

Accelerated the superdisintegrant action and mask the bitter taste of zolmitriptan. The designed tablets were evaluated for thickness, hardness, friability, weight variation, *in vitro* dispersion time, wetting time, water absorption ratio, disintegration time, drug content uniformity, *in vitro* dissolution rate (in pH 6.8 phosphate buffer), short term stability and drug excipient interactions (IR spectroscopy).

OBJECTIVES OF THE WORK:

The present work is an attempt:

1. To formulate and evaluate orodispersible tablets.
2. To enhance the bioavailibity.
3. Ease of administration to paediatrics and geriatrics.
4. To evaluate for the pre-formulation characteristics of powder mixture like bulk density, flow property, angle of repose, compressibility index etc.
5. To evaluate the post-formulation characteristics of the tablet like hardness, friability, disintegration time, dispersion time, etc.
6. To carry out *in vitro* dissolution studies of the tablet formulations.
7. To carry out stability studies according to ICH guidelines

To formulate orally disintegrating tablets of Zolmitriptan, 5 mg by a simple direct compression process and to evaluate the physico-chemical characteristics of the designed tablets against the marketed product.

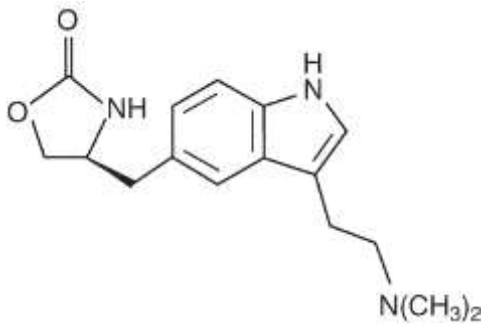
4. PLAN OF WORK

- Literature survey
- Procurement of raw materials and drug (zolmitriptan)
- Preformulation studies of zolmitriptan
- Characterization of zolmitriptan
- Preparation of zolmitriptan - ethylcellulose mixture (Taste masking)
- Pre-compression evaluation
- Compression of final blend into tablets
- Post-compression evaluation
- In-vitro drug release studies
- Comparison of optimized formulation and marketed ODT preparation
- Stability studies
- Drug release kinetics

5. DRUG & EXCIPIENT PROFILE

5.1 ZOLMTIPTAN

Chemical Structure



IUPAC Name **:**(*S*)-4-({3-[2-(dimethylamino)ethyl]-1*H*-indol-5-yl}methyl)-1,3-oxazolidin-2-one

Description **:** Zolmitriptan is a synthetic tryptamine derivative and appears as a white powder that is partially soluble in water.

Drug class **:** Antimigraine agents.

Bioavailability **:** 40% Oral.

Protein binding **:** 25%.

Absorption **:** Zolmitriptan is well absorbed after oral administration. Zolmitriptan displays linear kinetics over the dose range of 2.5 to 50 mg.

Distribution **:** Mean absolute bioavailability is approximately 40%. The mean apparent volume of distribution is 7.0 L/kg. Plasma protein binding of Zolmitriptan is 25% over the concentration range of 10- 1000 mg/ml.

Metabolism **:** Hepatic (CYP1A2-mediated, to active metabolite). Zolmitriptan is converted to an active N-desmethyl metabolite; the metabolite concentrations are about two-thirds that of zolmitriptan. Because the 5HT1B/1D potency of the metabolite is 2 to 6 times that of the parent compound, the metabolite may contribute a substantial portion of the overall effect after zolmitriptan administration.

Excretion: Renal (65%) and faecal (35%). Mean total plasma clearance is 31.5 mL/min/kg, of which one-sixth is renal clearance. The renal clearance is greater than the glomerular filtration rate suggesting renal tubular secretion.

Mechanism of action: Zolmitriptan is a new serotonergic agonist with excellent oral bioavailability exhibiting a potent symptomatic antimigraine effect. Zolmitriptan is a selective agonist of 5-HT1B/D receptors. 5-HT1B receptors are concentrated in the wall of the cranial extra cerebral arteries. 5-HT1D receptors are located on the trigeminal terminals which receive pain from the leptomeningeal vessels. Migraine pain has its origin on cranial vessels. In fact, during a migraine attack the trigemino vascular system, which is composed by the cranial vessels and its trigeminal terminals, is activated. The activation of this system induces both dilatation and aseptic inflammation of cranial vessels. Zolmitriptan blocks both vascular phenomena. Its agonist action upon the 5-HT1D receptor ends the aseptic inflammation by inhibiting the release of vasoactive peptides. The dilatation of meningeal vessels disappears due to the stimulation of Zolmitriptan of 5-HT1B receptors. As this drug crosses the blood brain barrier, Zolmitriptan has both peripheral and central actions over the spinal trigeminal nucleus, which is rich in 5-HT1B/D receptors. Thus, the mechanism of action of Zolmitriptan is double. On the one hand, Zolmitriptan acts peripherally inhibiting dilatation and inflammation of

cranial vessels. On the other, Zolmitriptan exhibits a central nociceptive action in the brainstem nuclei. This dual action of Zolmitriptan on migraine pain is completed with its beneficial effects on nausea and vomiting, due to its binding to the nucleus of the tract us solitaries, the centre for control of vomiting.

Brand names **:** Zomig, Zomig-ZMT.

Uses **:** Migraines, Cluster headaches and cyclic vomiting syndrome.

Indications and usage **:** Zolmitriptan is indicated for the acute treatment of migraine with or without aura in adults.

Limitation of use **:** Only use Zolmitriptan if a clear diagnosis of migraine has been established. If a patient has no response to Zolmitriptan treatment for the first migraine attack, reconsider the diagnosis of migraine before Zolmitriptan is administered to treat any subsequent attacks. Zolmitriptan is not indicated for the prevention of migraine attacks. Safety and effectiveness of Zolmitriptan have not been established for cluster headache.

Dosing in Patients with Hepatic Impairment

The recommended dose of Zolmitriptan in patients with moderate to severe hepatic impairment is 1.25 mg because of increased Zolmitriptan blood levels in these patients and elevation of blood pressure in some of these patients. Limit the total daily dose in patients with severe hepatic impairment to not more than 5 mg per day.

Contraindications

- Ischemic coronary artery disease (angina pectoris, history of myocardial infarction, or documented silent ischemia),

- Wolff-Parkinson-White Syndrome or arrhythmias,
- History of stroke, transient ischemic attack (TIA), or history of hemiplegic or basilar migraine because these patients are at a higher risk of stroke**,**
- Peripheral vascular disease (PVD),
- Ischemic bowel disease,
- Uncontrolled hypertension.

Medication Overuse Headache

Overuse of acute migraine drugs (e.g. ergotamine, triptans, opioids, or a combination of drugs for 10 or more days per month) may lead to exacerbation of headache (medication overuse headache). Detoxification of patients, including withdrawal of the overused drugs, and treatment of withdrawal symptoms (which often includes a transient worsening of headache) may be necessary.

Adverse Reactions

The following adverse reactions are described elsewhere in other sections of the prescribing information:

- Myocardial Ischemia, Myocardial Infarction, and Prinzmetal Angina.
- Arrthymias.
- Chest and or Throat, Neck and Jaw Pain/Tightness/Pressure.
- Cerebrovascular Events.
- Other Vasospasm Reactions.
- Medication Overuse Headache.
- Serotonin Syndrome.
- Increase in Blood Pressure.

DRUG INTERACTIONS

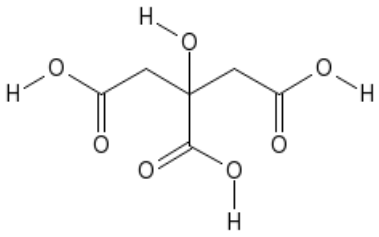
Zolmitriptan is contraindicated to patients to use along with the following class of drugs

- Ergot-containing Drugs,
- MAO-A Inhibitors ,
- 5-HT1B/1D agonists ,
- Selective Serotonin Reuptake Inhibitors and Serotonin Norepinephrine Reuptake Inhibitors and
- Cimetidine.

EXCIPIENT PROFILE

5.2 CITRIC ACID

Chemical structure



Non-proprietary names

BP: Citric acid monohydrate

JP: Citric acid

PhEur: Acidumcitricummonohydricum

USP: Citric acid

Synonyms

E330, 2-hydroxypropane-1,2,3-tricarboxylic acid monohydrate.

Functional Category

Acidifying agent, antioxidant, buffering agent, chelating agent and flavour enhancer.

Applications in Pharmaceutical Formulation or technology:

Citric acid is widely used in pharmaceutical formulations and food products, primarily to adjust the pH of solutions. It has also been used experimentally to adjust the pH of tablet matrices in enteric coated formulations for colon-specific drug delivery. Citric acid monohydrate is used in the preparation of effervescent granules, while anhydrous citric acid is widely used in the preparation of effervescent tablets. Citric acid has also been shown to improve the stability of spray dried insulin powder in inhalation formulations.

In food products, citric acid is used as a flavour enhancer for its teat, acidic taste. Citric acid monohydrate is used as a sequestering agent and antioxidant synergist. It is also a component of anti-coagulant citrate solutions. Therapeutically, preparations containing citric acid have been used to dissolve renal calculi.

Use	Concentration (%)
Buffer solutions	0.1-2.0
Flavor enhancer for liquid formulations	0.3-2.0
Sequestering agent	0.3-2.0

Table 2.Uses of Citric acid at various concentrations.

Description

Citric acid monohydrate occurs as colourless or translucent crystals, or as a white crystalline, efflorescent powder. It is odourless and has a strong acidic taste. The crystal structure is orthorhombic.

Typical Properties

Acidity/alkalinity : pH 2.2 (1% w/v aqueous solution)

Density : 1.542 g/cm^3

Hygroscopicity: at relative humidities less than about 65%, citric acid monohydrate effloresces at 25ºC, the anhydrous acid being formed at relative humidities less than about 40%. At relative humidities between about 65% and 75%, citric acid monohydrate absorbs insignificant amounts of citric acid monohydrate absorbs insignificant amounts of moisture, but under more humid conditions substantial amounts of water are absorbed.

Melting point : 100 ºC (soften at 75 ºC)

Solubility: Soluble 1 in 1.5 parts of ethanol (95%) and 1 in less than 1 part of water; sparingly soluble in ether.

Viscosity (dynamic) : 6.5mPa s (6.5 cP) for a 50% w/v aqueous solution 35 ºC.

Incompatibilities

Citric acid is incompatible with potassium tartarate, alkali and alkaline earth carbonates and bicarbonates, acetates and sulfides. Incompatibilities also include oxidizing agents, bases, reducing agents, and nitrates. It is potentially explosive in

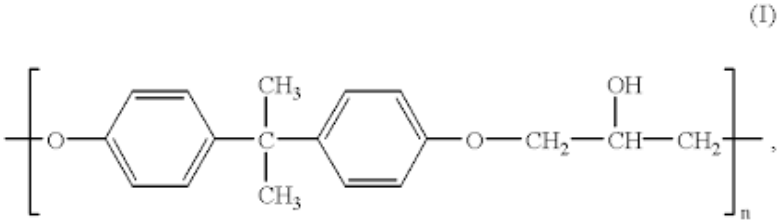
combination with metal nitrates. On storage, sucrose may crystallize from syrups in the presence of citric acid.

Related Substances

Anhydrous citric acid ; fumaric acid; malic acid ; sodium citrate dihydrate ; tartaric acid.

5.3 COLLOIDAL SILICON DI OXIDE

Chemical structure



Non Proprietary Names

BP: Colloidal anhydrous silica

PhEur: Silica colloidalisanhydrica

USPNF: Colloidal Silicon dioxide

Synonym

Aerosi, Cob-O-Sil M-5P, colloidal silica, fumed silica, light anhydrous silicic acid, silicic anhydride, silicon dioxide fumed, *wacker HDK.*

Functional category:

Adsorbent, anticaking agent, emulsion stabilizer, glidants, suspending agent, tablet disintegrants, thermal stabilizer and viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology:

Colloidal silicon dioxide is widely used in pharmaceuticals, cosmetics, and food products; It's small particle size and large specific surface area give it desirable flow characteristics that are exploited to improve the flow properties of dry powders in a number of processes such as tableting.

Colloidal Silicon dioxide is also used to stabilize emulsions and as a thixotropic thickening and suspending agent in gets and semisolid preparations. In aerosols, other than those for inhalation, Colloidal Silicon dioxide is used to promote particulate suspension, eliminate hard settling, and minimize the clogging of spray nozzles. Colloidal Silicon dioxide is also used as a tablet disintegrants and as an adsorbent dispersing agent for liquids in powders. Colloidal silica di oxide is used in suppositories for retarding the release profile.

Description

Colloidal silicon dioxide is sub microscopic fumed silica with a particle size of about 15nm. It is a light, loose, bluish-white-coloured, odourless, tasteless, non-gritty amorphous powder.

Typical Properties

Acidity/alkalinity	:	pH 3.5-4.4 (4% w/v aqueous dispersion)
Density (bulk)	:	0.029-0.042g/cm^3
Flowability	:	35.52%
Particle size distribution	:	7-16nm

Incompatibilities:

Incompatible with diethylstilbestrol preparations.

5.4 PANEXCEA ODT

Product Composition

PanExcea MC200G performance excipient contains a polyhydric sugar alcohol (mannitol) and a proprietary silicate salt (Calcium silicate). The novel Particle morphology makes it an excellent building block for orally disintegrating tablet applications.

Description

- Appearance : Odourless, white crystalline powder
- Morphology : Dense spherical particle
- Particle Morphology
- Particle Size Distribution
    - % Cumulative retained on 60 mesh 1.7%
    - % Cumulative retained on 200 mesh 77.0%
    - % Cumulative retained on 270 mesh 86.8%
    - d50 - 103 microns
- Bulk Density : 0.64 g/cc
- Tapped Density : 0.80 g/cc
- Compressibility(Carr Index) : 19.4
- Hausner's Ratio : 1.21
- Loss on Drying : 4%

Increased Revenues and Shortened Time to Market

PanExcea performance excipients improve supply chain, manufacturing and regulatory efficiencies — speeding your product to market while reducing your ownership costs and increasing your revenues.

• Eliminates Oral Disintegrating Tablet (ODT) technology licensing

• Formulation flexibility and scalability allowing:

- Manipulation of excipient functionality
- Masking of undesirable properties of the individual excipients
- Addition of taste masking or other auxiliary excipients

• Simplified tableting processes utilizing conventional direct compression equipment

• Delivers tablets of optimal strength and stability, enabling use of conventional packaging.

Application

PanExcea™ performance excipients for orally disintegrating tablet applications act as a building block that enables the rapid disintegration of a tablet, in the oral cavity without water, while providing excellent mouth feel.

- Tablet cost 5 to 10 times lower than conventional ODT technology.
- Rapid and complete disintegration with no residue.
- High Active Pharmaceutical Ingredient (API) loading capacity.
- Potential to reduce tablet size and total volume of excipient.
- Completely disintegrates in less than 30 seconds.
- Smooth, creamy mouth feel.
- Increases drug loading capability as a result of the novel particle morphology.

5.5 PHARMABURST

Pharmaburst is a Quick Dissolving delivery system in which there is addition of active drug in a dry blend with Pharmaburst excipients and compress by tablet machine. Pharmaburst was found to be significantly more compactable, less friable, and more rapidly disintegrating. Pharmaburst is a coprocessed excipient system with specific excipients, which allows rapid disintegration and low adhesion to punches. Pharmaburst is smooth and creamy and helps to mask taste and grittiness of the actives. Main advantages Pharmaburst is highly compatible, rapid disintegration and cost effective

Description

Physical state	:	Solid
Appearance	:	White to off-white, free-flowing powder
Color	:	White
Loss on drying	:	NMT 3.0%
Bulk Density	:	0.31 – 0.51 g/mL
Tapped Density	:	0.38 – 0.68 g/mL
Total Polyol Content (db)	:	73.8 – 93.8%
% retain on a #20 U.S. sieve	:	NMT 1
% through a #325 U.S. sieve	:	NMT 18
Melting point	:	330.8°F (164 -169°C)
Boiling point	:	563°F (290 -295°C) decomposes
Flash point	:	> 300.2°F (149°C)
Auto-ignition temperature	:	860°F (460°C)
Solubility	:	Soluble

Storage conditions : Store at room temperature. Keep container tightly closed.

Incompatible products : Strong bases, Strong acids, Strong oxidizing agents.

Incompatible materials : Sources of ignition, direct sunlight.

5.6 PEARLITOL® FLASH

Pearlitol® Flash is a compound dedicated to **orodispersible tablets** obtained by **Direct Compression**.

