FORMULATION AND CHARACTERIZATION OF RIZATRIPTAN BENZOATE SUBLINGUAL TABLET WITH VARIOUS PERMEATION ENHANCERS

A Dissertation submitted to

THE TAMILNADU Dr. M.G.R. MEDICAL UNIVERSITY

CHENNAI – 600032

In partial fulfillment of the requirements for the award of degree of

MASTER OF PHARMACY IN PHARMACEUTICS

Submitted by

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Under the guidance of

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April - 2014

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EVALUATION OF THESIS

This is to certify that the research work embodied in this thesis entitled

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was carried out by

Reg. No.261211258

at College of Pharmacy, Madras Medical college

is evaluated and approved for award of the degree of

Master of Pharmacy in Pharmaceutics by The Tamil Nadu Dr. M.G.R. Medical University during the academic year 2013-2014.

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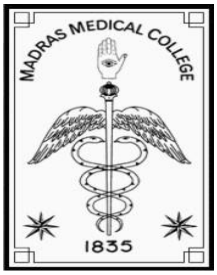
Place: Chennai



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DECLARATION BY THE CANDIDATE

I hereby declare that this thesis entitled

"FORMULATION AND CHARACTERIZATION OF RIZATRIPTAN BENZOATE SUBLINGUAL TABLET WITH VARIOUS PERMEATION ENHANCERS"

is a bonafide and genuine Research work

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ACKNOWLEDGEMENTS

"God is like a big circle, whose centre is everywhere but circumference is nowhere"

I take this opportunity to thanks ***LORD BALAJI*** *who always kept a blessing hand which protected me from falling down and kept me enthusiastic to keep going on.*

First and foremost indebt to my ***DAD, MOM AND BROTHER*** *for all their hard work to bring me up with a high quality education.*

I am immensely thankful to Respected ***Dr. A. Jerad Suresh M.Pharm., Ph.D., MBA.,*** *Principal and Professor of Pharmaceutical Chemistry, College of Pharmacy, Madras Medical College, Chennai-03 for granting me permission of carrying out my research work.*

I consider myself most lucky to work under the competent guidance of ***Prof. K. Elango M.Pharm., (Ph.D.),*** *Professor and Head, Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai-03. I take this opportunity to express my heartfelt gratitude to my reverend guide. His discipline, principles, simplicity, caring attitude and provision of fearless work environment will be cherished in all walks of my life.*

I am very much grateful to him for his valuable guidance and ever-lasting encouragement throughout my course.

It is my privilege to express my gratitude and heartfulness to my guide ***Dr. N. Deattu M.Pharm., (Ph.D),*** *Tutor, Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai-03, for his constant guidance and*

tremendous encouragement and his optimistic approach in bringing out this project as a successful one.

It is a great pleasure to extend my thanks to all my staff members of the Department of Pharmaceutics ***Mrs. S. Daisy Chellakumari M.Pharm., (Ph.D.)*** *and* ***Mrs. R. Devi Damayanthi M.Pharm., (Ph.D.)*** *for their precious suggestions and benevolent attention.*

I extend my thanks to ***Mr. R. Marthandan*** *(Lab supervisor) and* ***Mrs. R. Shankari*** *(Lab technician), Department of Pharmaceutics, College of Pharmacy, Madras Medical College, Chennai-03.*

I express my special thanks to ***Drugs Inspectors Mr. P. Vijayan M.Pharm.,*** *and* ***Mr. M.P. Muralikrishnan M.Pharm.,*** *for arranging me gift samples of Excipients to carry out my project work.*

I extend my special thanks to ***Mr. V. Surendran B.Pharm.,*** *and* ***Mr. S. Chinnaraja M.Pharm.,*** *for arranging me gift samples of API to carry out my project work.*

I am extending my special thanks to ***Bench Chemist Mr. S.P. Boopathy M.Pharm.,*** *for providing me IR analytical results of samples.*

I am extending my special thanks to ***Apex pharmaceutical Pvt. Ltd., Chennai, Madras Pharmaceuticals Pvt. Ltd., Chennai*** *and* ***Panvo Organics Pvt Ltd, Chennai*** *for providing me gift samples of API and Excipients to carry out my project work.*

I take great pleasure in sharing the credit of this project with my dear friends ***S. Chinnaraja, D. David Selvakumar, S. Kishore Kumar, Al. Akilandeswari, V. Catherin, B. Priya, R. Rajakumari and G. Suhasini*** *for giving me encouragement and timely suggestions.*

I extend my thanks to my juniors ***D. Jaison, K. Gnanasuriyan, B. Prabakaran, V.Sundarraj, D.Renuka, M. Adhi Lakshmi, T.Chitra, R. Elavarasi, S. Kiruthika*** *and* ***K. Thangalakshmi*** *for timely help.*

I extend my thanks to my juniors ***Mr. Selvam*** *and* ***Mr. Thiyagarajan*** *for timely help.*

I also express my sincere thanks to all my juniors and UG students for their timely help.

And above all, words fail to express my feeling to my dear brother

P. Sankar,

his constant source of inspiration and encouragement those days with him.

"Remembering you is easy, I do it everyday. Missing you is the heartache that never goes away".

I really miss you my dear brother.

DEDICATED TO MY BELOVED PARENTS, BROTHER AND SANKAR

CONTENTS

LIST OF ABBREVIATIONS

RZB	Rizatriptan Benzoate
Conc.	Concentration
^0C	Degree Centigrade
FT-IR	Fourier Transform Infra-Red
g	Grams
mg	milligram
mcg/µg	microgram
µg/ ml	microgram per milliliter
mL	Milliliter
mins/ min/ M	Minutes
secs/sec/s	Seconds
mm	Millimeter
No./#	Number
S.No	Serial Number
%	Percentage
RH	Relative Humidity
UV	Ultra Violet
λ_{max}	Absorption maxima
ID	Internal Diameter
rpm	Revolution Per Minute
nm	Nanometer
NC	No Changes
Cm^{-1}	Per Centimeter
ICH	International Conference on Harmonization
HCl	Hydrochloride
HPMC	Hydroxy Propyl Methyl Cellulose
SSG	Sodium Starch Glycolate

CCS	Cross Carmellose Sodium
PVP	Poly Vinyl Pyrrolidine
ANOVA	Analysis of Variance
HPLC	High Performance Liquid Chromatography
MTH	Metoclopromide HCl
IR	Infra-Red
mmHg	millimeter of Mercury
COX-2	Cycloxygenase-2
ODT	Orodispersible Tablet
BCS	Biopharmaceutical Classification System
5HT	5-Hydroxy Triptamine
CGRP	Calcitonin Gene Related Peptide
CSD	Cortical Spreading Depression
NK	Neurokinin
API	Active Pharmaceutical Ingredients
MEKC	Micellar Electrokinetic Chromatography
DMSO	Dimethyl Sulphoxide
CNS	Central Nervous System
MAO-A	Mono Amine Oxidase-A
Hrs/h	Hours
C_{max}	Maximum Concentration
CAS	Chemical Abstract Service
mRNA	Messenger Ribonucleic Acid
NADH	Nicotinamide Adenine Dihydrogen
SP	Substance-P
BoNT-A	Botulinium Toxin-A
NSAIDS	Non-Steroidal Anti-Inflammatory Drugs
H_3	Histamine
GABA	Gamma Amino Butyric Acid
WHO	World Health Organization

BP	British Pharmacopeia
Ph.Eur	European Pharmacopeia
USP-NF	United Sates Pharmacopeia- National Formulary
IP	Indian Pharmacopeia
JP	Japanese Pharmacopeia
KBr	Potassium Bromide

Introduction

1. INTRODUCTION

Development of a formulation involves a great deal of study and experimental work to get optimum results. While doing so we have to keep in mind various factors like choice of excipients, drug bioavailability, drug stability in required dosage form, cost effectiveness, manufacturing aspects, the patients' compliance and convenience.

Nowadays formulation research is breaking barriers of conventional methods. Today, active ingredients can be delivered with a level of convenience, performance and bioavailability.

First pass metabolism can be overcome by sublingual drug delivery and quick drug delivery into the systemic circulation can be obtained. Sublingual administration can offer an attractive alternative route of administration. The advantage of the sublingual drug delivery is that the drug can be directly absorbed into systemic circulation bypassing enzyme degradation in the gut and liver. These formulations are particularly beneficial to pediatric and geriatric patients. In addition, sublingual mucosa and abundance of blood supply at the sublingual region allow excellent drug penetration to achieve high plasma drug concentration with rapid onset of an action. [1, 2]

1.1 Oral Mucosa

Oral mucosal drug delivery is an alternative method of systemic drug delivery and offers several advantages over both injectable and enteral methods. Because the oral mucosa is highly vascularized, drugs that are absorbed through the oral mucosa directly enter the systemic circulation, bypassing the gastrointestinal tract and first-pass metabolism in the liver. For some drugs, this results in rapid onset of action via a more comfortable and convenient delivery route than the intravenous route. Not all drugs, however, can be administered through the oral mucosa because of the characteristics of the oral mucosa and the physicochemical properties of the drug. [3]

The mucosal lining of the oral cavity are readily accessible, robust and heal rapidly after local stress or damage. Oral mucosal drug delivery systems can be localized easily and are well accepted by patients. Therefore, it is evident that the oral cavity can serve as a site for systemic drug delivery. The total surface area of the oral cavity is about 100 cm. The mucosal membrane of the oral cavity can be divided into five regions: the floor of the mouth (sublingual), the buccal mucosa (cheeks), the gums (gingiva), the palatal mucosa

and the lining of the lips. These oral mucosal regions are different from each other in terms of anatomy, permeability to drug and their ability to retain a system for a desired length of time. The buccal mucosa is less permeable than the sublingual mucosa. [4] In addition, the sublingual route has general advantages over other delivery routes, such as nasal, pulmonary, oral and transdermal systems.

Advantages

- Rapid onset of effect - particularly good for pain, emesis, insomnia or allergy relief
- Easy, painless, discrete and convenient self-administration
- Virtually all of drug absorbed across mucosa, none swallowed
- Avoids first pass liver metabolism
- Less variability in therapeutic effect, more predictable pharmacokinetics
- Optimal effect achieved with less drugs, less side effects
- No need for water, easy for patients who have difficulty in swallowing
- Inexpensive to manufacture per dose
- Flexible formulation options
- No irritation or damage to tissues
- For drugs which are unstable in gastric pH
- The blood supply is rich with a capillary network close to mucosa

Within the oral mucosal cavity, delivery of drugs is classified into three categories,

1. Sublingual delivery: This is systemic delivery of drugs through the mucosal membranes lining the floor of the mouth.[5]
2. Buccal delivery: This is the drug administration through the mucosal membranes lining the cheeks (buccal mucosa).[6]
3. Local delivery: This is drug delivery into the oral cavity.[7]

1.1.1. Sublingual absorption

Sublingual literally meaning “Under the Tongue”, refers to a method of administering substances via the mouth in such a way that the substances are rapidly absorbed via the blood vessels under the tongue rather than via the digestive tract. The

route of absorption via the highly vascularized buccal mucosa allow the substance a more direct access to the blood circulation, thus providing direct systemic administration.

Medically, sublingual drug administration is applied in the field of cardiovascular drugs, steroids, some barbiturates and enzymes. It has been a developing field in the administration of many vitamins and minerals which are found to be readily and thoroughly absorbed by this method. [8, 9]

There is considerable evidence that most sublingual substances are absorbed by simple diffusion; the sublingual areas acting rather like litmus paper, readily soaking up the substance. However, not all substances are permeable and accessible to the buccal mucosa. The mucosa functions primarily as a barrier-similar to skin. It was once believed that the barrier of human skin was 'impenetrable' (e.g., Vitamins E and C creams, hormones, nicotine patches) but still it is a growing field of endeavor. Similarly the buccal mucosa presents an ideal site for absorption.

One of the best known drugs used regularly with great success is glyceryl trinitrate a potent coronary vasodilator which is used for the rapid symptomatic relief of angina. It has been found impressively effective and when administered sublingually; pharmacologically active after only 1-2 minutes. The administration via an aerosol spray was found to provide rapid relief of symptoms, with first-pass metabolism. The extent of first-pass metabolism when compared to the sublingual spray decreased to 48% with sublingual tablets and 28% with oral dose.[10]

Following sublingual administration, nitrates appears in plasma, concentration can be maintained for 24 hrs. Sublingual verapamil (a calcium channel blocker prescribed for the management of angina, hypertension and certain supraventricular arrhythmias) was effective in controlling the ventricular rate in patients symptomatically and rapidly appeared in the plasma following sublingual administration.[11] Experiments with some analgesics showed many times more rapid absorption from the mouth than the less lipid soluble morphine. Impressive absorption has been attained with sublingual administration of desoxycortisone acetate, morphine, captopril, nifedepine and 17-β oestradiol interestingly; it has also been shown that the sublingual administration of 17-β Oestradiol requires only one fourth of the oral dose. [12, 13, 14]

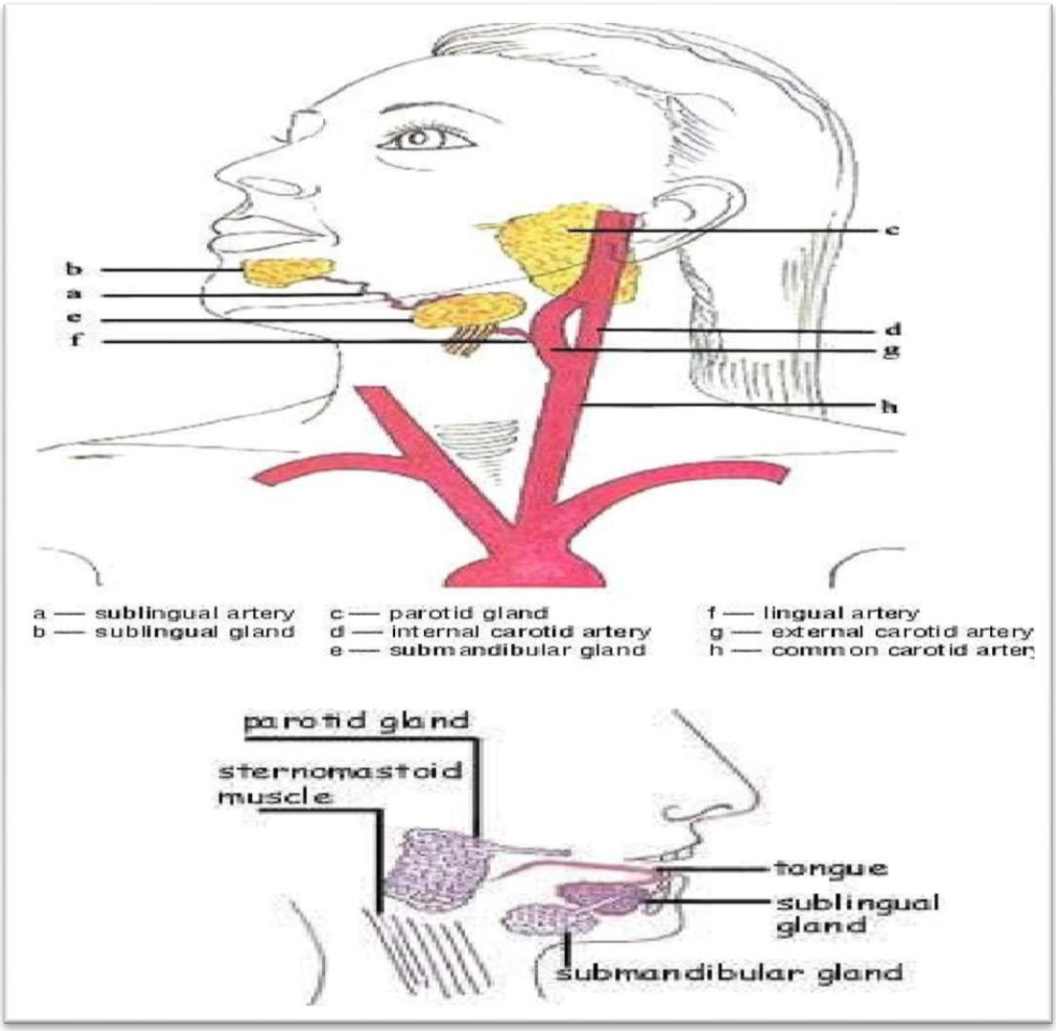


Figure: 1.1. Diagram of Sublingual Gland and Sublingual Artery

1.1.2 The mechanism of Sublingual absorption [8, 9]

The absorption potential of the buccal or sublingual mucosa is influenced by the lipid solubility and therefore the permeability of the solution (osmosis), the ionization (pH) and the molecular weight of the substances. For example, absorption of some drugs via buccal or sublingual mucosa epithelium. It is also unlikely that active transport processes operate within the oral mucosa. However, it is believed that acidic stimulation and uptake into the circulatory system occurs.

The mouth is lined with mucous membrane which is covered with squamous epithelium and contains mucous glands. The buccal mucosa is similar to the sublingual mucosal tissue.

The salivary glands consist of lobules of cells which secrete saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the parotid, the

submandibular and the sublingual which lies on the floor of the mouth. The more acid the taste, the greater the stimulation of salivary output, serving also to avoid potential harm to acid sensitive tooth enamel by bathing the mouth in copious neutralizing fluid. With stimulation of salivary secretion, oxygen is consumed and vasodilator substances are produced and the glandular blood flow increases, due to increased glandular metabolism.

The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighbouring muscles and to the mucous membranes of the mouth, tongue and gums. Two symmetrical branches travel behind the jaw bone under the tongue to meet and join at its tip. Another branch meets and anastomoses with the sub mental branches of the facial artery. The sublingual artery system stems from the lingual artery – the body's main blood supply to the tongue and the floor of the mouth – which arises from the external carotid artery. The proximity with the internal carotid artery allows fast access to its route supplying the greater part of the cerebral hemisphere.

1.1.3 Osmosis [8, 15]

In order for a nutrient to be effectively absorbed sublingually, it needs to be able to travel across the buccal mucosa membranes by a process of diffusion known as osmosis which applies to all forms of absorption by the body, governing both intestinal and sublingual absorption. The distribution of water across the cell walls depends on the osmotic difference in the blood, between the intracellular and extracellular fluid. The distribution of water across the blood vessel walls is determined by the *in-vivo* osmotic pressure of plasma and the total outward hydrostatic pressure. Unlike the cell membrane, the capillary wall is freely and rapidly permeable to small molecules.

The diffusion of water across a membrane that is only permeable to water depends on the molecular weight of the particle. Small particles that readily dissolve in water, rarely present a problem in permeation and diffusion, and so are able to move freely between the tissues of the body. Active transportation into cells leads to rapid metabolism of the substances. Molecules such as glucose (fructose) and amino acids are essential for cell metabolism and special mechanisms have evolved to facilitate their rapid diffusion and permeation across cell membranes.

1.1.4 Structure of Oral Mucosa [16]

In general terms, the oral mucosa is made up of an outermost layer of stratified squamous epithelium, which is covered with the mucous and consists of stratum

distendum, stratum filamentosum, stratum suprabasale and a stratum basale. Below these lie a basal lamina, the lamina propria and the sub mucosa. The epithelium serves as the mechanical barrier that protects underlying tissues, whereas the lamina propria acts as a mechanical support and also carries the blood vessels and nerves. Some regions of the oral mucosa are keratinized, whereas others are not. The non-keratinized regions, such as buccal and sublingual are more permeable than the keratinized regions. This is due to some extent, to the composition of intracellular lipids comprising the particular region. Whereas keratinized regions contain predominantly neutral lipids (ceramides). Non-keratinized areas are composed of glycosyl ceramides that appears to be derived from membrane coating granules that differ morphologically from the lamellate membrane-coating granules of keratinized tissue.

In general it appears that the patterns of epithelial differentiation in the oral mucosa vary to produce a surface layer that sufficiently meets the demands placed upon that particular tissue. Furthermore, in dealing with drug delivery, the amount of a certain drug absorbed through the oral mucosa is determined by many factors, including the pKa of the base, the rate of partition of the unionized form of the drug, the lipid–water partition coefficient of that particular drug, and lastly, on the pH of the solution.

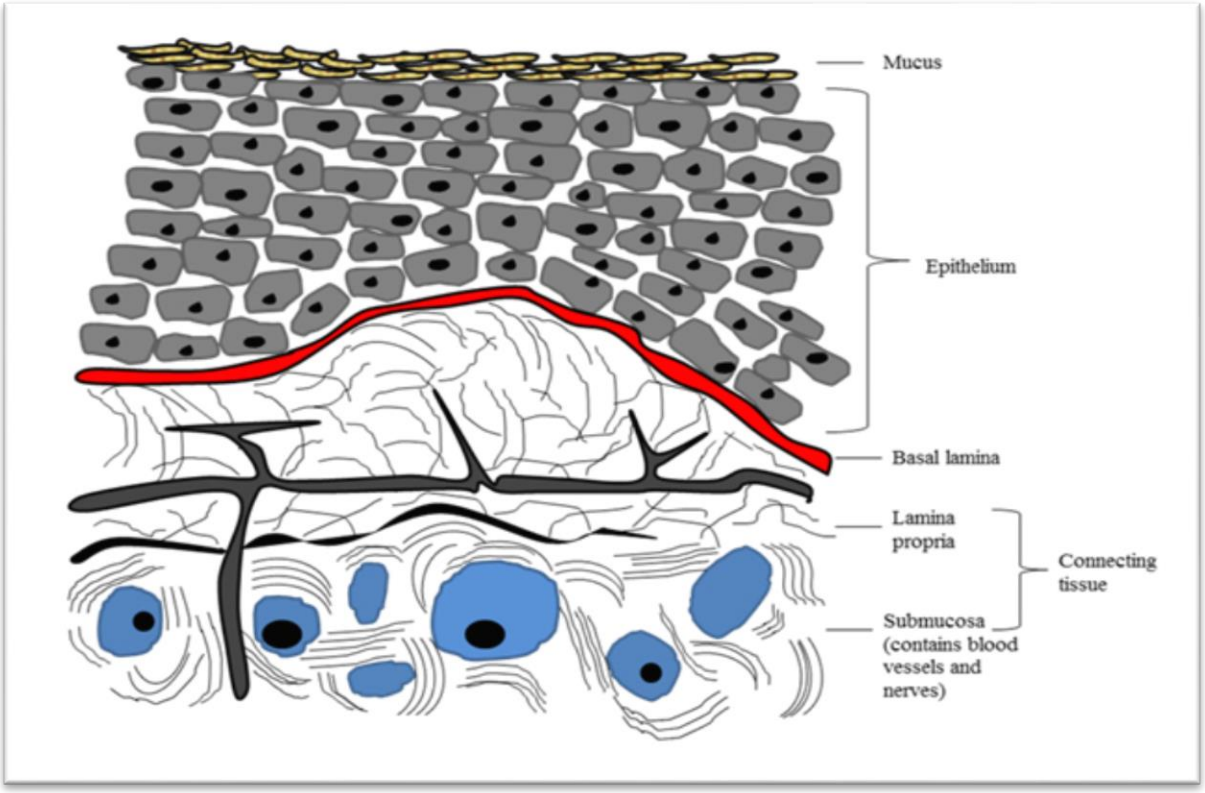


Figure 1.2. Structure of the oral mucosa

1.2. Sublingual Dosage Forms

These dosage forms are designed to deliver the drugs in the vicinity of sublingual mucosa. Drugs administered by this route produce systemic/local effects. In general, rapid absorption form this route is observed because of the thin mucous membrane and rich blood supply.