Description

White, odourless, slightly sweet tasting, crystalline powder

Functional Category

Rapid Release Agent, Disintegrant

Particle Size

200 µm

Advantages

- Pleasing taste
- A fast melting in the mouth
- An easy DC tableting process
- A robust DC excipient
- A surprisingly simple formulation

5.7 PEPPERMINT FLAVOR

Description: Brown fine powder from leaf of mentha.

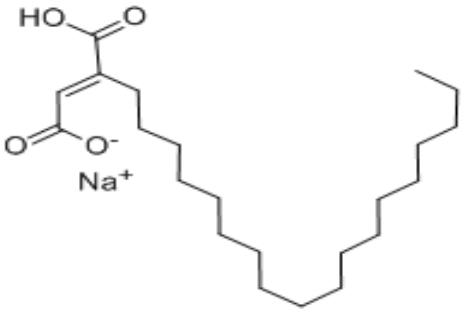
Functional Category: Flavouring agent.

Applications in pharmaceutical Formulation or technology:

Peppermint flavour is used in medicine to mask or impart taste to medications. A flavour, as used in the pharmaceutical industry for inactive ingredients, refers to natural or artificial tastes, which may include fragrances and colours of the flavouring. Flavours are used for orally consumed products such as syrups, chewable tablets, suspensions, or gums that impart beneficial therapeutic effect, as well. Peppermint is a common and popular flavour used in medications.

5.8 SODIUM STEARYL FUMARATE

Chemical structure



Nonproprietary Names

BP: Sodium Stearyl Fumarate

PhEur: Natriistearylisfumaras

USPNF: Sodium Stearyl Fumarate

Synonym

Fumaric acid, octadecyl ester, sodium salt, *pruv*; sodium monostearyl Fumarate

Functional Category:

Tablet and capsule lubricant

Applications in pharmaceutical Formulation or technology

Sodium Stearyl Fumarate is used as a lubricant in capsule and tablet formulation at 0.5-2.0% ww concentration. It is also used in certain food applications

Description

Sodium Stearyl Fumarate is used as a fine, white powder with agglomerates of flat, circular-shaped particles.

Typical Properties

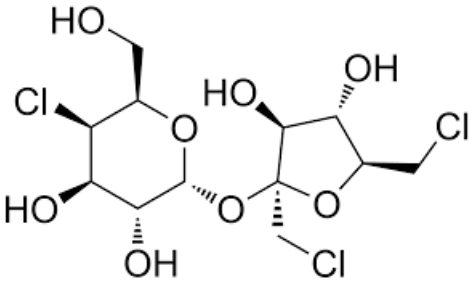
Acidity/alkalinity	:	pH 8.3for a 5%w/v aqueous solution at 90ºC.
Density	:	1.107g/cm^3
Bulk density	:	0.2-0.35 g/cm^3
Tapped density	:	0.3-0.5 g/cm^3
Melting point	:	224-245ºC(with decomposition)

Incompatibilities

Sodium Stearyl Fumarate is reported to be incomparible with chlorhexidine acetate.

5.9 SUCRALOSE

Chemical structure



Nonproprietary Names

USPNF: Sucralose

Synonym

Splenda*;* TGS; 1',4',6'-trichlorogalactosucrose; 4,1',6'-tri-chloro-4,1',6'-trideoxy-galacto-sucrose.

Functional Category:

Sweetening agent

Applications in pharmaceutical Formulation or technology:

Sucralose is used as a sweetening agent in beverages, foods, and pharmaceutical applications. It has a sweetening power approximately300-1000 times that of sucrose and has no aftertaste. It has no nutritional value, is noncarcinogenic, and produces no glycemic response.

Description

Sucralose is a white to off-white coloured, free-flowing and crystalline powder.

Typical Properties

Acidity/alkalinity : pH 5-6 (10% w/v aqueous solution at 20ºC)

Density (bulk) : 0.35 g/cm^3

Density (tapped) : 0.62 g/cm^3

Density (true) : 1.63g/cm^3

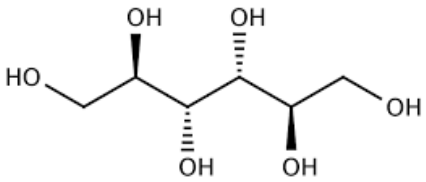
Melting point : 130ºC (for anhydrous crystalline form);

36.5ºC (for pentahydrate).

Particle size distribution: 90% <12µm in size.

5.10 MANNITOL

Chemical structure



Nonproprietary Names

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitolum

USP: Mannitol

Synonyms

Cordycepic acid; C*PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol

Chemical Name and CAS Registry Number

D-Mannitol [69-65-8]

Functional Category Diluent;

Diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent;

Applications in Pharmaceutical Formulation or Technology;

Mannitol is widely used in pharmaceutical formulations and food products. In pharmaceutical preparations it is primarily used as a diluent (10–90% w/w) in tablet formulations, where it is of particular value since it is not hygroscopic and may thus be used with moisture-sensitive active ingredients. Mannitol may be used in direct-compression tablet applications, for which the granular and spray-dried forms are available, or in wet granulations. Granulations containing mannitol have the advantage of being dried easily. Specific tablet applications include antacid preparations, glyceryl trinitrate tablets, and vitamin preparations. Mannitol is commonly used as an excipient in the manufacture of chewable tablet formulations because of its negative heat of solution, sweetness, and ‘mouth feel’. In lyophilized preparations, mannitol (20–90% w/w) has been included as a carrier to produce a stiff, homogeneous cake that improves the appearance of the lyophilized plug in a vial. A pyrogen-free form is available specifically for this use. Mannitol has also been used to prevent thickening in aqueous antacid suspensions of aluminium hydroxide

Description

Mannitol is D-Mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odourless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose, and imparts a cooling sensation in the mouth. Microscopically, it appears as orthorhombic needles when crystallized from alcohol. Mannitol shows polymorphism.

Typical Properties Compressibility:

1. Bulk density : 0.430 g/cm3 for powder; 0.7 g/cm3 for granules.
2. Tapped density : 0.734 g/cm3 for powder; 0.8 g/cm3 for granules.
3. True density : 1.514 g/cm3
4. pKa = 13.5 at 188C Flash point

Stability and Storage Conditions;

Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects. In solution, mannitol is not attacked by cold, dilute acids or alkalis, or by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Maillard reactions. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Mannitol solutions, 20% w/v or stronger, may be salted out by potassium chloride or sodium chloride. Precipitation has been reported to occur when a 25% w/v mannitol solution was allowed to contact plastic. Sodium cephapirin at 2 mg/ml and 30 mg/ml concentration is incompatible with 20% w/v aqueous mannitol solution. Mannitol is incompatible with xylitol infusion and may form complexes with some metals such as aluminium, copper, and iron. Reducing sugar impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation. Mannitol was found to reduce the oral bioavailability of cimetidine compared to sucrose.

Safety

Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement 'excessive consumption may have a laxative effect'. After intravenous injection, mannitol is not metabolized to any appreciable extent and is minimally reabsorbed by the renal tubule, about 80% of a dose being excreted in the urine in 3 hours. A number of adverse reactions to mannitol have been reported, primarily following the therapeutic use of 20% w/v aqueous intravenous infusions. The quantity of mannitol used as an excipient is considerably less than that used therapeutically and is consequently associated with a lower incidence of adverse reactions. However, allergic, hypersensitive-type reactions may occur when mannitol is used as an excipient

An acceptable daily intake of mannitol has not been specified by the WHO since the amount consumed as a sweetening agent was not considered to represent a hazard to health. LD50 (mouse, IP): 14 g/kg LD50 (mouse, IV): 7.47 g/kg LD50 (mouse, oral): 22 g/kg LD50 (rat, IV): 9.69 g/kg LD50 (rat, oral): 13.5 g/kg.

Handling Precautions;

Observe normal precautions appropriate to the circumstances and quantity of material handled. Mannitol may be irritant to the eyes; eye protection is recommended

Regulatory Status GRAS listed.

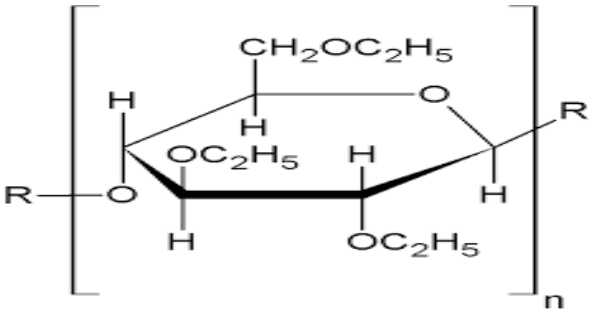
Accepted for use as a food additive in Europe, Included in the FDA Inactive Ingredients Guide (IP, IM, IV, and SC injections; infusions; buccal, oral and sublingual tablets, powders and capsules; ophthalmic preparations; topical solutions). Included in non-parenteral and parenteral medicines licensed in the UK;

Related Substances

Sorbitol

5.11 ETHYL CELLULOSE

Chemical structure



Nonproprietary Names

BP: Ethylcellulose

PhEur: Ethylcellulosum

USPNF: Ethylcellulose

Synonyms

Aquacoat ECD; Aqualon; E462; Ethocel; Surelease.

Chemical Name and CAS Registry Number

Cellulose ethyl ether [9004-57-3]

Empirical Formula and Molecular Weight

Ethylcellulose with complete ethoxyl substitution is C12H23O6 (C12H22O5) nC12H23O5 where n can vary to provide a wide variety of molecular weights. Ethylcellulose, an ethyl ether of cellulose, is a long-chain polymer of anhydrousglucose units joined together by acetal linkages.

Functional Category

Coating agent; flavouring fixative; tablet binder; tablet filler; viscosity-increasing agent.

Applications in Pharmaceutical Formulation or Technology

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. The main use of ethylcellulose in oral formulations is as a hydrophobic coating agent for tablets and granules. Ethylcellulose coatings are used to modify the release of a drug, to mask an unpleasant taste, or to improve the stability of a formulation; for example,

where granules are coated with ethylcellulose to inhibit oxidation. Modified release tablet formulations may also be produced using ethylcellulose as a matrix former. Ethylcellulose, dissolved in an organic solvent or solvent mixture, can be used on its own to produce water-insoluble films. Higher-viscosity ethylcellulose grades tend to produce stronger and more durable films. Ethylcellulose films may be modified to alter their solubility, by the addition of hypromellose or a plasticizer. An aqueous polymer dispersion (or latex) of ethylcellulose such as Aquacoat ECD (FMC Biopolymer) or Surelease (Colorcon) may also be used to produce ethylcellulose films without the need for organic solvents. Drug release through ethylcellulose-coated dosage forms can be controlled by diffusion through the film coating. This can be a slow process unless a large surface area (e.g. pellets or granules compared with tablets) is utilized. In those instances, aqueous ethylcellulose dispersions are generally used to coat granules or pellets. Ethylcellulose-coated beads and granules have also demonstrated the ability to absorb pressure and hence protect the coating from fracture during compression. High-viscosity grades of ethylcellulose are used in drug microencapsulation. Release of a drug from an ethylcellulose microcapsule is a function of the microcapsule wall thickness and surface area. In tablet formulations, ethylcellulose may additionally be employed as a binder, the ethylcellulose being blended dry or wet-granulated with a solvent such as ethanol (95%). Ethylcellulose produces hard tablets with low friability, although they may demonstrate poor dissolution. Ethylcellulose has also been used as an agent for delivering therapeutic agents from oral (e.g. dental) appliances. In topical formulations, ethylcellulose is used as a thickening agent in creams, lotions, or gels, provided an appropriate solvent is used. Ethylcellulose has been studied as a stabilizer for emulsions. Ethylcellulose is additionally used in cosmetics and food products.

Description

Ethylcellulose is a tasteless, free-flowing, and white to light tan colored powder.

Typical Properties

Bulk density: 0.4 g/cm3

Glass transition temperature: 129–1338C

Moisture content: Ethylcellulose absorbs very little water from humid air or during immersion, and that small amount evaporates readily.

Stability and Storage Conditions

Ethylcellulose is a stable, slightly hygroscopic material. It is chemically resistant to alkalis, both dilute and concentrated, and to salt solutions, although it is more sensitive to acidic materials than are cellulose esters. Ethylcellulose is subject to oxidative degradation in the presence of sunlight or UV light at elevated temperatures. This may be prevented by the use of antioxidant and chemical additives that absorb light in the 230–340 nm range. Ethylcellulose should be stored at a temperature not exceeding 328C (908F) in a dry area away from all sources of heat. It should not be stored next to peroxides or other oxidizing agents.

Incompatibilities

Incompatible with paraffin wax and microcrystalline wax

Safety

Ethylcellulose is widely used in oral and topical pharmaceutical formulations. It is also used in food products. Ethylcellulose is not metabolized following oral

consumption and is therefore a noncalorific substance. Because ethylcellulose is not metabolized it is not recommended for parenteral products; parenteral use may be harmful to the kidneys.

Ethylcellulose is generally regarded as a nontoxic, nonallergenic, and nonirritating material. As ethylcellulose is not considered to be a health hazard, the WHO has not specified an acceptable daily intake. LD50 (rabbit, skin) : >5 g/kg (30) LD50 (rat, oral) : >5 g/kg

Handling Precautions

It is important to prevent fine dust clouds of ethylcellulose from reaching potentially explosive levels in the air. Ethylcellulose is combustible. Ethylcellulose powder may be an irritant to the eyes and eye protection should be worn.

Regulatory Status GRAS listed.

Accepted for use as a food additive in Europe. Included in the FDA Inactive Ingredients Guide (oral capsules, suspensions and tablets; topical emulsions and vaginal preparations). Included in non-parenteral medicines licensed in Europe. Included in the Canadian List of Acceptable Non medicinal Ingredients.

6. MATERIALS AND MEHODS

6.1 Materials used

S.NO	Ingredients	Manufacturer
1.	Zolmitriptan USP	Aurobindo Pharma
2.	Pharmaburst	SPI Pharma
3.	Pearlitol Flash	RoquettePharma
4.	PanExcea ODT	Avantor Performance Materials
5.	Peppermint Flavour 501500 TP0504	FirmenichPharma
6.	Citric Acid Anhydrous, USP	Avantor Performance Materials
7.	Sucralose	JK Sucralose
8.	Colloidal Silicon Dioxide (100)	EvonikPharma
9.	Sodium Stearyl Fumarate (Pruv)	JRS Pharma
10.	Mannitol	Global pharma
11.	Ethyl cellulose	Shreejipharma international
12.	Orange flavour powder	Prakash chemicals agencies
13.	Pearlitol Flash	FirmenichPharma

Table 3. Materials used in formulations

6.2 Instruments used

S.NO	Name of the instrument	Manufacturer
1.	Analytical balance,	Essae -teraoku Ltd
2.	Sieves #40 and #60 mesh,	Cansons
3.	Double cone blender 5L,	Pharma pack
4.	compression machine,	Cadmach
5.	Digital vernier calliper,	Lab India
6.	Friability tester,	Electrolab
7.	Hardness tester,	Erweka
8.	Tap Density Tester,	Electrolab
9.	Disintegration Tester,	Electrolab
10.	Moisture analyser,	Ohaus
11.	Vibrosifter,	Cansons
12.	Funnel and stand for Angle of repose,	Borosil
13.	Dissolution test apparatus,	Labindia, disso 2000
14.	Water's HPLC.	Elico Li 120

Table 4. Instruments used in Formulation

6.3PREPARATION OF STANDARD CURVE FOR ZOLMITRIPTAN

PREPARATION OF PH 6.8 BUFFER (phosphate buffer)

27.218 gm of potassium dihydrogen orthophosphate was dissolved in 1000 ml of distilled water. And to prepare 0.1 N sodium hydroxide solution. Then from this Potassium dihydrogen orthophosphate solution 250 ml was taken and mixed with 112 ml of 0.1 N Sodium hydroxide solutions. Finally to make up 1000 ml by using distilled water.

PREPARATION OF STANDARD CURVE FOR ZOLMITRIPTAN

100 mg of Zolmitriptan was accurately weighed and dissolved in small portion of phosphate buffer pH 6.8 in a 100 ml of volumetric flask and the volume was made up to 100 ml with buffer. This is the primary stock solution. From the primary stock solution 10 ml was accurately pippetted out and transferred into a 100 ml volumetric flask. Then the volume was made up to 100 ml with buffer. From the secondary stock solution aliquots equivalent to 2-10 mcg (2ml, 4ml, 6ml, 8ml, and 10 ml) were pippeted out into a series of 10 with buffer. The absorbance of above set solutions was against the phosphate buffer pH 6.8 as blank at 248nm. Then calibration curve was plotted taking concentration on X-axis and absorbance on Y-axis.