The sublingual dosage forms can be classified into the following:

- Sublingual Tablets
- Sublingual Spray
- Sublingual Capsules
- Sublingual Films

1.2.1. Sublingual Tablets [17]

Sublingual tablets are intended to be placed beneath the tongue and held until absorption has taken place. They must dissolve or disintegrate quickly, allowing the medicament to be rapidly absorbed.

1.2.2 Sublingual Spray [18]

Sublingual sprays are the dosage forms in which the drug is dissolved or dispersed in a vehicle and filled in vials with metered value. On actuation, a desired dose of the drug will deliver through the valve.

1.2.3. Sublingual Capsules [18]

These are the solid dosage forms in which the powder is filled into capsule, it should be cut open and the contents are poured below the tongue.

e. g. Nifedepine sublingual capsule.

1.2.4. Sublingual Films [19]

These are thin, transparent films, which are kept under the tongue form which drug will reach and get absorbed into blood stream. e. g. diazepam

1.3. Formulation of Sublingual Tablets

The distinct feature in the formulation of sublingual tablets involves the selection of suitable excipients of bland taste that shall ultimately result in a rapid disintegrating

tablet there by enhancing the dissolution of active ingredient.

There are two different types of sublingual tablets:

A. Molded Sublingual Tablets

B. Compressed Sublingual Tablets

1.3.1. Molded Sublingual Tablets [20]

Molded sublingual tablets are usually prepared from soluble ingredients so that the tablets are completely and rapidly soluble. They contain, in addition to drug, excipients or base namely lactose, dextrose, sucrose, mannitol, or other rapidly soluble materials or mixtures of these ingredients.

This tablet shows the same bioavailability as conventional tablets but has the advantage of markedly improved stability. In contrast to conventional tablets, which often develop marked inter tablet dose variation within 1 month, the stabilized tablet maintains its content uniformity for long periods, even at 37 ºC and 45 ºC, thus assuring a more uniform and predictable dose to the patient.

1.3.2. Compressed Sublingual Tablets [21]

The requirements for sublingual tablets are speed of absorption and a correspondingly rapid physiological response, which are normally best achieved with a rapidly soluble molded tablet. Compressed sublingual tablets can be prepared by two different methods:

a) Wet Granulation Method

b) Direct Compression Method.

1.3.2.1.Wet Granulation Method

The wet granulation method of the tablet production is essentially a process of size enlargement, sticking particles of the drug and excipients together using an adhesive, to produce a granular product with improved flow properties and an increased ability to cohere under pressure.

The drug and excipients are passed through particular sieve, and are mixed together to get uniform mixture. Suitable granulating agents like water, starch paste, povidone are added to the powder mixture in the appropriate proportion to produce a

coherent mass. This mass is passed through a suitable sieve and dried at optimum temperature and sieved to get uniform granules. Then the granules are lubricated and compressed into a tablet.

1.3.2.1. Direct Compression Method

Direct compression is the easiest way to manufacture tablets and also fast melting tablets. The term direct compression is used to define a process by which tablets are compressed directly from the powder blends of active ingredients and suitable excipients, which will flow uniformly into the die cavity and form into a firm compact. The great advantage of direct compression is the manufacturing cost. It uses conventional equipment, commonly available excipients and a limited number of process steps.

1.4. Major mechanisms by which tablet disintegrate in mouth [22]

1.4.1 Swelling by Disintegrants

Although not all effective disintegrants swell in contact with water, swelling is believed to be a mechanism by which certain disintegrants impart their disintegrating effect. By swelling in contact with water, the adhesiveness of other ingredients in a tablet is overcome causing the tablet to fall apart. Swelling could be of following types,

- Swelling extensively in all dimensions
- Recover shape with little swelling
- Swell readily and strengthen out as seen in the case of fibrous material

1.4.2 Porosity and Capillary Action (Wicking)

Effective disintegrating action is available through porosity and capillary action. Tablet porosity provides pathways for the penetration of fluid into the tablets. The Disintegrate particles (with low cohesiveness and compressibility) themselves act to enhance porosity and provide these pathways into the tablet. Liquid is drawn up or ‘wicked’ into these pathways through capillary action and rupture the inter-particulate bonds causing the tablet to break apart.

1.4.3 Deformation

Starch grains are generally thought to be “elastic” in nature meaning that the grains that are deformed under pressure will return to their original shape when that pressure is removed. But with the compression forces involved with tabulating, these grains are believed to be deformed more permanently and are said to be “energy rich” with this energy being released upon exposure to water. In other words, the ability of starch to swell is higher in “energy rich” starch grains than it is for starch grains that have not been deformed under pressure.

It is believed that no single mechanism is responsible for the action of most disintegrants. But rather, it is more likely the result of interrelationship between these major mechanisms.

1.5. General Technology [23]

- Freeze Drying
- Tablet Molding

1.5.1 Freeze Drying

Freeze drying is also commonly known as lyophilization process in which water is sublimated from the product after freezing. The ideal drug characteristics for this process are relative water insolubility with fine particle size and good aqueous stability in suspension. Primary problems associated with water soluble drugs are formation of eutectic mixture resulting in freezing point depression and formation of glassy solid on freezing, which might collapse during sublimation. Therefore additions of cryoprotectants like crystal forming agents induce crystallinity and impart rigidity to amorphous solid.

This technique allows drying of heat sensitive drugs and biologicals at low temperature thereby eliminating adverse thermal effects and can be stored in dry state with relatively new shelf life. Freeze dried forms offer more rapid dissolution time than other solid products because this technique offers highly porous powder with a very high specific surface area.

1.5.2 Tablet Molding

In this method, tablets are produced by molding of solid dispersion usually consisting of water soluble additives, drug and other excipients. Initially the dry blend of all the ingredients is wetted with a hydro alcoholic solvent and then compressed into tablets using low compression forces. Porous tablets are formed as the solvent present inside the tablet is removed by air drying.

Different mold techniques employed are

- Compression molding : Here the powdered mixture previously moistened with a solvent like ethanol/water is compressed into moulds plate to form a wetted mass
- Heat molding : The molded forms can be obtained from a molten matrix in which the drug is dispersed
- No vacuum lyophilization: In this process, at standard pressure the solvent from the drug solution or suspension is evaporated

1.6. Other Techniques [24]

1.6.1. Sublimation

Compressed tablets composed of water soluble excipients as tablet matrix often does not disintegrate due to low porosity. Therefore to increase the porosity of tablet an inert solid ingredient that volatilizes readily, example camphor, ammonium bicarbonate, naphthalene, urea etc. are mixed with other ingredients and then the mixture is compressed into tablets. The volatile material is removed via sublimation, which generates porous structure.

1.6.2. Spray Drying

Spray drying technique produces highly porous and fine powders as the processing solvent is evaporated during the process. This technique provides tablets that show fast disintegration and enhanced dissolution. Allen, Wang et al reported a spray drying technique using hydrolyzed and non-hydrolyzed gelatin as a support matrix, mannitol as a bulking agent, sodium starch glycolate as disintegrant, an acidic material like citric acid and/or alkaline material i.e. sodium bicarbonate. The tablets made from this technology are claimed to disintegrate within 20 seconds.

Table 1.1. Some Marketed Sublingual Tablets [25]

Brand name	Drug	Category	Strength
Abstral	Fentanyl citrate	Opioid analgesics	50,100,200,300,400,600 and 800 mcg
Subutex	Buprenorphine	Opioid analgesics	2 and 8 mg
Avitan	Lorazepam	Antianxiety	1 and 2 mg
Edular	Zolpidem tartrate	Sedative/ hypnotics	5 and 10 mg
Isordil	Isosorbide dinitrate	Vasodilators	2.5,5 and 10 mg
Suboxone	Buprenorphine HCl + naloxone	Narcotic + Opioid analgesics	2/0.5, 8/ 2 mg
Saphris	Asenapine	Antipsychotic agent	5 and 10 mg
Prohealth melatonin	Melatonin	Hormone	2 mg
Nitrostat	Nitroglycerine	Antianginal	0.3, 0.4 and 0.6 mg
Temegesic	Buprenorphine	Opioid analgesics	200mcg

Review of Literature

2. REVIEW OF LITERATURE

Amarjit P. Rajput (2013) *et al.* [26] (2013) reported comparative study of various permeation enhancers for development of sumatriptan succinate buccal tablet. The aim of the present study was to prepare buccoadhesive sustained release tablets of sumatriptan succinate using various permeation enhancers to release the drug for extended period of time with reduction in dosing frequency. Fulvic acid was characterized by various spectroscopic techniques. Buccoadhesive sustained release tablets of sumatriptan succinate with various permeation enhancers were prepared by direct compression method using bioadhesive polymers like Carbopol 934 and HPMC K100M. The physical characteristics like surface pH, swelling index, *in vitro* mucoadhesion time, in vitro mucoadhesion strength, *in vitro* drug release study and *in vitro* permeation study were studied. The *in vitro* release study showed 99.88%, 99% and 99.40% of drug release with fulvic acid, chitosan and beta cyclodextrin respectively. The permeation study showed 90%, 82% and 78% of drug permeated with fulvic acid, chitosan and beta cyclodextrin respectively. Sumatriptan succinate release from the buccoadhesive system was extended and exhibited a non fickian drug release kinetics approaching to first order as the values of release rate exponent varied between 0. 97 to 0.99 resulting in a regulated and complete release until 8 hours.

Balusu Haarika *et al.* [27] (2012) reported formulation and evaluation of fast disintegrating rizatriptan benzoate sublingual tablets. Sublingual formulation has the advantage of offering fast relief from migraine due to faster drug delivery. The present study involves the formulation and evaluation of fast disintegrating sublingual tablets of rizatriptan benzoate to produce intended effects. The sublingual rizatriptan benzoate tablets were prepared by the method of direct compression. The superdisintegrants used were sodium starch glycolate, cross carmellose sodium and cross povidone. The powder flow properties of all formulations were evaluated for diameter, thickness, weight variation, hardness, friability, wetting time, water absorption ratio, drug content, *in vitro* and *in vivo* disintegration time as well as in vitro release and were found to be satisfactory. The optimised formulation containing cross povidone disintegrated very fast and *in vitro* drug release was very high. Based on disintegration and dissolution

studies, the optimised formulation was also evaluated for *in vivo* release studies using rabbit model.

Rameshwari S *et al.* [28] (2009) studied the sublingual tablets of nifedipine. Nifedipine sublingual tablets were prepared by direct compression method. Three different groups of formulation with variation of tablet excipients were prepared with each group containing five different formulations. Various excipients were used in the formulation like Avicel pH 101, mannitol, lactose, magnesium stearate, talc, sodium saccharin, aerosol, citric acid, SSG, croscarmelose sodium etc. All batches of the tablets were preliminarily evaluated for various physical parameters such as hardness, friability drug content, disintegration and dissolution. This study clearly indicated the fast disintegration and dissolution of the optimized nifedipine sublingual tablet, which is a prerequisite for the rapid management of anginal hypertension diseases.

Abraham S *et al.* [29] (2010) studied the sublingual tablets of rabeprazole sodium. Various excipients were used in the formulation like crospovidone, croscarmelose sodium, mannitol, mango flavor, aspartame, talc, lactose etc. 10 batches of tablets were prepared using Central composite design. In this study, the amount of Crospovidone and CCS were chosen as the independent formulation variables, and the dependent variables included wetting time and *in vitro* dispersion time. The effect of formulation variables on the response variables were statically evaluated by applying one-way ANOVA at 0.05 level using Design-Expert®. They gave optimized formula of sublingual tablet of rabeprazole.