6.4 Preformulation

It is the first step in rational development of dosage forms of drug substance. Preformulation testing is defined as investigation of physical and chemical properties of a drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms that can be mass-produced.

Preformulation investigations are designed to identify those physicochemical properties and excipients that may influence the formulation design, method of manufacture and pharmacokinetic biopharmaceutical properties of the resulting product.

Preformulation parameters

6.4.1 Organoleptic properties

This includes recording of colour, odour and taste of the drug using descriptive terminology. Record of colour of early batches is very useful in establishing appropriate specifications for later production. Drugs generally have a characteristic odour and taste. Unpleasant ones are masked later during formulation.

Organoleptic Parameter	Observation
Colour	White
Odour	Peppermint odour
Taste	Peppermint flavour

Table 5. Organoleptic parameters and its observations

6.4.2 Physicochemical characterization:

Density measurement:

Granules density may influence compressibility, tablet porosity, dissolution and other properties. Different types of density calculation were done to characterize the drug and its flow property. Generally two types of density are determined i.e., bulk density

and tapped density. The methods followed for calculation of the above two densities are determined by the following ways.

Bulk density:

It is a measure used to describe the packing of particles or granules. An accurately weighed quantity of powder, which was previously passed through sieve #40 [USP] and carefully poured bed, was made uniform without disturbing. Then volume measure was called as the bulk volume and the bulk density is calculated by following formula.

Bulk density= weight of powder / Bulk volume

Tapped density:

After measuring the bulk volume the same measuring cylinder was set into tap density apparatus. The tap density apparatus was set to300 taps drop per minute and operated for 500 taps. Volume was noted as (V_a) and again tapped for750 times and volume was noted as (V_b). If the difference between V_a and V_b not greater than 2% then V_b is considered as final tapped volume. The tapped density is calculated by the following formula.

Tapped density= Weight of powder /Tapped volume

6.4.3 Flow properties:

The flow properties from a material result from many forces. There are many types of forces hat can act between solid particles: frictional forces, surface tension forces, mechanical forces caused by interlocking of particles of irregular shapes, electrostatic forces and cohesive or vander vaals forces. These forces can effect

granule properties such as particle size, particle size distribution, particle shape, surface texture or roughness, residual surface energy and surface area.

6.4.4 Compressibility index:

Pharmaceutical powders are broadly classified into free flowing and cohesive. Powders are more often compressed into tablets using a pressure of 5kg/cm^2. This is called compression or compaction. During this process the porosity of the powder changes. The compression properties of most drugs are very poor. Therefore compression vehicles such as lactose, calcium phosphate and microcrystalline cellulose are included in tablet formulations. Normally low dose drugs (<50mg) are prepared by direct compression. Tablet materials should be plastic that is capable of undergoing permanent deformation yet exhibit brittleness. Percentage compressibility also known as Carr's consolidation index is indirectly related to the relative flow rate, cohesiveness and particle size. It is a simple, fast and popular method for predicting powder flow characteristics.

Percentage compressibility	**Flowability**
5-10	Excellent
12-16	Good
18-21	Fair
23-25	Poor

Table 6; Percentage compressibility and corresponding Flowability

Carr's consolidation index = [(Tapped density-Fluff density)/tapped density]*100

Compressibility index can be a measure of the potential strength that a powder could build up in its arch in a hopper and also the ease with which such an arch should be broken.

6.4.5 Angle of repose

The angle of Repose is defined as the maximum angle possible between the surface of a pile of powder and the horizontal plane.

$$\theta = \mathbf{Tan^{-1}\ (h/r)}$$

Where

'h' = height of the pile

'r' = radius of the pile

Values of Θ are rarely less than 20^0, and values of up to 40^0 indicate reasonably flow potential. Above 50^0, however, the powder flows only with great difficulty. In general, the angle of repose increased with decreasing particle size. The addition of talk in low concentration decreases the repose angle, but in higher concentration it increases the angle.

Flow Property	**Angle of Repose(degree)**
Excellent	25-30
Good	31-35
Fair – aid not needed	36-40
Passable - may hang up	41-45
Poor – must agitate, vibrate	46-55
Very poor	56-65
Very very poor	>66

Table 7: Flow Properties and Corresponding Angles of Repose

6.4.6 Hausner's ratio:

It is the ratio of bulk volume or tapped density to bulk density. Hausner's ratio is an important character to determine the flow property of powder and granules. Thiscan be calculated by the formula

Hausner 's ratio=Tapped density/Bulk density

Value<1.25 indicate good flow(=20% carr's index)

While>1.50 indicate poor flow(-35% carr's index)

Flow Character	Hausner's Ratio
Excellent	1.2-1.3
Good	1.3-1.4
Fair	1.4-1.5
Poor	1.5-1.6

Table 8. Flow property and corresponding Hausner's ratio.

6.4.7 Particle size distribution

Particle size distribution is a very important in process technique of final blend after blending. It is an important parameter to determine the amount of fines as well as particle with larger particle size in final blend. It also helps in keeping a check over uniformity of distribution of blend over various sizes while carrying out consecutive batches. Particle size determination was carried by arranging various sieves of sizes #20, #40, #60, #80, #100, #140, #200 and Pan (for finer particles which passes even #200 sieve) in ascending order (i.e.,#20 sieve lies on top and pan at the bottom). Then the final blend of accurately weighed quantity was placed on the top sieve. And the sieves are placed in vibrosifter and allowed to run at1.0 amplitude for 10 minutes.

After the procedure difference of initial and final weight of sieves were noted to calculate the percentage retention of the blend in various sieves.

6.5. DRUG EXCIPIENT COMPATABILITY STUDY BY FTIR ANALYSIS

Compatibility of the drug with excipients was determined by FT-IR spectral analysis, this study was carried out to detect any changes on chemical constitution of the drug after combined it with the excipients.

Infrared spectra for pure Zolmitriptan, drug with polymers, and best formulation that determined to check the intactness of the drug in the formulation.

The Table no- 14 shows the wave number for the characteristic bands in the infrared spectra of pure Zolmitriptan.

6.6 PROCEDURE FOR PREPARATION OF ZOLMITRIPTAN – ETHYL CELLULOSE MIXTURE FOR TASTE MASKING

- API is weighed accurately and sifted through # 40 mesh.
- Ethyl cellulose is weighed accurately and dissolved in isopropyl alcohol in the required ratio (5:1, 5:2, and 5:3).
- API is granulated with the ethylcellulose solution and initially air dried followed by drying with rapid drier.
- The dried mixture is tested for taste evaluation (organoleptic character) orally and until the taste found satisfactory the concentration of ethyl cellulose against the API is increased.

6.6.1 PROCEDURE FOR FORMULATION AND COMPRESSION OF TABLETS (FOR FORMULATION FZ1, FZ5, FZ6, FZ7, FZ8 AND FZ9)

- All the ingredients were weighed accurately as per the formula made
- Initially all the listed ingredients were sifted through #40 mesh

- API mixture was added to the blend geometrically by mixing with the other excipients while sifting
- Load the sifted ingredients in a 5L Double Cone Blender and blend for 5 minutes at 15 RPM
- Unload the blended materials and again sift through #40 mesh.
- Load the sifted materials again in the 5L Double Cone Blender and blend for 20 minutes at 15 RPM
- Sift Colloidal Silicon Dioxide and Sodium Stearyl Fumarate through #60 mesh
- Blend the sifted materials along with blended materials in a 5L Double Cone Blender and blend for 5 minutes at 15 RPM
- Compress the blended materials using 7.15 mm Round Flat Faced Bevel Edged Plain Tooling

6.6.2 PROCEDURE FOR FORMULATION AND COMPRESSION OF TABLETS (FOR FORMULATIONFZ2, FZ3 AND FZ4)

- All the ingredients were weighed accurately as per the formula made
- Initially all the listed ingredients were sifted through #40 mesh
- API mixture was added to the blend geometrically by mixing with the other excipients while sifting
- Load the sifted ingredients in a 5L High shear mixture granulator and granulate with purified water with impeller and chopper at high speed for three minutes.
- Dry it in the rapid dryer until it reaches the LOD of 2.5%.
- Unload the dried materials and again sift through #40 mesh.

- Load the sifted materials along with the extra granular material in the 5L Double Cone Blender and blend for 20 minutes at 15 RPM
- Sift Colloidal Silicon (if applicable) Dioxide and Sodium Stearyl Fumarate through #60 mesh
- Blend the sifted materials along with blended materials in a 5L Double Cone Blender and blend for 5 minutes at 15 RPM
- Compress the blended materials using 7.15 mm Round Flat Faced Bevel Edged Plain Tooling

6.6.3 BLENDING

Blending (Pre Lubrication)

The blending step involves mixing of additives using double cone blender (DCB). In this step all the ingredients are transferred into the DCB except the lubricating agents and the machine is allowed to rotate at the speed of 15±1RPMfor 5minutes. Then the blend is unloaded and sieved by using the sieve of #40 mesh. The sieved blend was again loaded into the blender and allowed to rotate for 25 minutes. The blend uniformity sample was taken at 20, 25 and 30 minutes from ten different positions using the sampling rod for optimizing the blending time for pre lubrication.

6.6.4 BLENDING (LUBRICATION)

Lubricating agents are added to the blend after sieving with #60 mesh. And the blend is allowed to rotate for 5 min for lubrication. The blend uniformity sample was taken at 4, 5 and 6 minutes from ten different positions using the sampling rod for optimizing the blending time for lubrication.

6.6.5 COMPRESSION

Compression is done by using machine Cadmach compression machine which is double rotary having 16stations. Compression was carried as per BMR using standard concave shaped punches with hard chrome platedtips.

Number of stations : 16

Type of tooling : "D" type

Procedure is done for description, average weight, disintegration time, friability, thickness and hardness.

6.6.6 Formulation and their composition:

S. No	Composition	Ratio (API: Ethyl cellulose: IPA)	Inference form organoleptic evaluation by selected volunteers
1	Zolmitriptan Ethyl cellulose Iso propyl alcohol	5 : 1 : 1	Bitterness was not efficiently .asked
2	Zolmitriptan Ethyl cellulose Iso propyl alcohol	5 : 2 : 1	Comparatively low, but bitterness still found.
3	Zolmitriptan Ethyl cellulose Iso propyl alcohol	5 : 3 : 1	Comparatively better taste.

Table: 9 Composition of unit dose of Zolmitriptan – ethylcellulose mixture for taste masking formulations

Various batches were planned and executed with the unit concentration of the ingredients used in the batch as shown in the table below.

S. No	Ingredients	Fz1 (mg)	Fz2 (mg)	Fz3 (mg)	Fz4 (mg)	Fz5 (mg)	Fz6 (mg)	Fz7 (mg)	Fz8 (mg)	Fz9 (mg)
Intragranular Portion										
1	Zolmitriptan	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00	5.00
2	Ethyl cellulose	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
3	Iso propyl alcohol	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00	1.00
4	Mannitol	109.00	109.0	104.0	99.00	-	-	-	-	-
5	Purified Water	-	10.00	10.00	10.00	-	-	-	-	-
6	Pearlitol Flash	-	-	-	-	109.0	-	-	-	-
7	Pharma Burst	-	-	-	-	-	109.0	-	-	-
8	Pan Excea ODT	-	-	-	-	-	-	109.0	107.7	106.5
9	Orange flavour	1.25	1.25	1.25	1.25	-	-	-	-	-
10	Peppermint Flavour	-	-	-	-	1.25	1.25	1.25	1.25	1.25
11	Citric Acid Anhydrous, USP	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00	4.00
12	Sucralose	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00	3.00
Extragranular portion										
13	PolyplasdoneXL 10	-	-	5.00	10.00	-	-	-	-	-
14	Colloidal Silicon Dioxide (Aerosil 200)	-	-	-	-	1.25	1.25	1.25	2.50	2.50
15	Sodium Stearyl Fumarate (Pruv)	1.25	1.25	1.25	1.25	1.25	1.25	1.25	1.25	2.50
16	Total	125.00	125.00	125.00	125.00	125.00	125.00	125.00	125.00	125.00

table 10. Composition of unit dose of various Formulations Characteristics of final blend

6.7 Evaluation parameters

Physical appearance

The physical appearance of a tablet, its visual identity and over all "elegance" is essential for consumer acceptance. Included in this category are tablet sizes, shape, colour, presence or absence of any odour, taste, surface texture, physical flaws and consistency and legibility of any identification marking.

Weight variation

Twenty tablets were selected randomly from the lot and weighed individually to check for weight variation. Each tablet weight was then compared with average weight variation. Each tablet weight was then compared with average weight to ascertain the weight of the tablets within the permissible limits. Not more than two of the individual weights should deviate from the permissible limits. Not more than two of the individual weights should deviate from the average weight by more than 5% for >300mg tablets and none by more than double that percentage.

Percentage deviation= [(Tablet weight- Average weight)/tablet weight] ×100

S.No	Weight(mg)	Maximum percentage difference allowed
1.	130 or Less	10
2.	130 - 324	7.5
3.	More than 324	5

Table 11; USP Specification for uniformity of weight

Loss on drying

Loss on drying is an important parameter to determine the moisture intake by blend during processing. Limit on loss on drying is established from the sum of percentage moisture intake values of each excipient used in the process. Percentage moisture in take was determined during in process by using Ohaus Moisture Analyser. In which 1gm of blend was placed after tarring the instrument at 105°C in auto mode.

Friability

Friability test is performed to assess the effect of friction and shocks, which may often cause the tablet to chip, cap or break. Roche friabilator was used for the purpose. This device subjects number of tablets to the combined effect of abrasion and shock by utilizing a plastic chamber that revolves at 25 rpm dropping the tablets at a distance of 6 inches with each revolution. Pre-weighed sample of tablets were dusted and reweighed. Compressed tablets should not lose more than 1% of their weight.

$$\textbf{Percentage friability} = [(w_2 - w_1)/w_1] \times 100$$

Where, W_1 = Weight of tablets before test; W2= Weight of tablets after test

Thickness

The thickness was measured by using vernier calliper and values were tabulated. Ten tablets of each batch were measured. Average and standard deviation was calculated.

Hardness

The hardness of tablet is an indication of its strength. Measuring the force required to break the tablet across tests it. The force is measured in kg and the hardness of about 3-5 kg/cm2 is considered to be satisfactory for uncoated tablets. Hardness of 10 tablets from each formulation is determined by Erweka hardness tester.

Disintegration test

Breaking of tablets into smaller particles or granules is known as disintegration and time taken for breaking of tablets in a suitable medium is called disintegration time (DT). This test is not applicable to modified-release tablets and tablets for use in the mouth. For those tablets for which the dissolution test is included in the individual monograph, the test for disintegration is not required. It is determined by USP apparatus (Electro lab Disintegration Tester). It consists of 6 glass tube each 3 inches long, open at top and has 10 mesh screens at the bottom end of basket rack. One tablet is placed in each tube and placed in a one litre beaker of water, simulated gastric fluid or simulated intestinal fluid at $37 \pm 2^{o}C$. It moves up and down through a distances of 5 to 6 cm at 28 to 32 cpm.

Uncoated tablet has disintegration time as low as 5 minutes. Majority of tablets has DT of 30 minutes. DT of enteric coated tablet is one hour in simulated gastric fluid and two hours in simulated intestinal fluid. DT for dispersible and soluble tablets is within 3 minutes.

Contend uniformity

Uniformity of contend is a pharmaceutical analysis parameter for the quality control of tablets or capsules. Multiple capsules or tablets are selected at random and a suitable analytical method is applied to assay the individual content of the active ingredient in each tablet or capsule.

Blend uniformity

It is to check the formulation in blending process can find the drug substance which distrusted with all other ingredients evenly ratio of the blend that course in granulation process.

Stability Studies

The optimized formulation of ODTs is subjected to stability study as per ICH guidelines to assess their stability with respect to their physical appearance and release characteristics.

Moisture

Clean the container with lid dries it and weighs it (W1).Take a specimen of the sample in the container and weigh with lid (W2).Keep the container in the oven with lid removed. Dry the specimen to constant weight maintaining the temperature between 60º C to 100º C for a period varying with the type of sample but usually 16 to 24 hours. Record the final constant weight (W3) of the container with dried sample.

Assay

Different aliquots (mL) of $200\,\mu g\,mL^{-1}$ ZMT solution were accurately measured and transferred into a series of 10 mL volumetric flasks, and the total

volume was brought to 4.5 mL with methanol. To each flask 1 mL of 4% vanillin was added followed by 1 mL of concentrated H_2SO_4 and kept aside for 10 minutes; finally the volume was brought up to mark with methanol. The absorbance was measured at 580 nm versus reagent blank. A calibration graph was prepared by plotting the measured absorbance versus concentration. The concentration of the unknown was read from the calibration graph or computed from the regression equation derived using the Beer's law data.