Bolourchian N *et al.* [30] (2009) reported sublingual tablets of physostigmine salicylate. The active ingredient was physostigmine salicylate. The other materials were as follows: polyvinyl pyrrolidone (PVP K10) and ammonium acetate, starch 1500, sodium starch glycolate, lactose, magnesium stearate and acetonitrile HPLC grade. Various parameters were evaluated like hardness, friability, disintegration, drug release etc. Increasing the percentage of PVP or starch 1500 and decreasing the amount of lactose in tablet formulation showed higher hardness value. This was predictable, because both PVP and starch 1500 have a binding effect in tablet formulation. For instance, an increase in starch 1500 concentration in tablets from 10 to 12 %, with the same amount of PVP, modified tablet hardness.

Bolourtchian N *et al.* [31] (2008) developed and optimized sublingual tablet formulation of Captopril which is an effective drug in the treatment of hypertension. Captopril containing tablets were prepared by direct compression method using different ingredients such as polyvinyl pyrrolidone, starch 1500, sodium starch glycolate and lactose (independent variables) and magnesium stearate, talc and aspartame (fixed components). Tablets were evaluated for the physical properties including hardness, disintegration time and friability which were considered as responses in a D-optimal experimental plan. Results were statistically examined using special cubic model and polynomial mathematical equations and found to be statistically significant ($p< 0.05$) for disintegration time and friability data. The physical data from the numerical optimization were verified and found to be very close to those predicted from the regression analysis. Additional experiments including drug content, *in vitro* drug dissolution rate and accelerated stability studies were also performed on the optimum formulation. All results were in accordance with the requirements of a sublingual tablet.

Sharma R *et al.* [32] (2010) Studied fast disintegrating sublingual tablets of glipizide. They used Glipizide, Crospovidone, Sodium starch glycolate & Lactose-IP, polyvinyl pyrrolidine and colloidal silicon dioxide, Magnesium stearate, naphthalene for formulation of glipizide sublingual tablet. For the preparation of tablets, vacuum drying technique was used and water insoluble diluents such as microcrystalline cellulose and dicalcium phosphate were not used in this study because they can be expected to cause an unacceptable feeling of grittiness in the patient mouth. These tablets were evaluated for weight variation test, hardness, friability, water absorption ratio, disintegration time and *in-vitro* dissolution rate. Naphthalene was used as sublimation agent. In this research work it was found that the amount of naphthalene and crospovidone considerably affect the various parameters such as wetting time, disintegration time, and percentage friability. It is thus concluded that by adopting a systematic formulation approach, an optimum point can be reached in the shortest time with minimum efforts.

Shirsand SB *et al.* [33] (2010) studied fast dissolving tablets of Metoclopramide hydrochloride. They used crosscarmelose, crospovidone, pearlitol SD 200 etc. Fast dissolving tablets of metoclopramide hydrochloride were prepared using the above co-processed superdisintegrants and evaluated for pre-compression and post-compression parameters. Directly compressible mannitol (Pearlitol SD 200) was used as a diluent to

enhance mouth feel. Co-processed superdisintegrants consisting of crospovidone and croscarmellose sodium exhibited good flow and compression characteristics. MTH tablets containing co-processed superdisintegrants exhibited quick disintegration and improved drug dissolution.

Bhanja SB *et al.* [34] (2011) studied sublingual tablets of Perindopril. The objective of the current study was to develop and optimize sublingual tablet of Perindopril which is an effective drug in the treatment of hypertension. Perindopril containing tablets were prepared by direct compression method using different ingredients such as crospovidone, sodium saccharin, mannitol, microcrystalline cellulose and magnesium stearate. The tablets were evaluated for physical properties including hardness, weight variation, thickness, friability, drug content, wetting time, water absorption ratio, *in-vitro* disintegration time, *in-vitro* dissolution study and drug release kinetic study. They found that formulation has high disintegration time because of presence of crospovidone.

Avulapati S *et al.* [35] (2011) Studied on fast disintegrating tablets of Losartan Potassium. The basic approach followed in this study was to incorporate a combination of superdisintegrants in optimum concentrations which can minimize disintegration time. The various superdisintegrants used in the present study were croscarmellose sodium, crospovidone and sodium starch glycolate. Various batches of FDTs were prepared by direct compression method and using conventional tablet machine. The formulated FDTs were evaluated for various physicochemical parameters, disintegration time and for *in vitro* drug release. All the batches of the formulations possessed required physicochemical parameters. The disintegration time of various formulations ranged from 16 to 51 seconds. *In vitro* drug release for various formulations ranges from 95.23 to 99.90 % end of 5 minutes.

Bhardwaj V *et al.* [36] (2010) prepared sublingual tablets of Amlodipine besylate. The aim of this study was to prepare fast disintegrating tablets of Amlodipine besylate by using different disintegrants and to evaluate the effect of increasing Amlodipine besylate load on the characteristics of fast disintegrating sublingual tablets for the potential emergency treatment of angina and hypertension. The superdisintegrant used in this study were Kollidon CL, Ac Di Sol and Sodium Starch Glycolate in varying concentrations (2 %, 4 %, and 6 %). The tablets were evaluated for weight variation, hardness, friability, wetting

time, water absorption ratio, and disintegration time and dissolution study. Using the same excipients, the tablets were prepared by direct compression and were evaluated in the similar way. From the results obtained, it can be concluded that the tablet formulation prepared with Ac Di Sol showed average disintegration time of 16 seconds *in vitro* that is faster than the other superdisintegrants used in the study. Also the hardness, friability, dissolution rate and assay of prepared tablets were found to be acceptable according to standard limits. The stability studies were performed as per ICH guidelines.

Nagendrakumar D *et al.* [37] (2010) prepared fast dissolving tablets of Granisetron. In the present work, fast dissolving tablets of Granisetron HCl were prepared using novel co-processed superdisintegrants consisting of crospovidone and sodium starchglycolate in different ratios (1:1, 1:2 & 1:3). The developed superdisintegrants were evaluated for angle of repose, Carr's index and Hausner's ratio in comparison with physical mixture of superdisintegrants. Fast dissolving tablets of Granisetron hydrochloride were prepared using the above co-processed superdisintegrants and evaluated for precompression and post-compression parameters. Based on *in vitro* dispersion time (approximately 20 sec), promising formulation was tested for *in vitro* drug release pattern in pH 6.8 Phosphate buffer and short-term stability (at 400^{o}C/75 % RH for 3 months) and drug excipients interaction (IR spectroscopy) were studied. Among the designed formulations, the formulation containing 4% w/w of co-processed superdisintegrant (1:1 mixture of crospovidone and sodium starchglycolate) emerged as the overall best formulation (t_{50} % 2.0 min) based on drug release characteristics in pH 6.8 phosphate buffer compared to commercial conventional tablet formulation (t_{50} % >15 min).

Jangam V *et al.* [38] (2011) studied orodispersible tablets of Carvedilol. The present study was aimed towards the formulation and evaluation of orodispersible tablets by direct compression technology using Carvedilol as a model drug. Orodispersible tablet of Carvedilol was formulated using lactose in different concentration (10%, 20%, and 30%) of superdisintegrants like crospovidone and sodium starch glycolate and diluents. Disintegration time and drug release were taken as the basis to optimize the orodispersible tablet. All the Prepared tablets were evaluated for thickness, hardness, friability, uniformity of weight, disintegration time, and dissolution study. Crospovidone in the concentration of 15 % gives faster disintegration time in 16 sec. and shows 100 % drug release within 15 min. This formula was selected as optimized formulation.

Gokel Y *et al.* [39] (2001) prepared sublingual tablets of Valsartan. The objective of this study was to assess the effect of sublingual valsartan in a group of patients with hypertensive urgency. Forty-one patients with hypertensive urgency and systolic blood pressure >200 mmHg, diastolic blood pressure >100 mmHg were studied in an emergency room. Supine blood pressure readings were taken and the patients were given 80 mg of valsartan sublingually. Blood pressure and heart rate were recorded at 15 min intervals over a 90 min period. Systolic blood pressure decreased from 211.22 ± 14.65 mmHg to 158.17 ± 15.48 mmHg, diastolic blood pressure dropped from 120.12 ± 13.44 mmHg to 93.05 ± 6.01 mmHg. The differences were statistically significant. The heart rate decreased from 87.90 ± 13.47 beats per minute to 82.59 ± 10.84 beats per minute. The results of the study indicate that sublingual valsartan is an effective drug in patients with hypertensive urgency and it is easy to use sublingually because it is in a capsule form and it is side-effect free. Further work is required to assess the effect of sublingual valsartan in patients with hypertensive urgency.

Bhowmik D *et al.* [40] (2009) studied on fast dissolving tablets of Telmisartan. Telmisartan is an Anti-hypertensive drug which is insoluble in water; hence the drug may be slowly or incompletely dissolves in the gastro-intestinal tract. So the rate of dissolution and therefore its bioavailability is less (bioavailability 42%). In the present study an attempt has been made to prepare fast dissolving tablets of Telmisartan by using superdisintegrants– crosspovidone, ac-di-sol, and sodium starch glycolate, level of addition to increase the rate of drug release from dosage form to increase the dissolution rate and hence its bioavailability. The tablets were prepared by direct compression methods and the prepared blend and tablets were evaluated for their physicochemical properties and *in-vitro* dissolution study. The evaluation study was performed such as weight variation, thickness, hardness, disintegrating time, wetting time, and *in-vitro* drug release and stability study. The disintegration time of fast dissolving tablets were increased by the addition of concentration of superdisintegrants.

Madan J *et al.* [41] (2009) studied fast dissolving tablets of Aloe Vera gel. The objective of this work was to prepare and evaluate fast dissolving tablets of the nutraceutical, freeze dried aloe vera gel. Fast dissolving tablets of the nutraceutical, freeze-dried aloe vera gel,

were prepared by dry granulation method. The tablets were evaluated for crushing strength, disintegration time, wetting time, friability, drug content and drug release. A 3^2 full factorial design was applied to investigate the combined effect of two formulation variables - amounts of microcrystalline cellulose and mannitol. The results of multiple regression analysis revealed that in order to obtain a fast dissolving tablet of the aloe vera gel, an optimum concentration of mannitol and a higher content of microcrystalline cellulose should be used. A response surface plot was also provided to graphically represent the effect of the independent variables on the disintegration time and wetting time. The validity of the generated mathematical model was tested by preparing a check point batch. This investigation has demonstrated that satisfactory fast dissolving Aloe Vera gel tablets can be formulated. It also showed the potential of experimental design in understanding the effect of formulation variables on the quality of fast dissolving tablets.

Tayel SA *et al.* [42] (2010) prepared sublingual tablets, containing the anti-asthmatic drug Ketotifen fumarate which suffers an extensive first-pass effect, using the fast-melt granulation technique. The powder mixtures containing the drug were agglomerated using a blend of polyethylene glycol 400 and 6000 as meltable hydrophilic binders. Granular mannitol or granular mannitol/sucrose mixture were used as fillers. The melt granulation technique is a process by which pharmaceutical powders are efficiently agglomerated by the use of a low melting point binder which is added to the other components of the powder. Once in a molten state, the binder acts as a granulating liquid. Preparation can take place by melting the low melting point compound, then, the water soluble excipients are added. The combination is mixed until congealing takes place to make granules. The objective of this work was to prepare a sublingual tablet containing the Anti-asthmatic and Anti-allergic drug Ketotifen fumarate, so as to improve its bioavailability, which was only 50 % following oral ingestion.

Madhu SS *et al.* [43] (2006) evaluated the effect of polymer type and tablet compaction parameters on the adhesive properties and drug release profile from mucoadhesive sublingual tablet formulations. Pentoxifylline was selected as the model drug because it has poor oral bioavailability due to extensive first-pass metabolism. Two polymers known to possess mucoadhesive properties, carbomer and hydroxypropyl methyl cellulose

(HPMC), were used to prepare the formulations. For drugs prone to presystemic losses, one of the approaches to improve drug bioavailability could be the use of buccal, sublingual, or gingival routes of administration, which could effectively minimize losses due to first-pass metabolism, enzymatic degradation, and/or degradation attributable to low pH environments. In addition, these routes of administration could offer the advantage of rapid onset of drug action as the rich supply of blood vessels in the oral cavity immediately transports the drug substance to the systemic circulation. It has been reported that the sublingual route is more permeable than buccal or gingival routes and also provides superior bioavailability with faster and less erratic absorption for many drugs.