Total impurity

A registration application should include documented evidence that the analytical procedures are validated and suitable for the detection and quantification of impurities. Technical factors (e.g., manufacturing capability and control methodology) can be considered as part of the justification for selection of alternative thresholds based on manufacturing experience with the proposed commercial process. The use of two decimal places for thresholds does not necessarily reflect the precision of the analytical procedure used for routine quality control purposes. Thus, the use of lower precision techniques (e.g., thin-layer chromatography) can be appropriate where justified and appropriately validated. Differences in the analytical procedures used during development and those proposed for the commercial product should be discussed in the registration application. The quantization limit for the analytical procedure should be not more than (≤) the reporting threshold.

The drug substance can be used as a standard to estimate the levels of impurities. In cases where the response factors of a drug substance and the relevant impurity are not close, this practice can still be appropriate, provided a correction factor is applied or the impurities are, in fact, being overestimated. Acceptance criteria and analytical

procedures used to estimate identified or unidentified impurities can be based on analytical assumptions (e.g., equivalent detector response). These assumptions should be discussed in registration applications.

6.8 Analytical methods

Method of analysis for Dissolution

Dissolution Parameters

Apparatus	USP Apparatus 2 (paddle)
RPM	50 RPM
Dissolution medium	pH 6.8 Phosphate buffer, 500 mL
Time	10, 20 and 30 minutes
Sample collection volume	10 mL
Temperature	37.0±0.5°C

Table 12: Dissolution parameters

6.9 Drug release kinetics:

Various models were tested for explaining the kinetics of drug release. To investigate the mechanism of drug release rate kinetics from the dosage form, the obtained data were fitted with zero-order, first-order, higuchi and korsmeyer - peppas release model.

Zero order release rate kinetics:

To investigate zero-order release kinetics, the drug release rate was fitted to the equation,

$$F = Ko.t$$

Where,

F = drug release, K= release rate constant and t = time taken for drug release. Plot of % drug release versus time is linear. **(Kenneth A Connors, 1991)**

First order release rate kinetics:

To investigate first-order release kinetics, the drug release rate data was fitted to the equation,

$$\text{Log } (100 - F) = K_t$$

A plot of Log % drug release versus time is linear. **(Kenneth A Connors, 1991)**

Higuchi release model:

To investigate Higuchi release kinetics, the release rate data were fitted to the following equation.

$$F = K_H\, t^{1/2}$$

Where K_H = Higuchi constant.

In Higuchi model, plot of % drug release verses square root of time is linear. (**Higuchi W I, 1962)**

Korsmeyer – peppas model:

To investigate Korsmeyer – peppas release kinetics, the release rate data were fitted to the following equation,

$$M_t/M_\infty = K.t^n$$

Where, M_t/M_∞ = fraction of drug released.

K = release constant.

t= time taken for release.

n= diffusion exponent.

If n is equal to 0.89, the release is zero order.

In this model, a plot of log (M_t/M_∞) versus log time is linear**. (Koresmeyer et al,. 1977)**

7. RESULTS AND DISCUSSION

7.1 Zolmitriptan Characteristics

Bulk density : 0.34 g / mL

Tapped density : 0.42 g / mL

Compressibility index : 19.05

Hausner ratio : 1.24

Loss on Drying (105°C / Automode) : 3.18%

PSD by Malvern master Sizer

d10 : 6 microns

d50 : 11 microns

d90 : 16 microns

Drug Manufacturer : Aurobindo Pharma, Hyderabad.

Batch No : ZIP1004110

7.2 Calibration curve data for Zolmitriptan

Concentration(µg/ml)	Absorbance
1	0.130±0.003
2	0.264±0.001
3	0.385±0.002
4	0.495±0.001
5	0.640±0.002
6	0.758±0.004
7	0.877±0.001
8	0.979±0.003