Ravishankar *et al.* [44] (2011) studied sublingual Piroxicam in migraine. The aim of the present study was to compare the analgesic efficacy of a single dose of sublingual Piroxicam to that of a placebo during acute attacks of migraine without aura. The drug or a placebo was administered, on randomisation and double-blind basis, to 60 patients between 18 and 50 years of age suffering from migraine without aura. The patients were instructed to take a single tablet sublingually [corresponding to piroxicam 40mg or placebo] and the severity of the painful symptomatology and associated symptoms were evaluated by this study. The patients treated with sublingual piroxicam showed a significant decrease in pain intensity 15 min. after ingestion; they went on to show a further reduction in the 24 h after drug administration. On the contrary, the group treated with placebo showed a significant reduction of symptoms only after seven hours of observation.

Bredenberg S *et al.* [45] (2003) introduced a new tablet system for sublingual administration and rapid drug absorption. The tablet is based on interactive mixtures of components, consisting of carrier particles partially covered by fine dry particles of the drug, in this case Fentanyl citrate. In the interests of increasing retention of the drug at the site of absorption in the oral cavity, a bioadhesive component was also added to the carrier particles. Tablets containing 100, 200 and 400 µg of fentanyl were tested both *in vitro* and *in vivo*. Plasma concentrations of fentanyl were obtained within 10 min, with no second peak. A rapid onset of pharmacological effect is often desired from drugs, especially in the treatment of acute disorders. This can effectively be achieved by parenteral administration, but this method may not always be convenient for the patient. Therefore, there is growing interest in developing new, non-parenteral, reliable and convenient dosage forms using

administration routes where a rapidly dissolved drug is immediately absorbed into the systemic circulation. Tablet formulations are generally the first choice for drug administration because of ease of both production and usage.

Deveci S *et al.* [46] (2004) studied the effect of sublingual Sildenafil. Aim of the study was to show the efficacy and safety of sublingual Sildenafil with a faster onset of action in this mode of application. It was concluded that 20 mg sublingual Sildenafil is safe and effective in the treatment of erectile dysfunction. Sublingual administration has some advantages as it is not affected by food ingestion and quickly appears in the circulation. These advantages provide a faster onset of action with a lower dose when compared to oral Sildenafil. Sublingual use of Sildenafil may be more cost-effective and possibly provides a more predictable onset of action.

Kulkarni SV *et al.* [47] (2010) prepared fast disintegrating tablets of Meloxicam that disintegrate in the oral cavity upon contact with saliva and thereby improve therapeutic efficacy. Meloxicam is newer selective COX-2 inhibitor. The tablets were prepared by wet granulation procedure. The influence of superdisintegrants like crosspovidone, croscaremellose sodium on disintegration time, wetting time and water absorption ratio were studied. Tablets were evaluated for weight and thickness variation, disintegration time, drug content, *in vitro* dissolution, wetting time and water absorption ratio. The *in vitro* disintegration time of the best fast disintegrating tablets was found to be 18 sec. Tablets containing crospovidone exhibit quick disintegration time than tablets containing croscaremellose sodium. The fast disintegrating tablets of Meloxicam with shorter disintegration time, acceptable taste and sufficient hardness could be prepared using crospovidone and other excipients at optimum concentration.

Narendra C *et al.* [48] (2005) formulated a sublingual tablet formulation of Terbutaline for rapid action, and to improve both bioavailability and patient compliance to therapy. A wet granulation technique was adapted to prepare the granules. Granule formulations were prepared using an adapted wet granulation technique based on a 3^2 full factorial design. Conventional dosage forms for the management of asthma include tablets, capsules, syrups, injections and metered dose inhalers. Meter dose inhalers provide effective rapid relief, but at the same time, they present the disadvantage of requiring sophisticated equipment to manufacture, may be harmful to the environment and are expensive. In this

study, an attempt has been made to formulate sublingual dosage formulations of Terbutaline by using experimental design technique.

R.V.Kenny *et al* [49] (2010) studied formulation and evaluation of rizatriptan benzoate mouth disintegrating tablets. Mouth disintegrating tablets of rizatriptan benzoate were prepared using superdisintegrants crospovidone, carboxy methyl cellulose calcium, Indion 414 and Indion 234 using the direct compression method. The tablets prepared were evaluated for thickness, uniformity of weight, content uniformity, hardness, friability, wetting time, *in vitro* and *in vivo* disintegration time, mouth feel, *in-vitro* drug release and assay by high performance liquid chromatography. The tablets disintegrated *in vitro* and *in vivo* within 4 to 7 s and 6 to 19 s, respectively. Almost 90% of drug was released from all formulations within 20 min. The drug release from the formulations followed first order kinetics. Stability studies of the tablets at 40±2°/75%±5% RH for 1 month showed non-significant drug loss. The formulation containing combination of crospovidone and Indion 234 was found to give the best results. Apart from fulfilling all official and other specifications, the tablets exhibited higher rate of release.

Amit Alexander *et al*. [50] (2011) studied the effect of polymers, permeation enhancers and specialized components of mucoadhesives. Mucoadhesive polymers have recently gained interest among pharmaceutical scientists as a means of improving drug delivery by promoting dosage form residence time and contact time with the mucous membranes. Mucoadhesion occurs between two surfaces, one of which is a mucous membrane and another is drug delivery system. Pharmaceutical aspects of mucoadhesion have been the subject of great interest during recent years because mucoadhesion could be a solution for bioavailability problems that result from a too short length of stay of the pharmaceutical dosage form at the absorption site within the gastro-intestinal tract. It has been a great challenge to the pharmaceutical sciences in order to enhance localized drug delivery or to deliver 'difficult' molecules (proteins and oligonucleotides) into the systemic circulation. Mucoadhesive systems remain in close contact with the absorption tissue, the mucous membrane, releasing the drug at the site of action leading to increase in bioavailability (both local and systemic effects). Extending the residence time of a dosage form at a particular site and controlling the release of drug from the dosage form are useful especially for achieving controlled plasma level of the drug as well as improving bioavailability.

The present review describes mucoadhesion, mucoadhesive polymers and use of these polymers in designing different types of mucoadhesive drug delivery systems.

Alpana P. Kulkarni *et al.* [51] (2012) reported the development of oral disintegrating tablet of Rizatriptan benzoate with inhibited bitter taste. Taste masking was done by mass extrusion with aminoalkylmethacrylate copolymer, Eudragit EPO, in different ratios. The drug: polymer ratio was optimized based on bitterness score and RZB -polymer interaction. Taste masking was evaluated by checking the *in vitro* release of RZB in simulated salivary fluid (SSF) of pH 6.8 and by sensory evaluation in human volunteers. For formulation of rapid- disintegrating tablets of RZB, the batch that depicted optimum release of RZB in SSF was considered. ODTs of Rizatriptan benzoate were prepared by using superdisintegrants namely, sodium starch glycolate, crospovidone and croscarmellose sodium using the direct compression method. The tablets were evaluated for hardness, friability, wetting time, *in vitro* disintegration time. Eudragit EPO was able to mask the bitter taste of Rizatriptan benzoate effectively in 1:1 ratio by mass extrusion method. ODTs containing crospovidone (5% w/w) depicted minimum disintegration time. Taste evaluation of ODT in human volunteers revealed considerable taste masking, with all 6 volunteers, reporting the taste of ODTs as good in comparison with RB. Thus, results conclusively demonstrated successful taste masking and rapid disintegration of the formulated tablets in the oral cavity with adequate dissolution. The research work suggests a rapid, simple and cost effective mass extrusion method for formulation of ODT of Rizatriptan benzoate.

Aim and Objective

3. AIM AND OBJECTIVE

3.1. Aim

Rizatriptan benzoate is a Serotonin 5-HT $_{1B/1D}$ receptor agonist. It is clinically used as an antimigraine agent. Rizatriptan benzoate is rapidly absorbed after oral administration and has relatively low bioavailability i.e. 45% which is due to high first pass metabolism via Mono amino oxidase-A enzyme and also reported to be degraded in stomach. It has low permeability with high solubility (BCS-III Class) and biological half-life of less than 3 hours and is used orally in dose of 5-10 mg twice or thrice a day. [53]

- Drug therapy of Migraine has to be individualized based on severity & frequency of attacks, where in the subject requires repeated or frequent dosing.[52]
- The conventional dosage forms available are associated with low bioavailability problems due to extensive first pass metabolism.
- In order to overcome these drawbacks, drugs can be developed in form of sublingual drug delivery system.
- Sublingual delivery of drugs provide an attractive alternative to oral route of drug administration, particularly in overcoming deficiencies such as high first pass metabolism and drug degradation in the harsh environment.
- Sublingual tablets have the advantage of increased drug permeability time, which in turn results in better bioavailability and quick onset of action

3.2. OBJECTIVE OF THE PROPOSED RESEARCH WORK

1. To carry out preformulation studies on drug and permeation enhancer(s) and to establish their compatibility in formulation by FTIR study.
2. To formulate Sublingual tablets using varying concentrations of Rizatriptan benzoate (drug) and permeation enhancer(s) like β-Cyclodextrin, Chitosan lactate and Sodium lauryl sulphate. The Sublingual tablets will be prepared by direct compression method.

3. To study the effect of various factors like permeation enhancer(s) to drug ratio, permeation enhancer(s) ratio on the response parameters like release rate and permeability of drug across the sublingual route.
4. To study the release pattern and to conclude the better permeation enhancer which enhance the permeability in desired manner.

3.3. PLAN OF THE RESEARCH WORK

1. Design of the sublingual tablets.
2. Preformulation Studies
   - Physical compatibility study
   - FTIR study
3. Phase solubility study of Rizatriptan benzoate.
4. Preparation of standard curve for Rizatriptan benzoate.
5. Formulation development
   i. Formulation of varying concentration of β – Cyclodextrin with Rizatriptan benzoate.
   ii. Formulations of varying concentration of Chitosan lactate with Rizatriptan benzoate.
   iii. Formulation of varying concentration of Sodium lauryl sulphate with Rizatriptan benzoate.
6. Precompression studies of drug and blend
7. Preparation of tablets
8. Post – compression evaluation of tablets
   - Physical Characteristics
     - Description
     - Uniformity of Weight
     - Hardness
     - Diameter and Thickness
     - Friability

- Drug content
- Disintegration time
- Wetting time
- Uniformity of content
- *In vitro* Dissolution study of tablets
- *In vitro* Permeation study of tablets in egg membrane.
- *Ex vivo* Permeation study of tablets in goat sublingual mucosa

9. Evaluation of optimized formulation.

Rationale of the Study

4. RATIONALE OF THE STUDY

In the present scenario, there is an ever-increasing demand for more patient compliant dosage forms. One important innovation in this direction is the development of fast dissolving/disintegrating oral dosage forms that dissolve or disintegrate instantly upon contact with recipient's tongue or buccal mucosa. They have proved to be ideal for geriatric and pediatric population, people suffering from migraine and for drugs undergoing high first pass metabolism. As tablets disintegrate in mouth, this could enhance the clinical effect of drug through pregastric absorption from the mouth, pharynx and esophagus. This leads to an increase in bioavailability by avoiding first pass liver metabolism [55]. Literature survey also revealed that, bioavailability of drug from fast dissolving tablet dosage forms is significantly greater than those observed from conventional tablet dosage forms. [56]

4.1. Rationale for the selection of drug [53, 57]

Rizatriptan benzoate is a Serotonin 5-HT $_{1B/1D}$ receptor agonist. It is clinically used as an antimigraine agent. Rizatriptan benzoate is rapidly absorbed after oral administration and has relatively low bioavailability i.e. 45% which is due to high first pass metabolism via Mono amino oxidase-A enzyme and also reported to be degraded in stomach. It has low permeability with high solubility (BCS-III Class) and biological half-life of less than 3 hours and is used orally in dose of 5-10 mg twice or thrice a day.

4.2. Rationale for selection of dosage form [26, 27, 54]

In the present study, attempts will be made to prepare fast dissolving sublingual tablet of Rizatriptan benzoate to provide relief to patients who suffer from severe migraine attack, enhance the permeability as well as dissolution rate and to improve the bioavailability by avoiding first pass metabolism.

Disease Profile

5. DISEASE PROFILE – MIGRAINE[52, 53, 57-60]

5.1. Migraine [58]

Migraine is a recurrent incapacitating neurovascular disorder characterized by attacks of debilitating pain associated with photophobia, phonophobia, nausea and vomiting. Migraine affects a substantial fraction of world population and is a major cause of disability in the work place. Though the pathophysiology of migraine is still unclear, three major theories proposed with regard to the mechanisms of migraine are vascular (due to cerebral vasodilatation), neurological (abnormal neurological firing which causes the spreading depression and migraine) and neurogenic dural inflammation (release of inflammatory neuropeptides). The modern understanding of the pathogenesis of migraine is based on the concept that it is a neurovascular disorder. The drugs used in the treatment of migraine either abolish the acute migraine headache or aim its prevention. The last decade has witnessed the advent of Sumatriptan and the Rizatriptan class of 5-HT1B/1D receptor agonists which have well established efficacy in treating migraine. Currently prophylactic treatments for migraine include calcium channel blockers, 5-HT2 receptor antagonists, beta adrenoceptor blockers and g-amino butyric acid (GABA) agonists. Unfortunately, many of these treatments are non-specific and not always effective. Despite such progress, in view of the complexity of the aetiology of migraine, it still remains undiagnosed and available therapies are underused.

5.2. Pathophysiology of migraine [59]

Migraine is characterized by episodes of head pain that is often throbbing and frequently unilateral and may be severe. In migraine without aura (previously known as common migraine) attacks are usually associated with nausea, vomiting, or sensitivity to light, sound, or movement and when treated, the attacks typically last 4 to 72 h. A combination of features is required for the diagnosis, but not all features are present in every attack or in every patient. These symptoms do distinguish migraine from tension type headache, the most common form of primary headache, which is characterized by the lack of associated features. Any severe and recurrent headache is most likely a form of migraine and should be responsive to antimigraine therapy. In 15% of patients, migraine attacks are usually preceded or accompanied by transient focal neurotic symptoms, which are usually visual; such patients have migraine with aura (previously known as classic migraine. In a recent, large population-based study, 64% of patients with migraine had

only migraine without aura, 18% had only migraine with aura and 13% had both types of migraine (the remaining 5% had aura without headache). Thus, up to 31% of patients with migraine have aura on some occasions, but clinicians who rely on the presence of aura for the diagnosis of migraine will miss many cases.

A recent survey by the World Health Organization (WHO), rates severe migraine, along with quadriplegia, psychosis, and dementia, as one of the most disabling chronic disorders. This ranking suggests that in the judgment of WHO, a day with severe migraine is as disabling as a day with quadriplegia.

5.3. Theories of migraine [59]

5.3.1. Vascular theory : In the late 1930's, Harold Wolff became the first researcher to place migraine on a scientific basis, Wolf measured the diameter of the extra cranial (temporal) arteries in patients suffering migraine attacks and found them to be dilated. These patients were treated with vasoconstrictors (ergotamine) which relieved the pain and decreased the arterial dilation. Although subsequent events leading to headache (and associated symptoms) are not completely understood, the increased vascular pulsation may activate stretch receptors. This would, in turn increase the activity of neuropeptide containing (mainly calcitonin gene-related peptide (CGRP) perivascular nerves which may ultimately cause pain and other associated symptoms. In line with the finding that carotid arteriovenous anastomoses dilatation play a role in the pathogenesis of migraine; it is reasonable to believe that compounds which produce a cranioselective vasoconstriction may have a potential therapeutic use in the treatment of migraine. In anaesthetized dogs and pigs acutely acting antimigraine drugs, ergot alkaloids (ergotamine and dihydroergotamine) and triptans (Sumatriptan and second generation triptans) produced potent vasoconstriction in the canine and porcine carotid vasculature. Further studies demonstrated that mainly 5-HT1B receptors mediate Sumatriptan-induced cranial vasoconstriction, involving carotid arteriovenous anastomoses and temporal and middle meningeal arteries.

5.3.2. Neurological theory: A second theory of migraine is the neurological theory of migraine. This theory suggests that migraine arises as a result of abnormal neuronal firing and neurotransmitter release in brain neurons. This theory focuses on an explanation for certain symptoms, such as premonitory symptoms occurring

prior to an attack (prodrome), which are difficult to explain based on the vascular hypothesis. The fact that migraine headaches begin and develop slowly coupled to the fact that external factors, such as stress, and hunger can precipitate migraine attacks to pathologies arising in the neuronal system, thus supporting a neurological basis of migraine. Cortical spreading depression, an expanding depolarization of cortical neurons which is well characterized in many species but not in man is often suggested to underlie the aura or prodrome associated with initiation of migraine attack. During spreading depression, cortical function is disrupted subsequent to neuronal depolarization and increased extracellular potassium. These cortical changes are thought to be the cause of the transient sensory or motor impairments that frequently precede the painful period of a migraine attack Many investigators hypothesize that neuronal activation in migraine may be mediated by cortical spreading depression (CSD).

5.3.2. Neurogenic theory: This theory demonstrates that blood flow changes similar to those known to occur in migraine could be produced by electrically stimulating brain stem structures.

This finding led to the neurogenic theory. Stimulation studies investigated the relationship between the trigeminal nerve and the cranial vasculature. Moskowitz showed that trigeminovascular axons from blood vessels of the pia mater and dura mater release vasoactive peptides producing a sterile inflammatory reaction with pain. During this neurogenic inflammation, the trigeminal ganglion is stimulated and this induces neurogenic protein extravasation. Vasodilatory peptides then released, including calcitonin gene related peptide (CGRP), substance P (SP) and neurokinin A. Neurogenic theory is an attempt to reconcile the vascular changes in the neuronal dysfunction that may occur in migraine headache and proposes that migraine pain is associated with inflammation and dilation of the meninges, particularly the dura, a membrane surrounding the brain. Neurogenic dural inflammation is thought to result from the actions of inflammatory neuropeptides released from the primary sensory nerve terminals innervating the dural blood vessels. In fact, the dural membrane surrounding the brain is the source for the majority of intracranial pain afferents and dural stimulation produces headache like pain in human. Stimulation or inflammation of sensory fibers release the inflammatory neuropeptides, substance P and calcitonin gene-related peptide onto

dural tissue, where these peptides produce a local response called neurogenic inflammation. Neurogenic inflammation may lower the nociceptive threshold required to stimulate meningial sensory fibers. According to neurogenic dural inflammation theory of migraine, release of these inflammatory neuropeptides in the dura-mater during migraine can act on vascular tissues to cause vasodilatation, plasma protein extravasation in the surrounding area, endothelial changes, platelet aggregation and subsequent release of serotonin and other mediators, white cell adhesion and subsequent inflammation. CGRP plays a facilitatory role in this process. Whereas substance P induces extravasation via activation of NK1 receptors, release of CGRP enhances the effects of substance P by increasing dural blood flow and by inhibiting an extracellular enzyme that normally can metabolize substance P. Therefore, these two sensory neuropeptides act in concert to produce painful dural inflammation. Although not reliably demonstrated, increased cranial venous concentration of CGRP have been observed during a migraine attack and the elevated concentrations of CGRP have returned to normal following treatment of the migraine in the serotonergic agonists. This theory is in consistent with the proposal that serotonergic agonist alleviate the acute pain of migraine by inhibiting the release of substance P and CGRP from trigeminal sensory afferent neurons surrounding the meninges.

5.4. Pain mechanisms in migraine [59]

The pathogenesis of pain in migraine is not completely understood so far, but three key factors merit considerations are: the cranial blood vessels, the trigeminal innervation of the vessels, and the reflex connection of the trigeminal system in the cranial parasympathetic outflow. The substance of the brain is largely insensate; pain can be generated by large cranial vessels, proximal intracranial vessels or by the dura mater. These vessels are innervated by branches of the ophthalmic division of the trigeminal nerve, whereas the structures of the posterior fossa are innervated by branches of the C2 nerve roots. In nonhuman primates, stimulation of vascular afferents leads to the activation of neurons in the superficial layers of the trigeminal nucleus caudalis in the region of the craniomedullary junction and the superficial layers of the dorsal horns C1 and C2 levels of the spinal cord trigeminocervical complex. Similarly, stimulation of branches of C2 activates neurons in the same regions of the brain. The involvement of ophthalmic division of the trigeminal nerve and the overlap with structures innervated by

C2 explain the common distribution of migraine pain over the frontal and temporal regions, as well as involvement of parietal, occipital and high cervical regions by what is, in essence, referred pain. Peripheral trigeminal activation in migraine is evidenced by release of CGRP, a vasodilator, but the mechanism of generation of pain is not clear. Studies in animals suggest that the pain may be caused by a sterile neurogenic inflammatory process in the dura mater, but this mechanism has not been clearly demonstrated to correlate in humans. The pain may be a combination of an altered perception as a result of peripheral or central sterilization of craniovascular input that is not usually painful and the activation of feed-forward neurovascular dilator mechanism that is functionally specific for the first (ophthalmic) division of the trigeminal nerve.

5.5. Emerging therapies [58]

5.5.1. Calcitonin gene-related peptide (CGRP) antagonists

In the recent past, there has been an upsurge in CGRP research and its notable role in migraine pathophysiology. Migraine headache is closely associated with the activation of trigeminovascular system. CGRP immunoreactive fibres, originating in the trigeminal ganglion, innervate cranial cerebral blood vessels. In animals, stimulation of these sensory nerve fibers has been shown to cause antidromic release of CGRP and subsequent vasodilatation in the cerebral vasculature. Plasma concentrations of CGRP in the jugular venous blood, but not of other neuropeptides were elevated during the headache phase of migraine.

Furthermore, in migraine patients:

(a) Strong correlation was found between plasma CGRP concentrations and migraine headache

(b) Infusion of CGRP produced a migraine-like headache

(c) Baseline CGRP levels were considerably higher

(d) The changes in plasma CGRP levels during migraine attacks significantly correlated with the headache intensity. Recently Peterson has demonstrated a concentration dependent relaxation in the middle cerebral artery when CGRP was applied abluminally, which suggest that CGRP mediated vasodilatation is not caused by interaction with luminally situated receptor but more likely by abluminal receptor on the smooth muscle cells. Hence, inhibition of CGRP or antagonism of CGRP receptors could be a viable therapeutic target for the pharmacological treatment of migraine.