Table 13. Calibration curve data for Zolmitriptan in 0.1N HCL

Standard curve of Zolmitriptan In 0.1N HCL

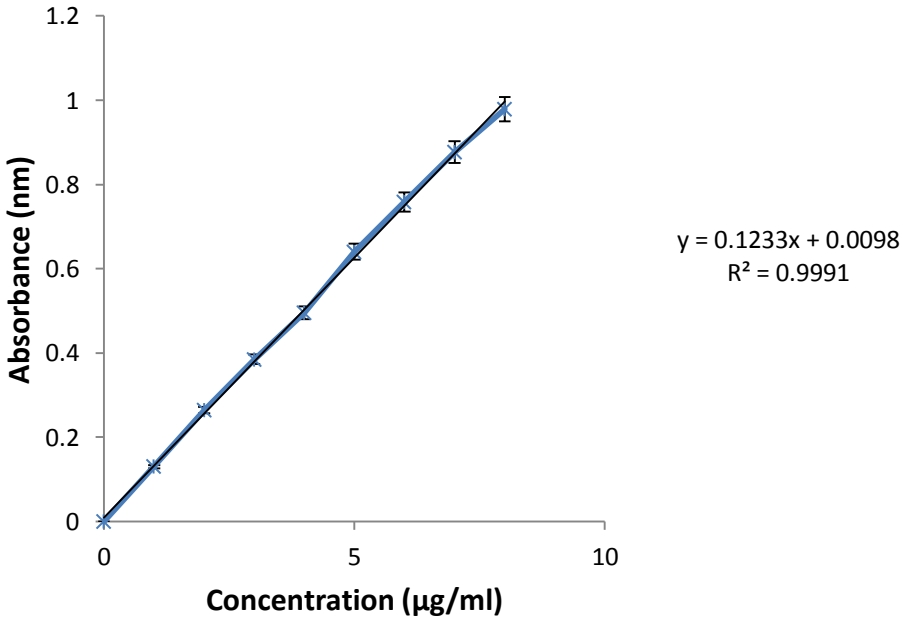


Figure 3: calibration curve of Zolmitriptan in .01N HCL

7.3 FTIR Spectra for Zolmitriptan

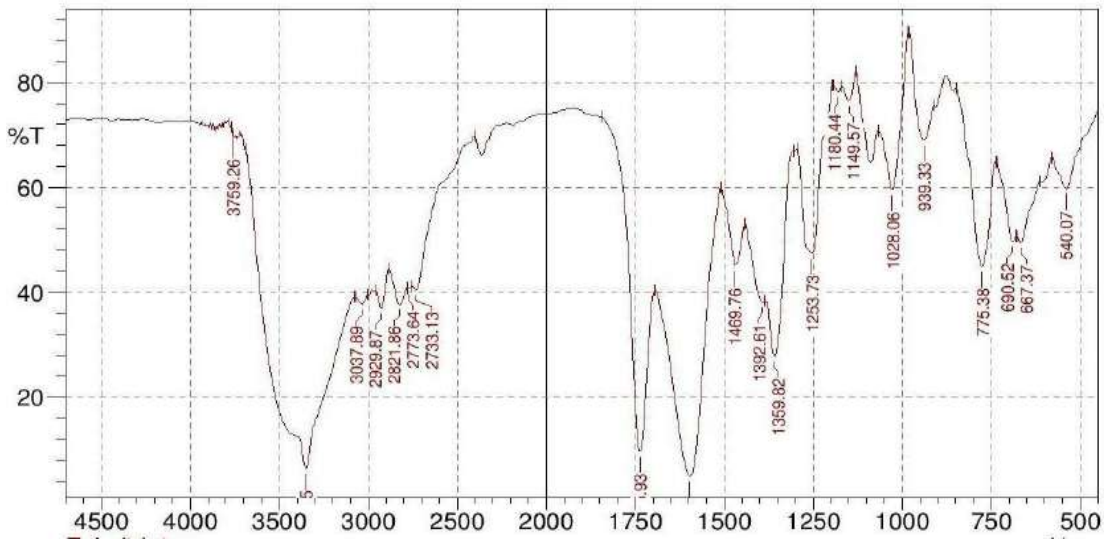


Figure 4: FTIR spectra of the Zolmitriptan

7.4 FTIR spectra for Zolmitriptan with excipients

7.4.1 FTIR spectra for Zolmitriptan with citric acid

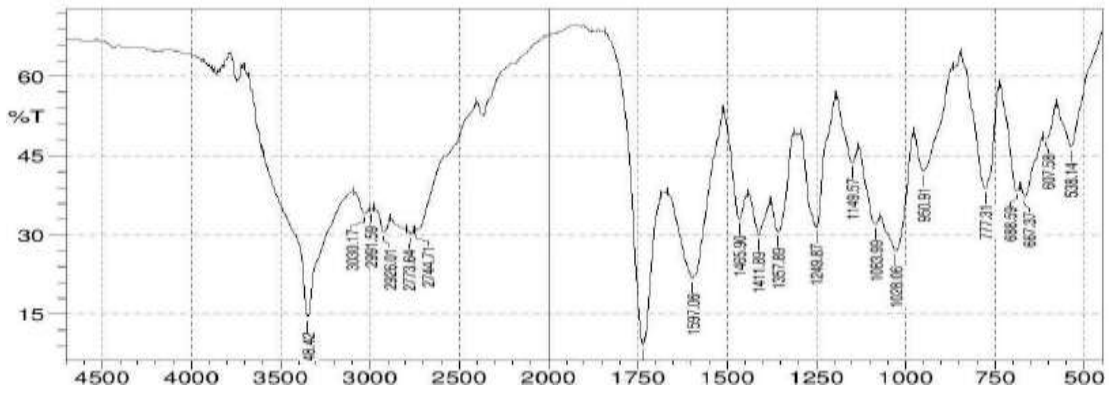


Figure 5: FTIR spectra for Zolmitriptan with citric acid

7.4.2 FTIR spectra for Zolmitriptan with sucralose

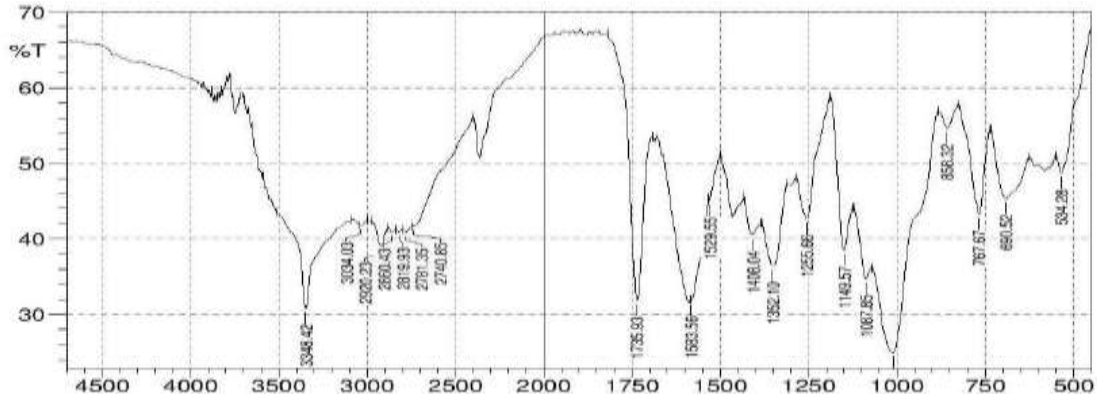


Figure 6: FTIR spectra for Zolmitriptan with sucralose

7.4.3 FTIR spectra for Zolmitriptan with mannitol

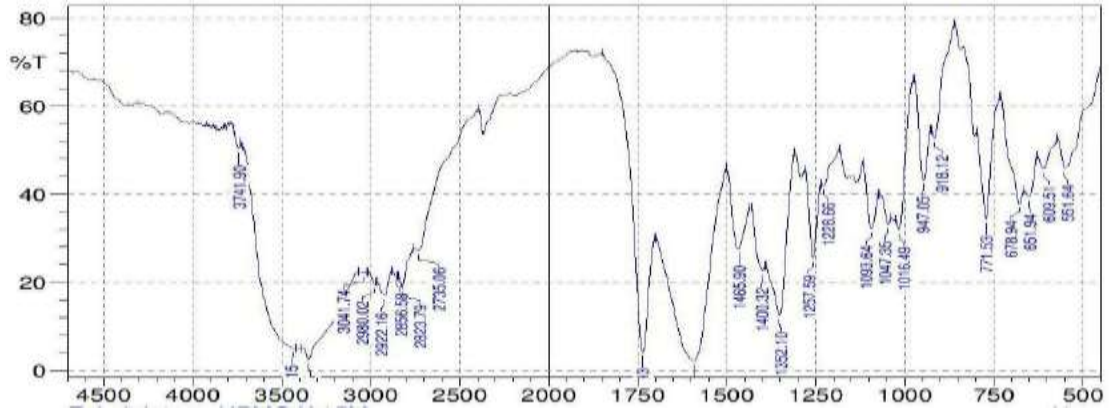


Figure7: FTIR spectra for Zolmitriptan with mannitol

7.4.4 FTIR spectra for Zolmitriptan with sodium Stearyl Fumarate

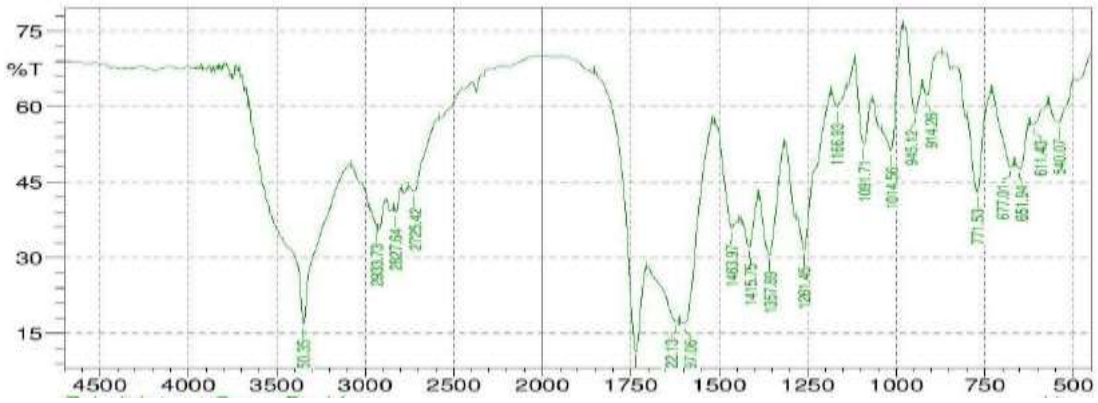


Figure 8: FTIR spectra for Zolmitriptan with sodium Stearyl Fumarate

7.4.5 FTIR spectra for Zolmitriptan with colloidal silicon dioxide

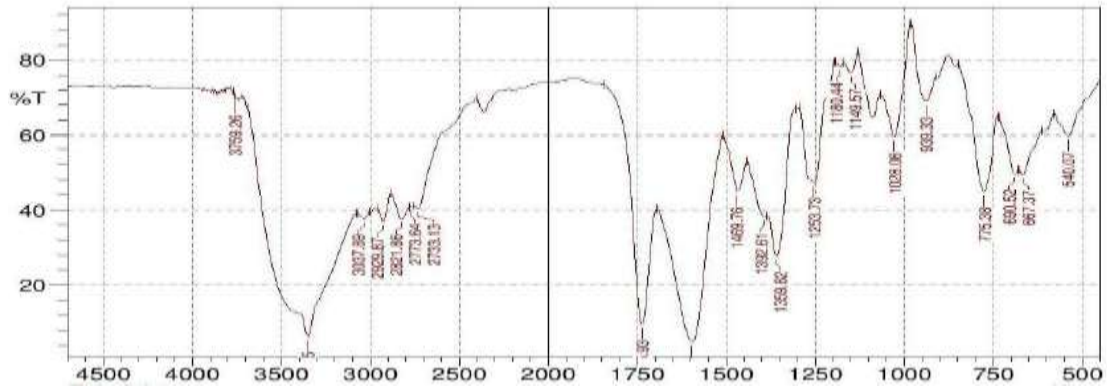


Figure 9: FTIR spectra for Zolmitriptan with colloidal silicon dioxide

7.4.6 FTIR spectra for Zolmitriptan with ethyl cellulose

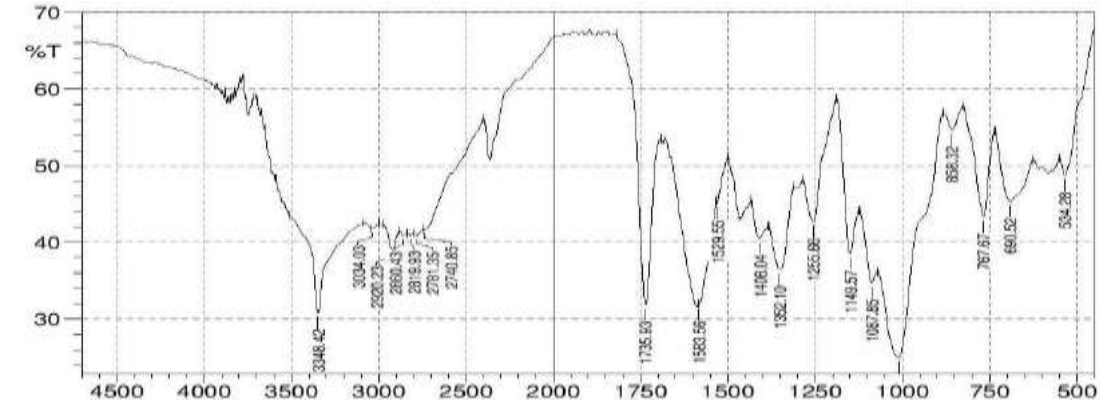


Figure 10: FTIR spectra for Zolmitriptan with ethyl cellulose

7.4.7 FTIR spectra for Zolmitriptan formulation FZ9

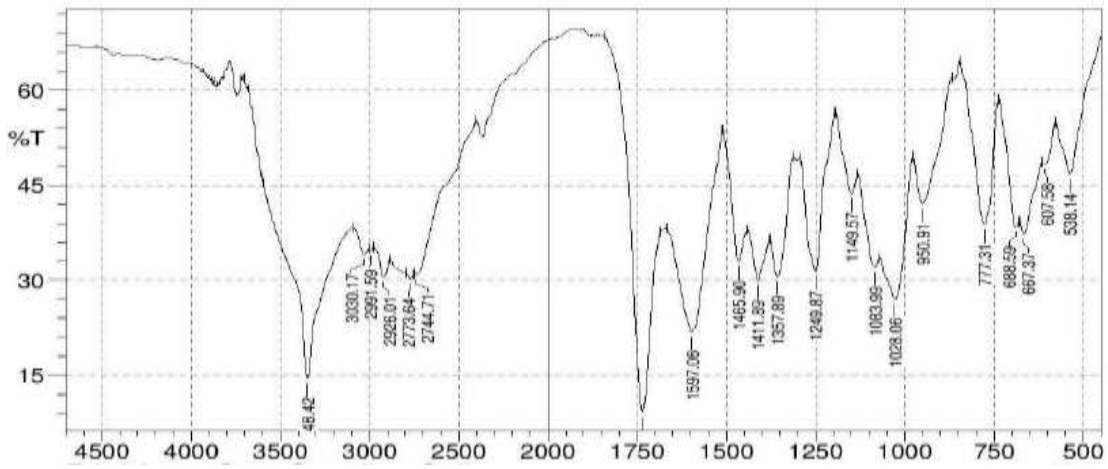


Figure 11: FTIR spectra for Zolmitriptan tablets

7.5 Drug and excipient compatibility studies of optimized formulation

The individual IR spectra of Zolmitriptan optimized formulation were shown in the figure. The following principle peaks were observed from the IR Spectral analysis.

The observed principle peaks were identical in the IR spectra of rug and the IR spectra of optimized formulation (FZ9). Hence there was no chemical or physical interaction between the drug and the excipient used in this investigation.

IR spectra of bands

S.No	Wave Number in cm^{-1}	Characteristic bands
1.	3551.32	O – H stretching
2.	3402.32	N – H stretching
3.	2931.47	C – H stretching
4.	1622.30	C = C stretching
5.	1455.80	C – H Bending
6.	1142.94	C – O stretching Ether
7.	1018.19	C – O stretching
8.	873.33, 766.75, 669.19,	C – H (OOP) For Aromatic rings
9.	465.97, 450.74, 444.88,	C – X stretching

Table 14. The principle peaks were observed from IR spectra of Zolmitriptan

Final blend was characterized with various parameters like bulk density, tapped density, angle of repose and loss on drying for each batch and their results were tabulated below.

S.	Parameters	FZ1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
1	Bulk Density(gm/mL)	0.33	0.35	0.36	0.34	0.38	0.38	0.41	0.39	0.41
2	Tapped Density (gm/mL)	0.38	0.39	0.4	0.38	0.48	0.48	0.51	0.49	0.50
3	Angle of Repose (°C)	33	31	31	32	31	31	29	29	28
4	Loss on Drying (%)	2.93	3.19	3.18	3.14	2.04	2.04	3.12	2.98	2.86

Table 15; Result for bulk density, tapped density, angle of repose and loss on drying.

7.6 Particle Size Distribution

Particle Size Distribution for final blend of the trial batches were performed and the results are tabulated below

S. No	Sieve size#	FZ 1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
1	20	0	0	0	0	0	0	0	0	0
2	40	0	2	1	1	1	0	0	0	0
3	60	5	10	11	12.1	12	7.5	15	15	11.1
4	80	30	5	6	7.2	5.5	5	5	20	13.9
5	100	10	5	7.5	9.4	9	17.5	5	17.5	19.4
6	140	10	43	46	43.8	42	5	20	20	27.8
7	200	7.5	20	17.5	15.4	17.6	17.5	20	17.5	16.7
8	Pan	27.5	15	11	11.1	12.9	37.5	35	10	11.1

Table 16; Particle size distribution results for the final blend

7.7 Blend Uniformity

Percentage content of samples from final blend of trial batches were analyzed and the results are tabulated below

S. No	Fz1	Fz2	Fz3	Fz4	Fz5	Fz6	Fz7	Fz8	Fz9
1	95.7	96.7	94.6	96.6	96.8	98.7	96.7	97.6	98.9
2	96.9	96.8	95.7	96.8	99.7	98.3	100.6	98.7	99.5
3	96.9	97.1	95.9	97.2	99.5	98.8	96.7	97.4	99.9
4	97.1	97.8	96.8	97.5	94.7	99.1	99.8	99.6	99.6
5	97.3	97.9	97.2	97.9	98.1	99.8	99.6	98.9	99.8
6	97.5	98.3	97.6	98.1	97.4	98.9	99.3	99.6	99.1
7	97.9	98.5	97.9	98.5	98.9	99.1	98.1	100.2	98.1
8	98.3	98.7	98.5	98.7	99.7	99.3	100.9	100.1	99.6
9	98.5	99.1	98.9	99.2	100.2	99.5	97.9	100	100.8
10	98.6	99.2	98.9	99.8	97.1	99.6	98.7	99.1	101.2
AVG	97.47	98.01	97.2	98.03	98.21	99.11	98.83	99.12	99.65
Min	95.7	96.7	94.6	96.6	94.7	98.3	96.7	97.4	98.1
Max	98.6	99.2	98.9	99.8	100.2	99.8	100.9	100.2	101.2
%RSD	0.92	0.93	1.49	1.06	1.76	0.46	1.50	1.00	0.89

Table 17. Results of Blend uniformity samples of final blend

7.8 Tablet Characterization

7.8.1Weight Variation:

Weight variation of all the batches were evaluated and the results are tabulated below

S. No	FZ1 (gm)	FZ2 (gm)	FZ3 (gm)	FZ4 (gm)	FZ5 (gm)	FZ6 (gm)	FZ7 (gm)	FZ8 (gm)	FZ9 (gm)
1	117.5	121.2	122.3	120.3	121.2	122.6	120.4	120.4	126.0
2	119.6	120.6	123.0	125.6	123.1	122.4	123.8	126.3	123.1
3	125.6	122.9	121.6	124.5	123.9	122.4	123.9	121.0	124.8
4	117.6	126.5	122.3	124.8	121.9	123.6	125.9	123.1	123.9
5	126.6	125.2	125.6	123.6	124.6	123.1	120.9	124.9	125.1
6	121.5	124.3	124.3	124.2	122.8	125.2	120.1	124.3	121.4
7	116.5	121.6	125.3	125.1	123.4	123.7	125.8	126.1	126.0
8	124.3	124.2	122.8	122.6	124.1	124.9	126.0	125.9	125.8
9	121.8	120.6	121.5	123.2	123.7	125.1	126.3	123.1	121.9
10	117.9	121.5	122.9	123.8	122.8	125.0	120.4	124.5	126.1
Avg	120.9	122.9	123.2	123.8	123.2	123.8	123.4	124.0	124.4
Min	116.5	120.6	121.5	120.3	121.2	122.4	120.1	120.4	121.4
Max	126.6	126.5	125.6	125.6	124.6	125.2	126.3	126.3	126.1

Table 18. Results for weight variation of the formulation

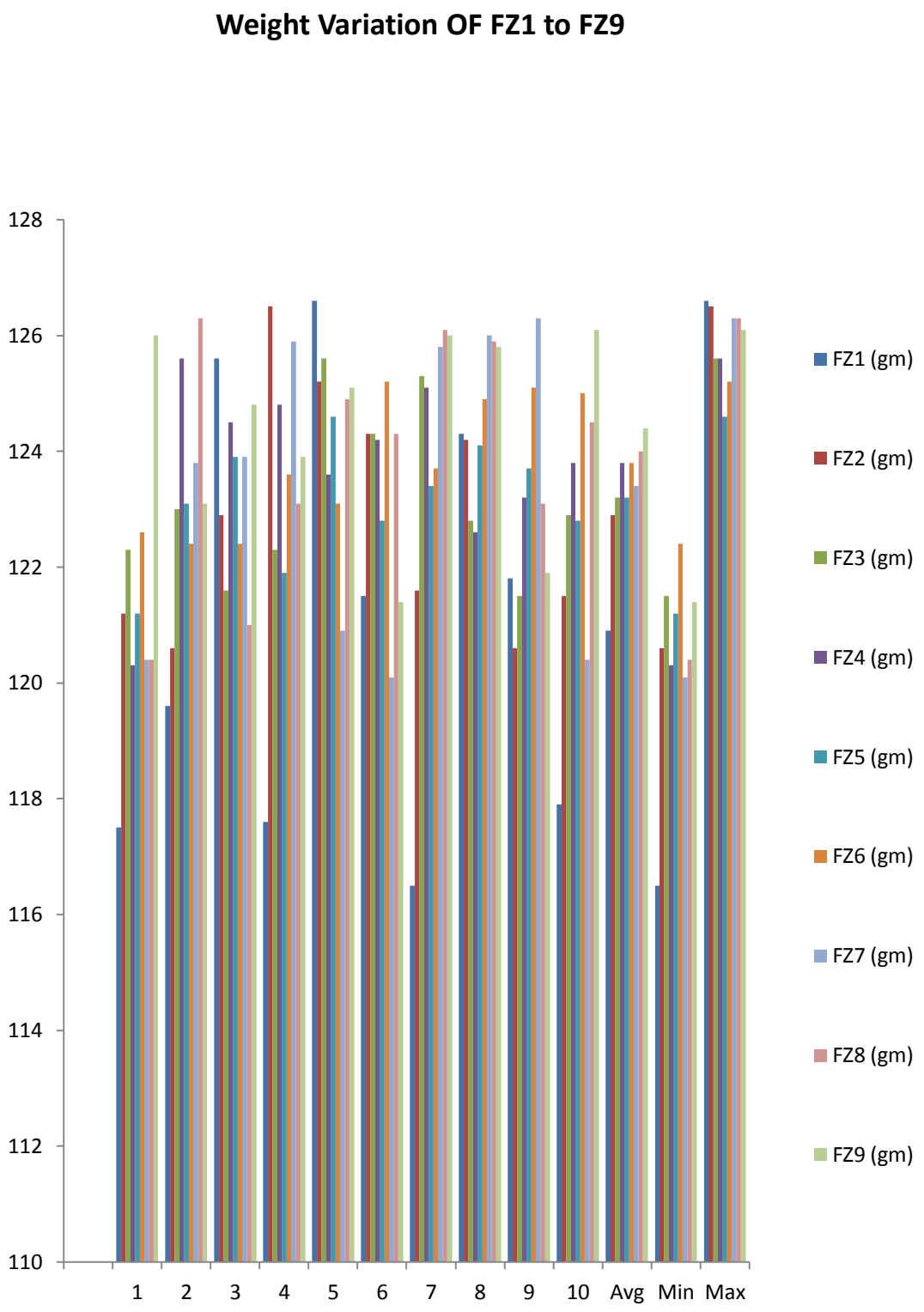


Figure 12; graphical representation of weight variation FZ1 to FZ9

7.9.2 Thickness

Thickness of ten tablets were evaluated from each batch and tabulated in the table below

S. No	FZ1 (mm)	FZ2 (mm)	FZ3 (mm)	FZ4 (mm)	FZ5 (mm)	FZ6 (mm)	FZ7 (mm)	FZ8 (mm)	FZ9 (mm)
1	2.62	2.85	2.88	2.91	2.82	2.89	2.93	2.93	2.9
2	2.65	2.86	2.89	2.85	2.82	2.89	2.97	2.93	2.99
3	2.68	2.81	2.87	2.86	2.91	2.86	2.96	2.94	2.91
4	2.65	2.83	2.86	2.87	2.91	2.87	2.97	2.97	2.93
5	2.64	2.85	2.87	2.86	2.91	2.86	2.97	2.94	2.91
6	2.68	2.86	2.88	2.85	2.83	2.87	2.98	2.93	2.93
7	2.69	2.87	2.89	2.84	2.82	2.86	2.93	2.98	2.94
8	2.64	2.85	2.85	2.87	2.83	2.86	2.97	2.96	2.94
9	2.65	2.83	2.87	2.86	2.83	2.95	2.96	2.97	2.94
10	2.63	2.87	2.89	2.89	2.9	2.94	2.95	2.97	2.93
Avg	2.65	2.85	2.88	2.87	2.86	2.89	2.96	2.95	2.93
Min	2.62	2.81	2.85	2.84	2.82	2.86	2.93	2.93	2.90
Max	2.69	2.87	2.89	2.91	2.91	2.95	2.98	2.98	2.99

Table 19.Thickness of tablets of the formulations

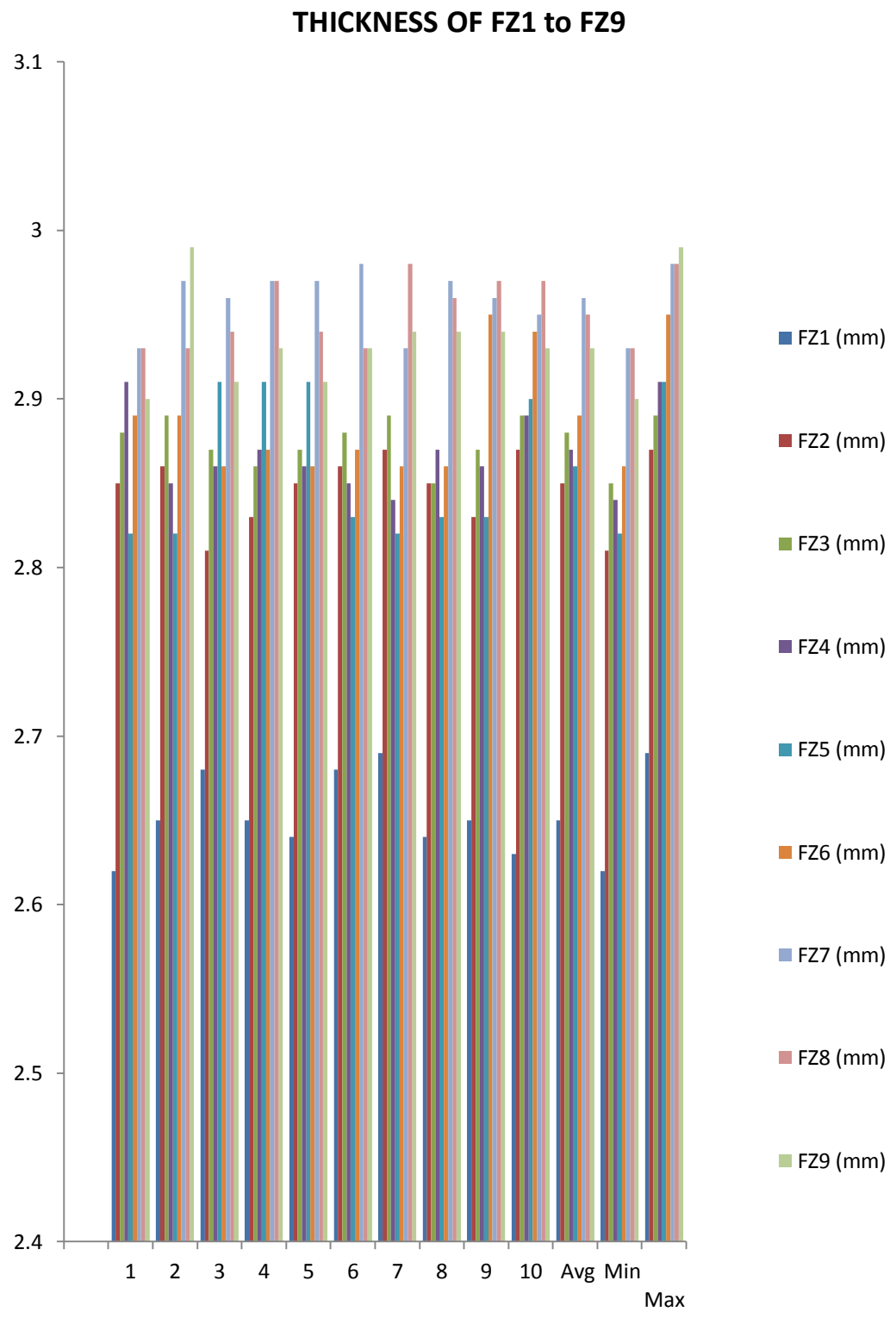


Figure13; graphical representation of thickness FZ1 to FZ9

7.9.3 Hardness:

Hardness for ten tablets for the trial batches was evaluated and the observation was tabulated below.