Table 5.1. Drugs for acute migraine attack [60]

Acute Migraine Agents	Contraindication	Indication
Acetaminophen	Liver disease	Pregnancy
Aspirin	Kidney Disease , Ulcer and Peptic Ulcer Disease	Coronary Artery Disease and Transient Ischemic Attack
NSAIDS	Kidney Disease , Gastritis, Ulcer and Peptic Ulcer Disease	Arthritis
Butabarbital, Caffeine and Analgesics	Use of the other Sedatives and History Medication Overuse	Acute Migraine Attack
Isometh- Heptane	Uncontrolled Hypertension, Coronary Artery Disease and Peripheral Vascular Disorder	Acute Migraine Attack
Opioids	Drugs Abusers	Acute Migraine Attack
Neuroleptics	Parkinson's Disease and Prolonged QTC Interval Patients	Acute Migraine Attack
Dihydroerogotamine Injection, Triptans and Intranasal Erogotamine	Uncontrolled Hypertension, Coronary Artery Disease and Peripheral Vascular Disorder	Acute Migraine Attack

Table 5.2. Drugs for migraine prophylaxis [60]

Preventive drugs	Contraindications	Indications
β – blockers	Asthma, Depression, Congestive Heart Failure, Raynaud's Disease and Diabetes	Hypertension and Angina
Antiserotonin – Pizotifen and Methysergide	Obesity and Peripheral Vascular Disease	Orthostatic Hypotension
Calcium channel blockers	Constipation and Hypotension	Migraine With Aura, Hypertension, Asthma and Angina
Flunarizine	Parkinson's Disease	Hypertension and Familial Hemiplegic Migraine
Tricyclics Antidepressants	Mania, Urinary Retention and Heart Block	Anxiety Disorder, Depression, Insomnia AND Other Pain Disorders
Serotonin Specific Reuptake Inhibitors	Mania	Depression and Obsessive Compulsive Disorder
Monoamine Oxidase Inhibitors	Glaucoma And Urinary Retention	Refractory Depression
Divalproex / Valproate	Liver Disease and Bleeding Disorders	Mania, Epilepsy and Anxiety Disorder
Gabapentin	Liver Disease and Bleeding Disorders	Mania, Epilepsy and Anxiety Disorder
NSAIDS	Ulcer Disease and Gastritis	Arthritis AND Other Pain Disorders
Topiramate	Kidney Stones	Mania, Epilepsy and Anxiety

In line with this concept, an important breakthrough in the field of CGRP is the development of potent CGRP receptor antagonist olcegepant (BIBN4096BS). In the *in vivo* animal models of migraine, olcegepant attenuated the vasodilation induced by trigeminal stimulation and capsaicin- induced anastomotic dilatation. Data from recently published clinical proof of concept study by Olesen demonstrated the effectiveness and safety of olcegepant for acute treatment of migraine, in which the response rate was found similar to oral triptans. No cardiovascular side effects have been reported following administration of olcegepant. The lack of cardiovascular side effects may prove to be a major advantage for using CGRP receptor antagonists to treat migraine.

5.5.2. Anticonvulsants

Migraine and epilepsy share several features and respond to many of the same pharmacological agents suggesting that similar mechanism may be involved in their pathophysiology, hence new targets are being investigated for the prophylactic therapy of migraine. Amongst these, anticonvulsants as a class of drugs hold promise for the migraine prophylaxis. These drugs are thought to act through multiple mechanisms involving voltage gated ion channels, ligand gated ion channels, GABA (g- amino butyric acid), glutamate etc. In the central nervous system, GABA is a major inhibitory neurotransmitter and known anticonvulsant drugs like sodium valproate, Topiramate and gabapentine have been shown to be effective in preventing migraine through modulation of GABA neurotransmission.

5.5.3. Histamine H3 agonists

In recent study, histamine H3 agonists are evaluated for the safety and efficacy for migraine prophylaxis. Milan-Guerrero et al in the first part of their study determined the undesirable symptomatic effects of N-alpha-methylhistamine, H3 receptor agonist in healthy human volunteers and failed to identify adverse effects and in their second part of their study N-alpha-methyl histamine, at doses 1 and 3 Dg was found to be significantly reduce the frequency, intensity and duration of migraine attacks as well as the need to rescue analgesics in 18 patients. Hence carefully controlled doses of H3 receptor agonist may offer an alternative approach to migraine prophylaxis.

5.5.4. Botulinum toxin type A

BoNT-A produced by the bacterium *Clostridium botolinium* consists of a heavy chain and light chain linked by a disulfide bond. BoNT-A binds to pre-synaptic nerve terminal and is internalized into the cell, where it inhibits acetylcholine release by interfering with vesicle docking. These effects make BoNT-A useful for the treatment of many disorders related to excessive muscle contraction, such as strabismus, blepharospasm, hemifacial spasm and cervical dystonia. New applications of BoNT-A in pain therapy support a mechanism for pain reduction that is more complex than a simple secondary effect of muscle relaxation. BoNT-A has been used successfully to treat several different types of headaches, including tension type headache, cervicogenic headache and migraine. Although some types of headaches may have been relieved by the inhibition of muscle contraction at trigger points, the efficacy of BoNT-A in treating migraine headache implies a direct action on sensory neurons, with an indirect central action. It is believed that release of vasoactive neuropeptides, such as SP and CGRP from the trigeminal nerve on to the vasculature produces vasodilatation and plasma protein extravasation due to increased permeability of post capillary venules. It is proposed that, the effectiveness of BoNT-A for the treatment of migraine in the clinical setting may be due to its inhibition of neurogenic inflammation induced by the peripheral release of SP and CGRP.

5.5.5. Coenzyme Q10

There has been recent interest in the role that mitochondria may play in migraine pathogenesis. It is clear from the recent studies that at least a subset of migraineurs has a dysfunction in mitochondrial energy metabolism. Coenzyme Q10 is an essential element of the mitochondrial electron transport chain. It is a naturally occurring, small hydrophobic substance that freely moves throughout the membrane transferring electrons from the NADH dehydrogenase complex and the succinate-Q-reductase complex to cytochrome C. In addition to its actions as an electron carrier, coenzyme Q10 may act as antioxidant and help protect the myocardium from post-ischaemic reperfusion injury. If mitochondrial dysfunction is playing a role in migraine genesis then coenzyme Q10 could improve mitochondrial function and thus prevent migraine headaches. This belief is not without precedence as riboflavin, in an open label study and a placebo-controlled trial has been shown to reduce migraine frequency. Riboflavin is indirectly involved in the electron transport chain as a precursor of flavin mononucleotides. Coenzyme Q10 is

an essential element of the electron transport chain, suggesting that it could also work as migraine preventive.

5.5.6. NK-1 receptors

According to neurogenic inflammation theory of migraine, SP induces dural inflammation and increases sensitization to migraine headache pain by stimulating NK-1 receptors. Lanepitant is a high affinity, non-peptide, competitive NK-1 receptor antagonist that acts both peripherally and centrally and reported to be effective in guinea pig model of dural inflammation. Thus, NK-1 receptor antagonists may have a role in migraine therapy.

5.5.7. Nociceptin

Nociceptin is an endogenous ligand for the opiate-4 (OP-4) receptor. The OP-4 receptor abundantly expressed in various CNS structures in rodents, nonhuman primates and in humans, supporting the role of nociceptin in multitude of CNS functions, including motor and balance control, reinforcement and reward, nociception, the stress response, sexual behaviour, aggression and autonomic control of physiologic processes. It has been reported that approximately 70% of neurons in the human trigeminal ganglion exhibit nociceptin immunoreactivity and express OP-4 receptor mRNA. In these cells Nociceptin is co-localized with CGRP and substance P, marker peptides of the trigeminovascular system. This distribution suggests that nociceptin may be involved in the regulation of neuropeptide release from trigeminal nerve terminals and perhaps in migraine. Interestingly, in an animal model, Nociceptin dose-dependently suppressed the neurogenic dural vasodilatation, while it had no effect on baseline vessel diameter, also in a recent study lower circulating levels of Nociceptin was observed during migraine attacks. Hence drugs targeting OP-4 receptor might be a promising alternative in the pharmacological treatment of migraine.

5.5.8. Melatonin

Melatonin is a derivative of essential amino acid tryptophan, synthesized in the pineal gland. It has wide therapeutic implications including sleeping disorders, circadian rhythm, insomnia in blind people, insomnia in elderly patients, aging and Alzheimer disease. It has been observed that some patients reporting their headaches predominantly or specifically at a certain period of the day. Both episodic and chronic migraineurs

reported waking up in the morning with headaches or being woken up at night by the headache. Also migraine patients without depression had lower levels of melatonin than controls. Since, melatonin is involved in cerebrovascular regulation; treatment of headache disorders including migraine is promising. Melatonin may also be involved in migraine co-morbidity. Insomnia in headache patients is the most likely associated condition in migraine to respond to melatonin therapy. However, the data from large human trials are yet come to provide a proof-of-concept for the potential role of melatonin therapy in migraine. [58-60]

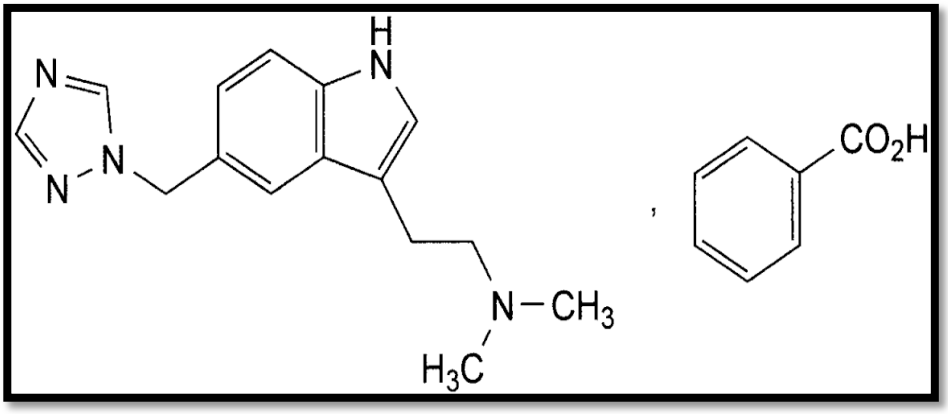
Materials and Methods

Drug Profile

6.1. DRUG PROFILE

RIZATRIPTAN BENZOATE [52, 57, 61, 62]

Chemical structure



Chemical name

N,*N*-Dimethyl-2-[5-(1*H*-1,2,4-triazol-1-yl-methyl)-1*H*-indol-3-yl]ethanamine benzoate.

CAS number

145202-66-0

Molecular formula

$C_{22}H_{25}N_5O_2$

Molecular weight

391.5

Description

White or almost white powder or crystals.

Solubility

Soluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride.

Melting point

178-180 °C

Category

Serotonin $5HT_1$ receptor agonist; treatment of migraine.

Pharmacology

Rizatriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type $_{1B}$ and $_{1D}$ receptors. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists and has only a weak affinity for 5-HT_{1A}, 5-HT_{5A}, and 5-HT_7 receptors and no significant affinity or pharmacological activity at 5-HT_2, 5-HT_3 or 5-HT_4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1; dopamine2; muscarinic, or benzodiazepine receptors. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that Rizatriptan also activates 5-HT_1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of Rizatriptan in humans.

Pharmacokinetics

Absorption

It shows rapid absorption following oral administration. Bioavailability is 45%. Food has no effect on the bioavailability of rizatriptan. However, administering rizatriptan with food will delay by 1 hour the time to reach peak plasma concentration. The rate of absorption is not affected by the presence of a migraine attack.

Distribution

Rizatriptan is minimally bound (14%) to plasma proteins. The volume of distribution is approximately 140 liters in male subjects, and 110 litters in female subjects. Studies in rats indicate that rizatriptan crosses the blood-brain barrier to a limited extent.

Protein binding

14 %

Half-life

2-3 hours

C_{max}

For oral ingestion tablets- 1 to 1.5 hrs

For orodispersible tablets- 1.6 to 2.5 hrs

Metabolism and Elimination

Rizatriptan is metabolized by monoamine oxidase A isoenzyme (MAO-A) to an inactive indole acetic acid metabolite. In addition, several other inactive metabolites are formed. An active metabolite, N-monodesmethyl-rizatriptan, with pharmacological activity similar to that of the parent compound has been identified in small concentrations (14%) in the plasma.

Approximately 14% of an oral dose is excreted in urine as unchanged rizatriptan while 51% is excreted as indole acetic acid metabolite, indicating substantial first pass metabolism.

Mechanism of Action

Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans: (1) stimulation of presynaptic 5-HT1D receptors, which serves to inhibit both dural vasodilation and inflammation; (2) direct inhibition of trigeminal nuclei cell excitability via 5-HT1B/1D receptor agonism in the brainstem and (3) vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT1B receptor agonism.