S.No	FZ1 (kg/cm^2)	FZ2 (kg/cm^2)	ZF3 (kg/cm^2)	FZ4 (kg/cm^2)	FZ5 (kg/cm^2)	FZ6 (kg/cm^2)	FZ7 (kg/cm^2)	FZ8 (kg/cm^2)	FZ9 (kg/cm^2)
1	3.4	3.4	4.3	4.0	3.1	3.6	4.0	4.1	3.5
2	3.6	3.5	4.0	4.8	3.8	3.8	4.0	4.5	3.9
3	3.6	3.6	3.9	4.6	3.7	3.2	3.8	4.4	3.5
4	3.8	3.5	3.8	4.7	3.6	3.8	3.6	4.6	3.6
5	3.5	4.3	3.7	4.1	3.9	4.1	3.9	4.1	3.8
6	4.3	3.7	4.4	4.2	4.1	3.9	4.1	4.3	4.5
7	3.9	3.8	4.7	4.1	4	4.3	4.8	4.5	4.6
8	3.5	4.1	4.6	3.6	4.7	4.6	4.3	3.9	4.4
9	4.1	4.2	4.8	3.9	4.5	4.5	4.9	3.8	4.1
10	4.1	4.2	3.6	3.6	4.2	4.1	3.9	3.9	4.0
Avg	3.8	3.8	4.2	4.2	4.0	4.0	4.1	4.2	4.0
Min	3.4	3.4	3.6	3.6	3.1	3.2	3.6	3.8	3.5
Max	4.3	4.3	4.8	4.8	4.7	4.6	4.9	4.6	4.6

Table 20. Hardness of ten tablets and its average for the formulations.

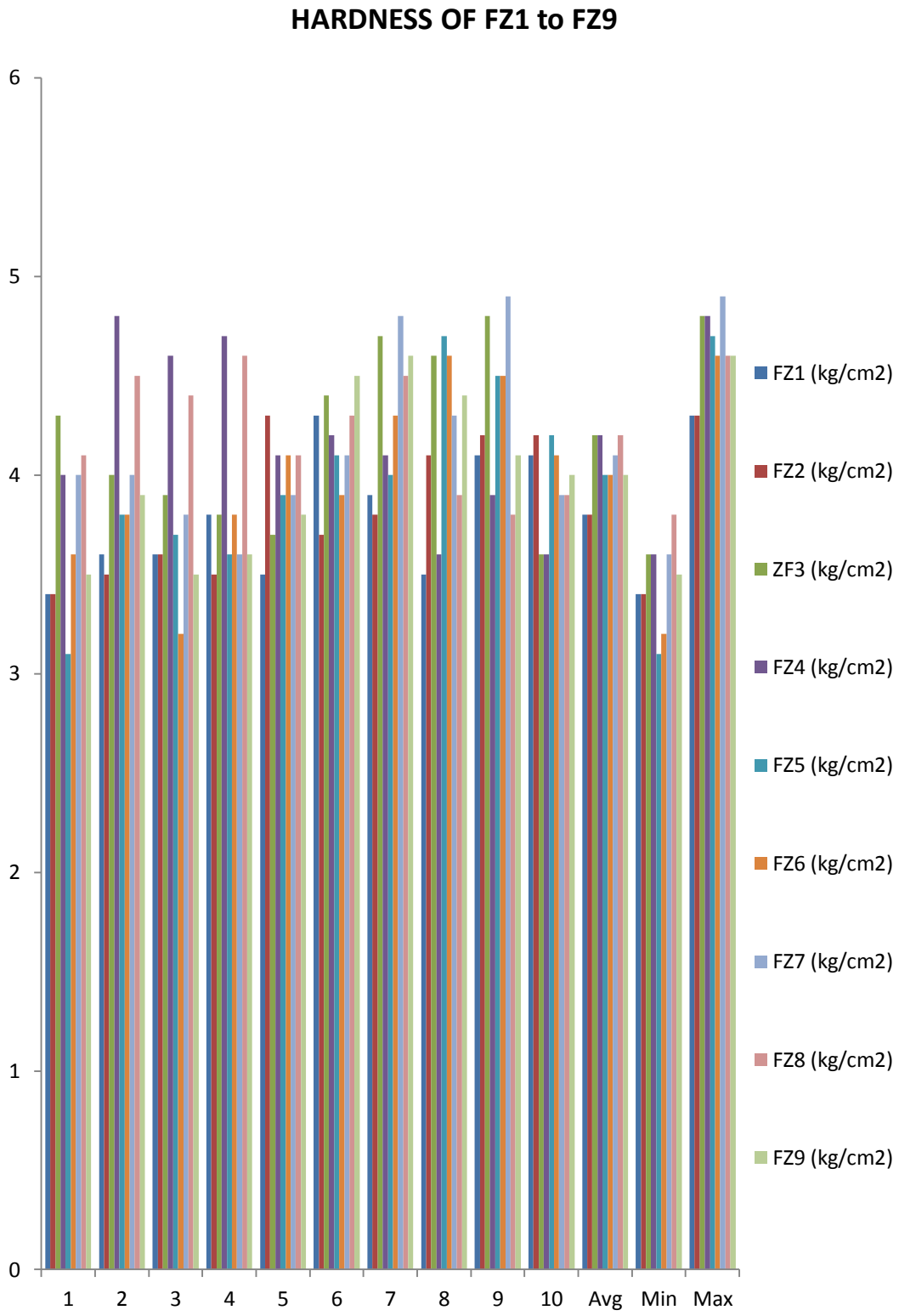

HARDNESS OF FZ1 to FZ9
6
5
4
3
2
1
0
1
2
3
4
5
6
7
8
9
10
Avg
Min
Max
FZ1 (kg/cm2)
FZ2 (kg/cm2)
ZF3 (kg/cm2)
FZ4 (kg/cm2)
FZ5 (kg/cm2)
FZ6 (kg/cm2)
FZ7 (kg/cm2)
FZ8 (kg/cm2)
FZ9 (kg/cm2)

Figure 14; graphical representation of hardness FZ1 to FZ9

7.9.4 Content Uniformity:

Ten tablets from each batch were analyzed for content uniformity and the results are tabulated in percentage is beneath.

S. No	FZ1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
1	98.7	99.9	98.6	99.9	99.7	96.7	98.9	99.6	98.9
2	102.3	96.6	98.2	101.1	96.5	100.3	98.6	98.4	100.1
3	103.1	98.7	99.1	98.6	96.9	98.1	98.7	99.8	99.6
4	99.2	97.8	98.3	97.7	97.9	99.2	97.2	96.4	99.8
5	99.6	99.9	100.6	98.2	99.1	96.5	99.1	100.1	98.6
6	104.3	99.5	97.3	98.6	99.3	99.8	99.7	99.8	98.9
7	100.3	99.1	99.6	100.8	95.8	100	99	99.1	100.1
8	95.6	99.6	98.3	98.9	99.1	99.9	99.2	99.6	99.9
9	96.6	99.9	97.9	102.3	99.5	100.8	99.7	100	100.3
10	100.9	99.3	99.6	99.2	99.7	100.3	99.5	98.9	99.7
AVG	100.06	99.03	98.75	99.53	98.35	99.16	98.96	99.17	99.59
Min	95.6	96.6	97.3	97.7	95.8	96.5	97.2	96.4	98.6
Max	104.3	99.9	100.6	102.3	99.7	100.8	99.7	100.1	100.3
%RSD	2.74	1.09	0.99	1.47	1.49	1.55	0.74	1.12	0.59

Table 21;Results of percentage content and %RSD of tablets of formulations

7.9.5 Friability:

Initial weight, final weight and percentage weight loss of tablets from each batch for checking whether they pass the test for friability. And the results are tabulated below.

Parameters	FZ1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
Initial Weight (gm)	6.7504	6.8002	6.7652	6.7786	6.8412	6.7351	6.7638	6.9967	6.8011
Final Weight (gm)	6.6918	6.7804	6.7700	6.7604	6.824	6.7102	6.7449	6.9716	6.7801
Percentage Weight loss (%)	0.87	0.29	-0.07	0.27	0.25	0.37	0.28	0.36	0.31

Table 22.Friability and its parameters for all the formulations

7.9.6 Disintegration Time:

Minimum and maximum time taken by the six tablets from each batch was noted and tabulated in the table below

Parameters	FZ1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
Minimum Time (min)	0’22	6'00	3'28"	1'45"	0’15	0’18	0’12	0’10	0’11
Maximum Time (min)	0’29	7'38"	4'45"	2'25"	0’21	0’24	0’16	0’15	0’16

Table 23. Disintegration time of each formulation

7.9.7Assay & Water by Kf

Results of assay and moisture content evaluated by karlfischer reagent was tabulated below

Parameters	FZ1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
Assay(%)	104.2	102.3	101.2	99.6	96.7	101.0	98.7	97.9	99.2
Water by Kf (%)	5.25	5.15	5.12	5.16	4.22	4.01	4.97	4.96	4.82

Table 24. Assay and water by kf results of the formulations.

7.9.8 Related substance

The analytical method for related substance was performed and the highest unknown impurity and total impurity values of the respective batches were tabulated below.

Parameters	FZ1	FZ2	ZF3	FZ4	FZ5	FZ6	FZ7	FZ8	FZ9
Highest Unknown Impurity (%)	0.09	0.77	0.33	0.11	0.23	0.39	0.03	0.02	0.03
Total Impurities (%)	2.29	2.95	3.00	3.01	3.20	3.19	0.07	0.08	0.06

Table 25. Highest unknown impurity and total impurities results of the respective formulations.

7.10 Dissolution

Percentage release of drug was analyzed during 15 minutes of dissolution and the results for the respective batches were tabulated below.

Formulations	5 min	10 min	15 min
FZ1	94.3±0.16	98.9±0.78	100.2±0.06
FZ2	66.8±0.48	85.9±0.95	94.8±0.07
FZ3	78.8±0.34	88.3±0.66	96.8±0.09
FZ4	88.0±0.38	94.2±0.57	98.8±0.04
FZ5	93.2±0.62	99.5±0.12	100.2±0.08
FZ6	86.5±0.41	96.4±0.18	99.7±0.02
FZ7	92.7±0.06	99.8±0.06	100.1±0.01
FZ8	94.8±0.09	100.1±0.12	99.8±0.04
FZ9	95.8±0.09	99.9±0.02	100.3±0.02

Table 26. Results of dissolution data of the formulations.

And the graphical representation of the batches is shown below.

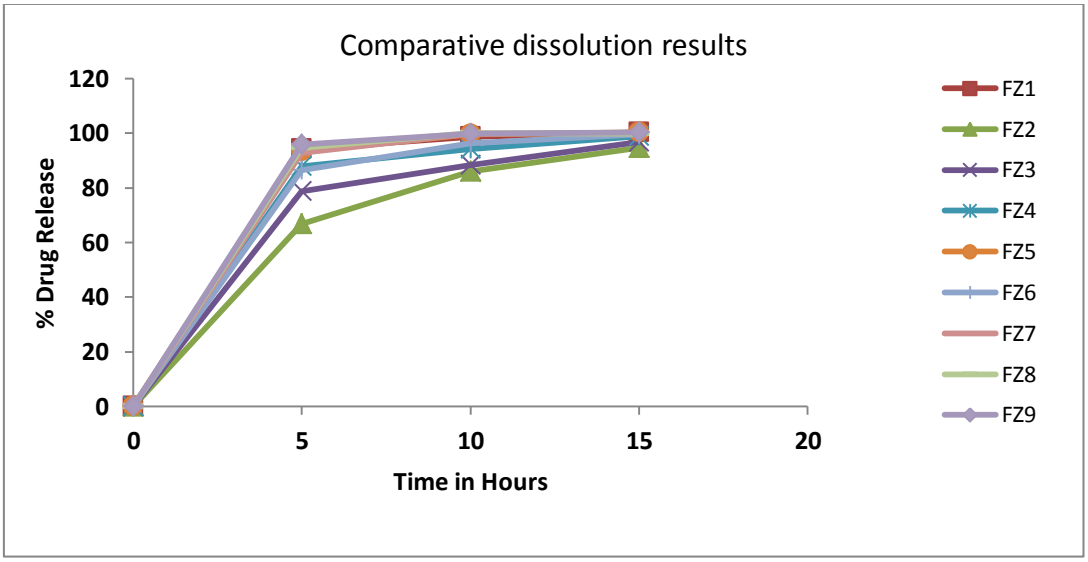


Figure 15: Graphical representation of Percentage dissolution of the formulations

7.11 Organoleptic evaluation

The organoleptic evaluation of the tablets was carried out and the observations of the respective batches were tabulated below.

Formulations	Organoleptic evaluation
FZ1	Average
FZ2	Average
FZ3	Average
FZ4	Average
FZ5	Average
FZ6	Average
FZ7	Good
FZ8	Good
FZ9	Good

Table 27; Organoleptic evaluation and its observation.

7.12 Accelerated stability studies

30 Tablets with one number of 1mg molecular sieve canister and 1g of oxygen absorber canister were used as desiccants along with 6g/yard of nylon coil as dunnage is packed in 75cc Heavy Weight HDPE Bottle capped with 33mm Child resistant closure having induction seal liner is loaded along with placebo for analytical use in each condition.

Condition : 40°C/75% RH- 1st Month

Description : White to off white colored plain flat bevel edged tablets

Water by Kf (%) : 5.16

Assay (%) : 99.7

7.12.1 Dissolution

Percentage drug release of the stability sample (40°C/75% RH- 1st Month) was evaluated and their result was tabulated in the table below.

S.No	Time(Min)	Percentage Drug Release
1	5	96.1±0.09
2	10	99.8±0.04
3	15	100.1±0.02

Table 28. Percentage drug release of Stability sample (40°C/75% RH- 1st Month)

And the graphical representation of the dissolution profile is shown below

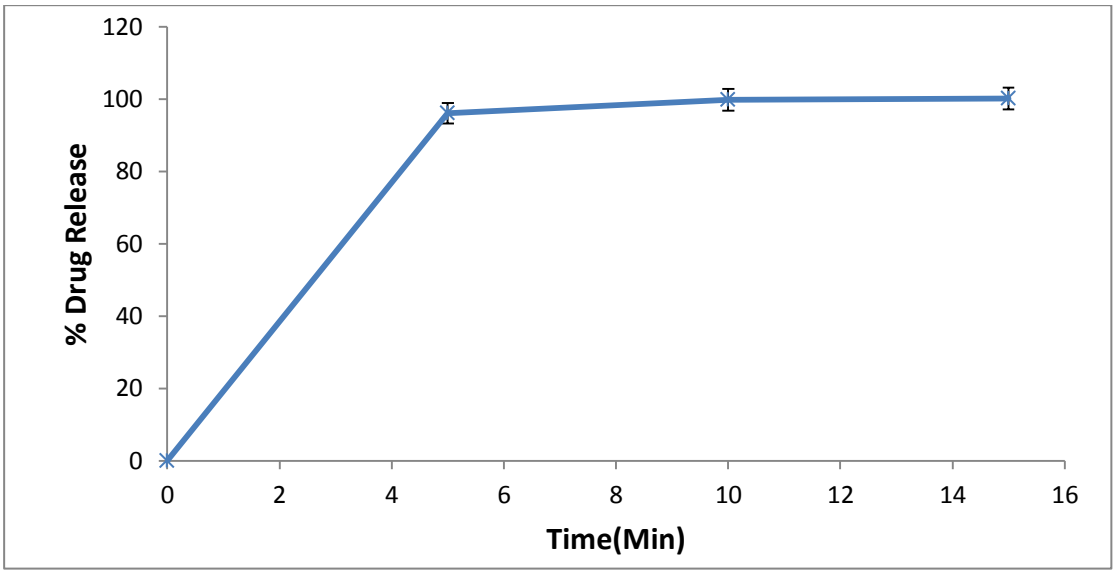


Figure 16: Percentage drug release of Stability sample (40°C/75% RH-1st Month)

Condition : 40°C/75% RH- 3rd Month

Description : White to off white colored plain flat bevel edged tablets

Water by Kf(%) : 5.46

Assay (%) : 99.6

7.12.2 Dissolution

Percentage drug release of the Stability sample (40°C/75% RH- 3rd Month) was evaluated and the results are tabulated.

S.No	Time (Min)	%Drug Release
1	5	97.4±0.07
2	10	99.8±0.05
3	15	100.3±0.02

Table 29. Percentage drug release of Stability sample (40°C/75% RH- 3rd Month)

And the graphical representation of the dissolution profile is shown below

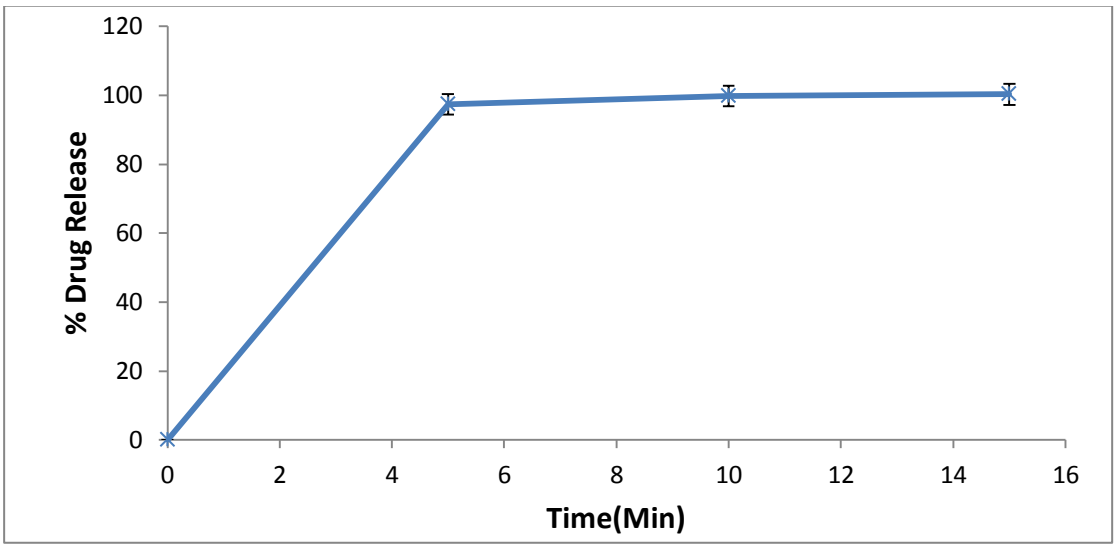


Figure 17:Percentage drug release of Stability sample (40°C/75% RH-3rd Month)

Condition: 40°C/75% RH- 6th Month

Description : White to off white colored plain flat bevel edged tablets

Water by Kf(%) : 5.61

Assay (%) : 99.8

7.12.3 Dissolution:

Percentage drug release of the Stability sample (40°C/75% RH- 6th Month) was evaluated and the results are tabulated.

S.No	Time(Min)	%Drug Release
1	5	95.2±0.05
2	10	98.7±0.03
3	15	99.8±0.02

Table 30. Percentage drug release of Stability sample (40°C/75% RH- 6th Month)

And the graphical representation of the dissolution profile is shown below

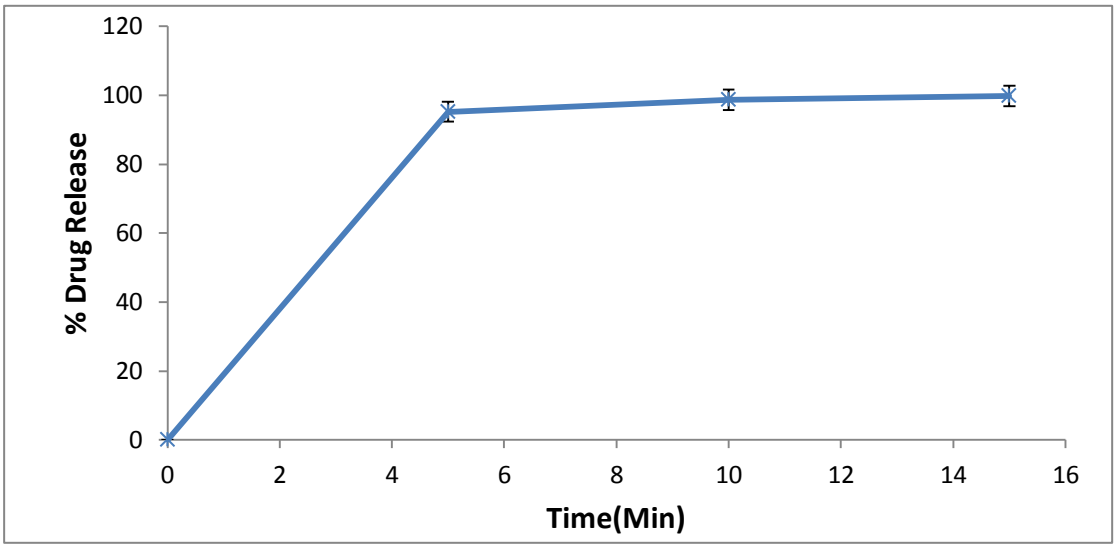


Figure18.Percentage drug release of Stability sample (40°C/75% RH- 6th Month)

7.13 Comparison drug release of optimized formulation and marketed preparation

Formulations	5 min	10 min	15 min
FZ9	95.8±0.06	99.9±0.02	100.3±0.02
Marketed product	94.5±0.09	100.1±0.12	99.8±0.04

Table 31. Comparison drug release of FZ9 and marketed preparation

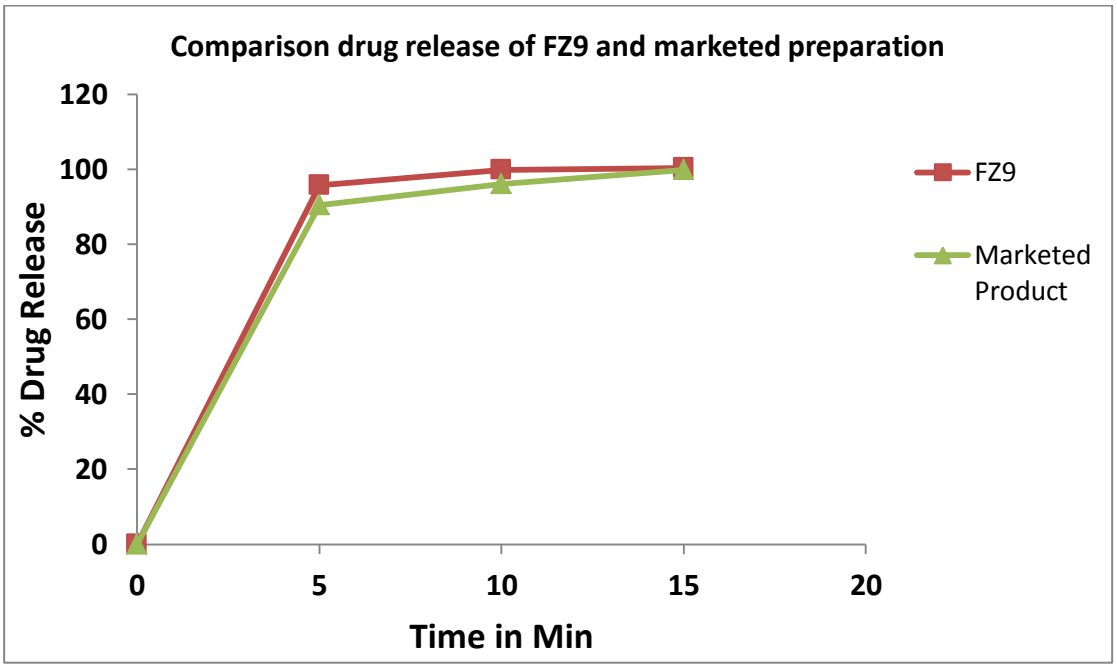


Figure 19: Comparison drug release of FZ9 and marketed preparation

7.14 COMPATIBILTY STUDY

Compatibility screening: Compatibility screening of a number of excipients were performed to obtain information regarding potential in compatibilities between Zolmitriptan and excipients, Closed vials containing the API blended with the excipients were incubated in oven at 40°/75%RH (2^{nd}& 4^{th} week) and 55°C (2 weeks) to mimic the conditions in the manufacturing process. No significant interactions between the drug and the excipients were observed. It was therefore concluded that

Zolmitriptan was compatible with commonly used excipients, including all excipients selected in the final formulation. The stability data generated for the compatibility screening is summarized. And the stability changes observed in API were initially noted and tabulated below

Drug	Tests	Initial	Duration / Storage conditions		
			2nd week 55°C	2nd week 40°C/75% RH	4th week 40°C/75% RH
Zolmitriptan	Assay %	99.5	100.3	100.7	99.1
	TI%	0.053	0.049	0.052	0.066
	Moisture%	0.18	0.43	0.13	0.37

Table 32. Stability changes in Zolmitriptan on storage in specific condition.

7.14.1 Compatibility study of drug and co processed excipients

Compatibility results of active pharmaceutical excipients with co processed excipients.

Zolmitriptan+ Excipients	Tests	Initial	Duration / Storage conditions		
			2nd week 55°C	2nd week 40°C/75% RH	4th week 40°C/75% RH
Zolmitriptan + Pearlitol Flash	Assay %	98.56	100.02	99.9	98.61
	TI%	0.198	0.173	0.108	0.103
	Moisture%	1.31	1.34	1.29	1.38
Zolmitriptan + Pharma burst	Assay %	97.99	95.39	97.6	97.55
	TI%	0.199	0.176	0.206	0.256
	Moisture%	0.45	0.67	0.77	0.89
Zolmitriptan+ PanExcea ODT	Assay %	97.32	99.89	96.13	99.01
	TI%	0.99	0.101	0.118	0.120
	Moisture%	0.31	0.25	0.24	0.33

Table 33. Compatibility study results with co processed excipients.

7.14.2 Compatibility of other diluents

Other commonly used diluents other than co processed excipients were also analyzed for compatibility with API. And the results are tabulated below.

Zolmitriptan+ Excipients	**Tests**	**Initial**	**Duration / Storage conditions**		
			2nd week 55°C	**2nd week 40°C/75% RH**	**4th week 40°C/75% RH**
Zolmitriptan+ Mannitol	Assay %	99.98	100.20	97.89	98.99
	TI%	0.063	0.044	0.079	0.082
	Moisture%	1.03	0.89	1.29	1.11
Zolmitriptan+ Ethyl cellulose	Assay %	98.66	98.18	100.42	99.85
	TI%	0.067	0.010	0.091	0.076
	Moisture%	1.01	1.37	1.47	1.69

Table 34: Compatibility study results with diluents with Zolmitriptan.

7.14.3 Compatibility with glidants and lubricants

Compatibility of various glidants and lubricants were analyzed and the results are tabulated below

API + Excipients	**Tests**	**Initial**	**Duration / Storage conditions**		
			2nd week 55°C	**2nd week 40°C/75% RH**	**4th week 40°C/75% RH**
Zolmitriptan +Colloidal Silicon Di oxide	Assay %	99.6	99.78	99.89	98.9
	TI%	0.099	0.045	0.067	0.100
	Moisture%	0.69	0.49	0.37	0.89
Zolmitriptan + Sodium Stearyl Fumarate	Assay %	100.53	100.01	99.01	99.97
	TI%	0.070	0.099	0.108	0.99
	Moisture%	0.71	1.00	0.99	1.10

Table 35: Compatibility of glidants and lubricants with Zolmitriptan

7.14.4 Compatibility study of Sweetening agents and flavouring agents

API + Excipients	Tests	Initial	Duration / Storage conditions		
			2^{nd} week 55°C	2^{nd} week 40°C/75% RH	4^{th} week 40°C/75% RH
Zolmitriptan API + Aspartame	Assay %	102.0	101.89	99.01	99.56
	TI%	0.099	0.106	0.078	0.136
	Moisture%	2.00	2.36	2.89	2.45
Zolmitriptan +Sucralose	Assay %	108.02	102.49	106.07	104.61
	TI%	0.080	0.555	0.076	0.949
	Moisture%	0.37	0.69	0.14	0.49
Zolmitriptan + Orange Flavor	Assay %	97.89	99.01	98.89	99.79
	TI%	0.023	0.067	0.081	0.091
	Moisture%	1.19	1.90	1.79	1.84
Zolmitriptan +Peppermint flavour	Assay %	99.01	99.76	97.89	96.9
	TI%	0.068	0.089	0.101	0.099
	Moisture%	0.77	0.90	1.07	0.68
Zolmitriptan +Citric Acid	Assay %	97.89	96.99	97.09	98.00
	TI%	0.099	0.089	0.067	0.023
	Moisture%	1.02	1.08	1.80	1.78

Table 36; Compatibility of flavour and sweetening agents with Zolmitriptan

7.15 Comparison of optimized formulation and marketed ODT preparation

S.No	Characteristics	Optimized formulation	Marketed preparation
1	Avg weight	125mg	180mg
2	Hardness	$4kg/cm^2$	$4.7kg/cm^2$
3	Thickness	2.93mm	3.6mm
4	Friability	0.31%	0.85%
5	Disintegration time	0’11	0’18
6	Dissolution	100.3%	99.1%
7	Weight variation	99.52%	100.5%
8	Mouth feel	Compare to better	Good
9	Assay (Avg)	99.6%	99%

Table 37; Comparison of optimized formulation and marketed ODT preparation

7.18 Drug release kinetics studies

7.18.1 Zero order release kinetics

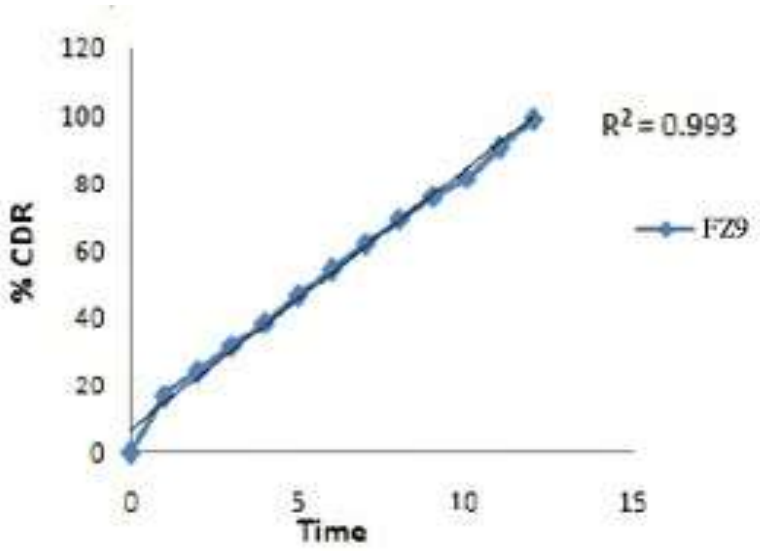


Figure 20; zero order release kinetic studies

7.18.2 First order release kinetics

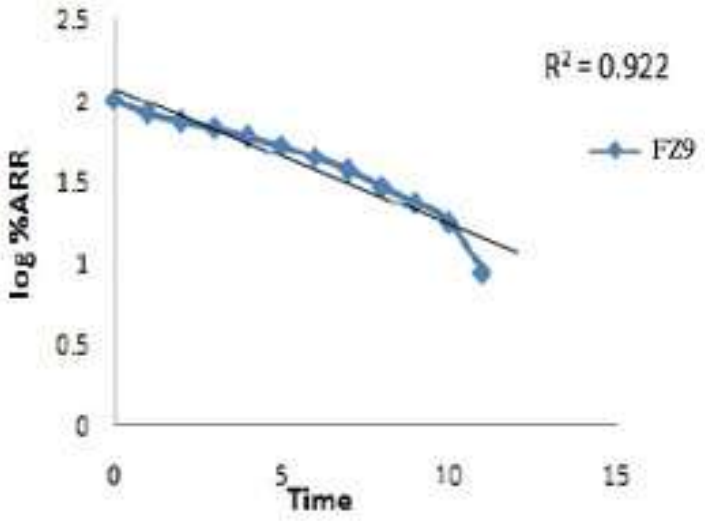


Figure 21; first order release kinetic studies

7.18.3 Higuchi release kinetics

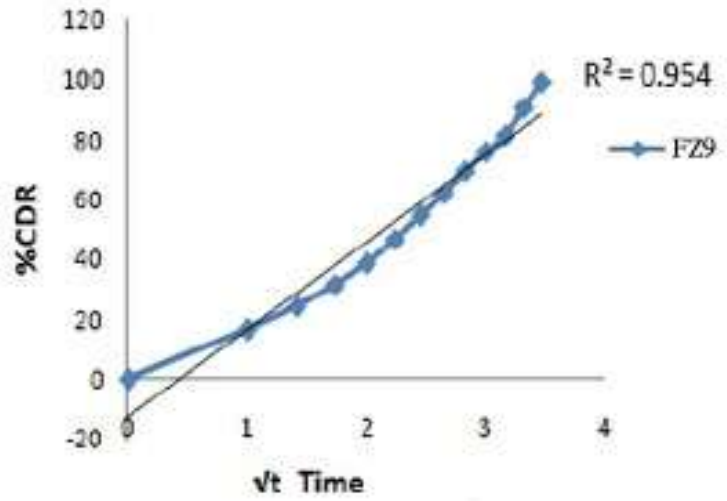


Figure 22; Higuchi release kinetics

7.18.4 Hixon-crowell cubic root kinetics

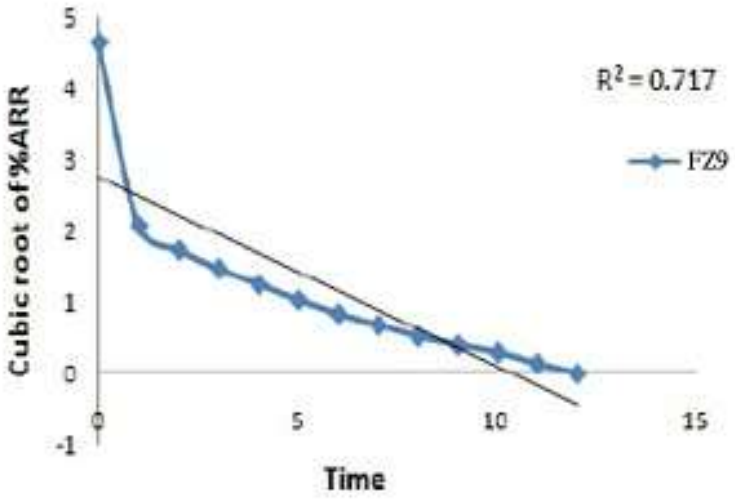


Figure 23; Hixon-crowell cubic root kinetics

7.18.5 Korse meyer peppas kinetics

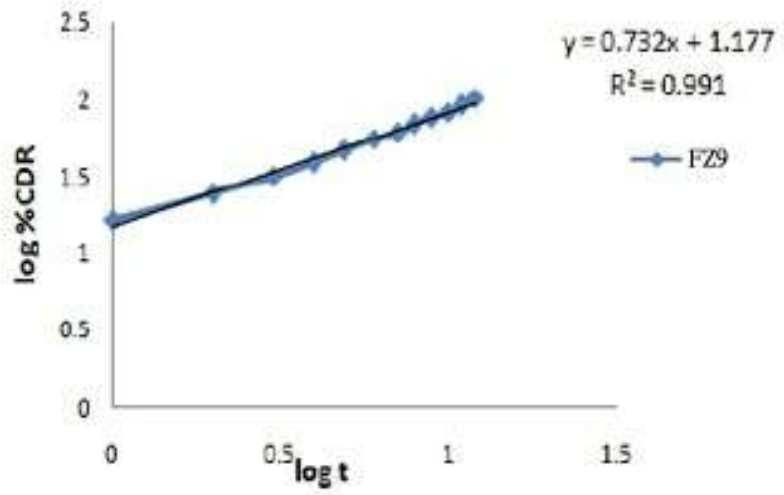


Figure 24; Korse meyer peppas kinetics

Regression values(R^2)	FZ9
Zero order release kinetics	0.993
First order release kinetics	0.922
Hixon-crowell cubic root kinetics	0.954
Higuchi release kinetics	0.717
Korse meyer peppas kinetics	0.991

Table 38: Regression values of in-vitro release kinetic study optimized Zolmitriptan immediate release Tablet (FZ9)

On the basis of highest f_2 and lowest f_1 value, the formulation FZ9 was chosen or drug release kinetic and mechanism of release studies. The in vitro dissolution data of Zolmitriptan immediate release tablets (FZ9) were fitted in different kinetic models viz. zero order, first order, Higuchi, Hixson-Crowell and Korse Meyer- Peppas equation; and the graphs were plotted figure. The Korse Mayer Peppa's kinetic plots

were found to be fairly linear as indicated by their highest regression values (0.991) for FZ9 formulation. The release exponent 'n' for optimized formulation FZ9 was found to be 0.991 ($0.5 < n < 1$), that appears to indicate a coupling of the diffusion and erosion mechanism so-called anomalous diffusion. So in present study in vitro drug release kinetic of Zolmitriptan immediate release tablet followed Peppas release kinetic model and the drug release mechanism was said to be anomalous diffusion coupled with erosion. The regression values of all the release kinetics were presented in the table 38.

DISCUSSION

Zolmitriptan fast dissolving tablets were prepared by direct compression method using superdisintegrants is Pharmaburst ODT, in varying concentrations.

Angle of repose: is 28° shows good flow**.**

Bulk density and tapped density: is 0.410(g/ml) and 0.500 (g/ml), respectively. The values for compressibility index and Hausner ratio is 19.05 and 1.24, respectively. The results for pre-compressed parameters are shown in Table 15.

Weight variation test is found 121.4 mg to 126.1 mg as per IP specification. Friability: Less than 0.31%, the results indicate that the percentage losses were not more than 1.0% (complies IP specifications). Thickness: Range from 2.90 mm to 2.99 mm; the results indicate that the tablets are suitable for packing.

Content uniformity was found in between 98.62% and 100.3%. Hardness of the tablet was found to be between 4 to 4.6 kg/cm^2. The results indicate that the tablets are mechanically strong and are in limit.

Disintegration time which was in-between 0'11 sec to 0'16 sec, the results indicate that disintegration time of tablets is within 30 seconds.

Dissolution study was carried out in 6.8 pH phosphate buffer for formulations FZ1, FZ2, FZ3, ZF4, FZ5, ZF6, FZ7, FZ8, and FZ9 from time 0 to 15 min, the results are shown in Table 26. And % assay for optimized batch was found to be 99.2 % as shown in Table 24

Comparative dissolution study was carried out in 6.8 pH phosphate buffer for formulations FZ9 and marketed product. The results are shown in table 31 and figure 19.

Storage condition: Tablets were stored at 45°C ± 2°C/75% for a storage period of 0, 30, 60, and 90 days, Hardness was increased with time but in all cases, hardness was within the limit. Disintegration time: At various storage conditions increases but maximum 20 sec which is < 30 seconds (specification of IP). Dissolution studies shows there was no significant change in dissolution data of formulations at initial and after specified storage period.

8. CONCLUSION

Orodispersible tablets of Zolmitriptan are prepared by direct compression method. The formulation FZ9 containing 10% of superdisintegrant (i.e) Pharmaburst ODT has shown best release with 100.3% at the end of 15minuts. The effervescent mixture further assists in taste masking of Zolmitriptan.

According to FTIR studies there is no incompatibility shown in FZ9. The formulation FZ9 was stable at 40°C±2ºC and 75%RH±5%RH.

In conclusion formulation FZ9 achieved the targets of the present study such as,

- Not require water to swallow, but it should dissolve or disintegrate in the mouth in matter of seconds.
- To mask the bitter taste.
- Have a pleasant mouth feel.
- Rapid dissolution of drug and absorption which may produce rapid, onset of action.
- Improved bioavailability.

9. BIBLIOGRAPHY

- Abdelbary G, Prinderre P, Eouani C, Joachim J, Reynier JP, Piccerelle Ph. The preparation of orally disintegrating tablets using a hydrophilic waxy binder. Int. J. Pharm. 2004; 278, 423–433.
- Ademir Barianni Rodero, Lucasde Souza Rodero, Reinaldo Azoubel. Toxicity of Sucralose in Humans: A Review. Int. J. Morphol., 2009; 27(1), 239-244.
- Ahmed IS, Nafadi MM, Fatahalla FA. Formulation of fast-dissolving ketoprofen tablet using freeze-drying in blisters technique. Drug Dev. Ind. Pharm. 2006; 32, 437-442.
- Allen LV, Wang B, Devies JD. Rapidly dissolving Tablets. US patent 6,066,2001; 337
- Alshehri SM, Park JB, Alsulays BB, Tiwari RV, Almutairy B, Alshetaili AS, Morott J, Shah S, Kulkarni V, Majumdar S, Martin ST, Mishra S, Wang L, Repka MA. Mefenamic acid taste-masked oral disintegrating tablets with enhanced solubility via molecular interaction produced by hot melt extrusion technology. 2012; 7(1), 127-135
- ArunArya, Amrish Chandra, Vijay Sharma and KamlaPathak. Fast Dissolving Oral Films: An Innovative Drug Delivery System and Dosage Form. Int.J. ChemTech Res. 2010; 2(1), 576-583.
- Aurora J, Pathak V. Oral disintegrating technologies: Oral disintegrating dosage forms: An overview. Drug Deliv Technol, 2005; 5(3): 50-54.
- Balmuralidhara V, Sreenivas SA, Gangadharappa HV, Pramod KTM. Investigationon the effect of different disintegrants on the orodispersible

tablets of rabeprazole: Asian journal of Scientific Research. 2009; 2 (4), 190-7.

- Battu SK, Repka MA, Majumdar S, Madhusudan RY. Formulation and evaluation of rapidly disintegrating fenoverine tablets: effect of superdisintegrants. Drug DevInd Pharm, 2007 Nov; 33(11), 1225-32.
- Bhowmik D, Chiranjib B, Krishnakanth, Pankaj, Chandira RM. Fast Dissolving Tablet: An Overview.Journal of Chemical and Pharmaceutical Research.2009; 1(1), 163-77.
- Bhupendra G. Prajapati, Satish N. Patel. Formulation, Evaluation and Optimization of Orally Disintegrating Tablet of Cinnarizine. e- Journal of Science & Technology, 5 sept 2010; 5, 9-21.
- Bi Y, Sunada H, Yonezawa Y, Danjo K, Otsuka A, Iida K. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. Chem. Pharm. Bull. 1996; 44, 2121-2127.
- Dinkar Sharma, Reetika Chopra, NeenaBedi. Development and evaluation of Paracetamol taste masked orally disintegrating tablets using polymer coating technique. Int J Pharm Sci; 4(3), 129-134.
- El-Setouhy DA, Basalious EB, Abdelmalak NS. Bioenhanced sublingual tablet of drug with limited permeability using novel surfactant binder and microencapsulated polysorbate: In vitro/in vivo evaluation. Eur J Pharm. Aug 2015; 94, 386-392.
- Farshid A, Rama B, GopalMuralidharan, NargundLvg. Formulation and evaluation of orodispersible tablets of Zolmitriptan. Asian J Pharm Clin Res, 2014; 7(1), 127-134.

- Gattani SG, Shiyani BG, Kakade KN, Patil AB, Surana SJ. Formulation and development of mouth dissolving tablet of Ondensetron hydrochloride by using superdisintegrants. Indian drugs.2009; 46: 44-50.
- Gillis PMV, Deconde VFV. Fast-dissolving Galanthamine hydrobromide tablet, US patent 6,099,863; 2000.
- Government of India Ministry of Health & Family Welfare. Indian Pharmacopoeia. Delhi: Controller of Publications; 2007, 1689-1690.
- Guideline for stability testing (SADC). [Cited 2004 Jan 1]; Available from: http://www.ich.org.
- HazeePeera N, Lohithasu D, Sahool SK, M. Santhosh Naidu, Mani Kumar K,
- Jaysukh J Hirani, Dhaval A Rathod, Kantilal R Vadalia.Tropical Journal of Pharmaceutical Research, April 2009; 8 (2), 161-172.
- Karsano, Juanita Tanuwijaya, DityaFatma. Formulation of Ibuprofen Orally Disintegrating Tablets (ODT's) by lyophlization method using gelatin and Mannitol.Int.J.PharmTech Res. 2014; 6(3), 996-1002.
- Koizumi IK. New Method of Preparing Highly Porous Rapidly saliva Soluble Tablets by Sublimation Technique. Int. J. Pharm. 1997; 152, 127-131.
- Kumar A, Garg T, Sarma GS, Rath G, Goyal AK. Optimization of combinational intranasal drug delivery system for the management of migraine by using statistical design. European Journal of Pharmaceutical Sciences. 5 April 2015; 70, 140-151.
- Liberman H, Lachman L.The Theory and Practice of Industrial Pharmacy, Third Edition, 1991, 293.

- Makino T, Yamado M, Kikuta JI. Fast Dissolving Tablet. US patent 5, 1998; 720, 974;.
- Manoj Ashok Wagh, Kothawade Parag Dilip, Kishor Sahebrao Salunkhe, Nayana VijayChavan, Vandana Radheshyam Daga. Techniques used in orally disintegrating drug delivery system, International Journal of Drug Delivery; 2010; 2, 98-107.
- Migraine[cited2013august1].Availablefrom:http://en.wikipedia.org/wiki/Migraine.
- Note for guidance on stability testing. Stability testing of new drug substances and products [cited 2008 Aug 02]; Available from: URL: http://www.tga.gov.
- Perissutti B, Rubessa F, Moneghini M, Voinovich D. Formulation design of carbamazepine fast-release tablets prepared by melt granulation technique. Int. J. Pharm. 2003; 256: 53–63.
- Prajapati ST, Patel MV, Patel CN.Preparation and evaluation of sublingual tablets of zolmitriptan. International Journal of Pharmaceutical Investigation, January 2014,4 (1),27-31.
- Pramod K, Rajkapoor B. Development of Zolmitriptan gels for nasal administration. Asian J Pharm. 2012; 5(3), 45-62.
- Priyanka Nagar, Kusum Singh, ItiChauhan, MadhuVerma, MohdYasir, Azad Khan, Rajat Sharma, Nandini Gupta. Orally disintegrating tablets: formulation, preparation techniques and evaluation. Journal of applied Pharmaceutical Science, 2011; 01(04), 35-45.

- RakeshPahwa, Mona Piplani, Prabodh C Sharma, DhirenderKaushik, Sanju Nanda.Orally disintegrating tablets- Friendly to Pediatrics and gediatrics.Arch. Apll. Sci. Res., 2010; 2(2), 35-48.
- RakeshPahwa, Mona Piplani, Vipin Kumar Garg, RekhaRao, Lamba HS. Formulation and evaluation of orally disintegrating tablets: Comparison of Natural and Synthetic Super disintegrants. Der Pharmacia Lettre, 2011;3 (2), 407-418.
- Reddy L. H, Ghosh B, and Rajneesh. Fast dissolving drug delivery systems: a review of the literature. Indian Journal of Pharmaceutical Science. 2002; 64(4): 331- 336.
- Sastry SV, Nyshdham JR, Fix JA. Recent technological advances in oral drug delivery: A review. Pharmaceutical Science and Technology Today. 2000; 3:138-45.
- Sharma Deepak, Kumar Dinesh, Singh Mankaran, Singh Gurmeet, RathoreMahendra Singh. Taste masking technologies: A novel approach for the improvement of organoleptic property of pharmaceutical active substance.IRJP. 2012; 3(4), 108-116.
- Shinde AKJ, Waghule AN, Paithane A, Harinath N. Development and characterization of oral fast dissolving tablet of nifedipine using camphor as a subliming material. RJPBCS, 2010 Jan; 1(1), 46.
- Subedi RK, Ryoo JP, Moon C, Choi HK. Influence of formulation variables in transdermal drug delivery system containing zolmitriptan. International Journal of Pharmaceutics, 31 October 2011, 419 (1-2), 209-214.
- Suresh B, Rajendar KM, Ramesh G, Yamsani MR. Orodispersible tablets: an overview. Asian J Pharm. 2008; 2(1), 2-11.

- The role of lubricants in solid oral dosage manufacturing. [Cited 2013 Aug].Available from:www.carterpharmaceuticalconsulting.com/articles/role-of-lubricants-in-solidoral-dosage manufacturing.html.
- Velmurugan S, Vinushitha S (2010) Oral Disintegrating Tablets: An Overview. Int J Chem Pharm Sci 1: 1-12.