Pharmacodynamics

Rizatriptan is a selective agonist of serotonin (5-hydroxytryptamine; 5-HT) type 1B and 1D receptors. It is structurally and pharmacologically related to other selective 5-HT1B/1D receptor agonists and has only a weak affinity for 5-HT1A, 5-HT5A, and 5-

HT7 receptors and no significant affinity or pharmacological activity at 5-HT2, 5-HT3 or 5-HT4 receptor subtypes or at alpha1-, alpha2-, or beta-adrenergic, dopamine1,; dopamine2; muscarinic, or benzodiazepine receptors. This action in humans correlates with the relief of migraine headache. In addition to causing vasoconstriction, experimental data from animal studies show that Rizatriptan also activates 5-HT1 receptors on peripheral terminals of the trigeminal nerve innervating cranial blood vessels, which may also contribute to the antimigrainous effect of Rizatriptan in humans.

Indication

Rizatriptan is indicated for the acute treatment of migraine attacks with or without aura, but are not intended for use in prophylaxis of migraine. Treatment should begin as soon as possible after onset of a migraine attack.

Dosage

The recommended oral dose of rizatriptan is 5–10 mg, repeatable after 2 hours up to a maximum dose of 30 mg over a 24-hour period.

Adverse Effect

- Dizziness
- Fainting
- Heart and Blood Vessel Problems
- High Blood Pressure
- Loss of Bowel and Bladder Control
- Slow Heartbeat
- Vomiting.

Precautions and Contraindication

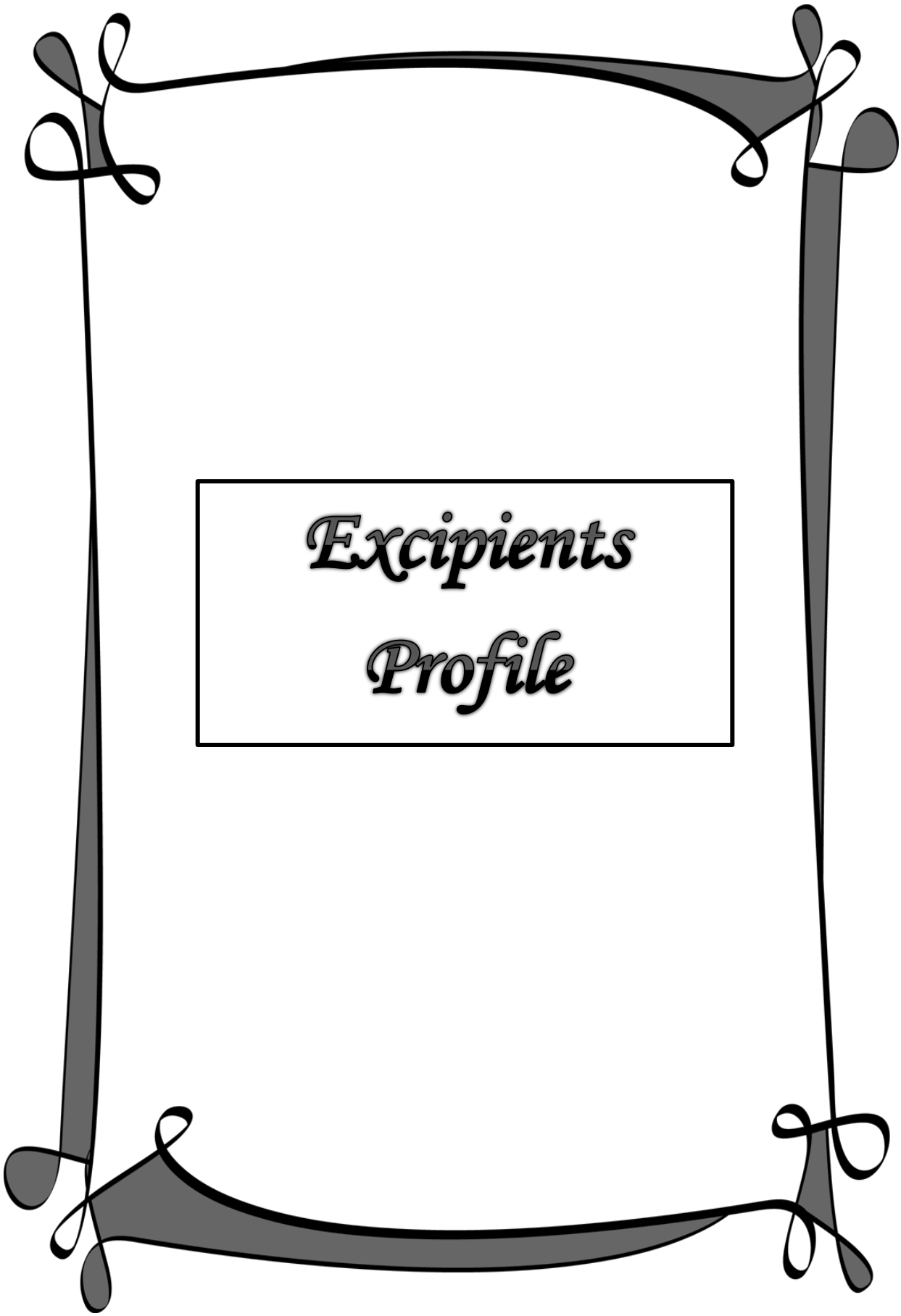
Rare but serious cardiac events have been associated with the administration of 5-HT1 agonists, including coronary artery vasospasm, transient myocardial ischemia, atrial and ventricular arrhythmias, and myocardial infarction, predominantly in patients with risk factors for coronary artery disease. Rizatriptan are contraindicated in patients with a history of significant cardiovascular disease. Because rizatriptan may cause an acute, usually small, increase in blood pressure, they also are contraindicated in patients with

uncontrolled hypertension. Rizatriptan should be used with caution in patients with renal or hepatic disease but is not contraindicated in such patients. Rizatriptan are contraindicated in patients who are taking MAO inhibitors. Triptans should not be used concurrently with (or within 24 hours of) an ergot derivative, nor should one triptan be used concurrently or within 24 hours of another.

Drug Interaction

Citalopram	Increased risk of CNS adverse effects
Desvenlafaxine	Increased risk of serotonin syndrome. Monitor for symptoms of serotonin syndrome.
Dihydroergotamine	Possible severe and prolonged vasoconstriction
Ergotamine	Possible severe and prolonged vasoconstriction
Escitalopram	Increased risk of CNS adverse effects
Fluoxetine	Increased risk of CNS adverse effects
Fluvoxamine	Increased risk of CNS adverse effects
Isocarboxazid	The MAO inhibitor, isocarboxazid, may decrease the metabolism and clearance of the serotonin 5-HT receptor agonist, rizatriptan. Concomitant therapy is contraindicated.
Methysergide	Possible severe and prolonged vasoconstriction
Moclobemide	The MAO inhibitor, moclobemide, may decrease the metabolism and clearance of the serotonin 5-HT receptor agonist, rizatriptan. Concomitant therapy is contraindicated.
Nefazodone	Increased risk of CNS adverse effects

Paroxetine	Increased risk of CNS adverse effects
Phenelzine	The MAO inhibitor, phenelzine, may decrease the metabolism and clearance of the serotonin 5-HT receptor agonist, rizatriptan. Concomitant therapy is contraindicated.
Propranolol	Propranolol increases the effect and toxicity of Rizatriptan
Tramadol	Increased risk of serotonin syndrome. Monitor for symptoms of serotonin syndrome.
Tranylcypromine	The MAO inhibitor, Tranylcypromine, may reduce the metabolism and clearance of the serotonin 5-HT1D receptor agonist, Rizatriptan. Risk of serotonin syndrome and Rizatriptan toxicity. Concomitant therapy should be avoided.
Trazodone	Increased risk of serotonin syndrome. Monitor for symptoms of serotonin syndrome.
Trimipramine	Increased risk of serotonin syndrome. Monitor for symptoms of serotonin syndrome.
Venlafaxine	Increased risk of serotonin syndrome. Monitor for symptoms of serotonin syndrome.
Zolmitriptan	Concomitant use of two serotonin 5-HT1D receptor agonists, such as zolmitriptan and rizatriptan, may result in additive vasoconstrictive effects. Concomitant use within 24 hours is contraindicated.


Excipients
Profile

6.2. EXCIPIENTS PROFILE

6.2.1. CROSPOVIDONE [63]

Non-proprietary Names

BP: Crospovidone

PhEur: Crospovidone

USP-NF: Crospovidone

Synonyms

Crospovidonum; Crospopharm ; crosslinked povidone; E1202;Kollidon CL; Kollidon CL-M ; Polyplasdone XL ; Polyplasdone XL-10 ; polyvinyl polypyrrolidone; PVPP; 1-vinyl-2-pyrrolidinone homopolymer.

Chemical Name and CAS Registry Number:

1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

Empirical Formula and Molecular Weight:

$(C_6 H_9NO)_n$, > 1 000 000

The USP32–NF27 describes crospovidone as a water-insoluble synthetic crosslinked homopolymer of N-vinyl-2-pyrrolidinone. An\exact determination of the molecular weight has not been established because of the insolubility of the material.

Functional Category

Tablet disintegrant.

Description

Crospovidone is a white to creamy-white, finely divided, free-flowing, practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility

Completely insoluble in water, acids, alkalis, and all organic solvents. Hygroscopic swells rapidly in water. Rapidly disperses in water, but does not gel even after prolonged exposure.

Applications in Pharmaceutical Formulation or Technology

Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2–5% concentration in tablets prepared by direct-compression or wet- and dry-granulation methods. It rapidly exhibits high capillary activity and pronounced hydration capacity, with little tendency to form gels. Studies suggest that the particle size of crospovidone strongly influences disintegration of analgesic tablets. Larger particles provide faster disintegration than smaller particles. Crospovidone can also be used as a solubility enhancer. With the technique of co-evaporation, crospovidone can be used to enhance the solubility of poorly soluble drugs. The drug is adsorbed on to crospovidone in the presence of a suitable solvent and the solvent is then evaporated. This technique results in faster dissolution rate.

Stability and Storage conditions

Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities

Crospovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, crospovidone may form molecular adducts within solution with sulfathiazole, sodium salicylate, salicylic acid, phenobarbital, tannin, and other compounds. The efficacy of some preservatives, e.g. thimerosal, may be adversely affected by the formation of complexes with povidone.

6.2.2. MICROCRYSTALLINE CELLULOSE [63]

Nonproprietary Names

BP: Microcrystalline Cellulose

JP: Microcrystalline Cellulose

PhEur: Cellulose, Microcrystalline

USP-NF: Microcrystalline Cellulose

Synonyms

Avicel PH; Cellets ; Celex; cellulose gel; hellulosum microcristalli-num; Celphere ; Ceolus KG ; crystalline cellulose; E460; Emcocel; Ethispheres ; Fibrocel; MCC Sanaq; Pharmacel; Tabulose ; Vivapur.

Chemical Name and CAS Registry Number:

Cellulose [9004-34-6]

Empirical Formula and Molecular Weight:

$(C_6H_{10}O_5)_n$, ≈ 36,000

Where,

n ≈ 220.

Functional Category

Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Description

Microcrystalline cellulose is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. It is commercially available in different particle sizes and moisture grades that have different properties and applications.

Solubility

Insoluble in water, dilute acids, and most organic solvents. Practically insoluble in sodium hydroxide.

Applications in Pharmaceutical Formulation or Technology

Microcrystalline cellulose is widely used in pharmaceuticals, primarily as a binder/diluent in oral tablet and capsule formulations where it is used in both wet-granulation and direct compression processes. In addition to its use as a binder/diluent, micro-crystalline cellulose also has some lubricant and disintegrant properties that make it useful in tableting.

Stability and Storage conditions

Microcrystalline cellulose is a stable though hygroscopic material. The bulk material should be stored in a well-closed container in a cool, dry place.

Incompatibilities

Microcrystalline cellulose is incompatible with strong oxidizing agents.

6.2.3. MANNITOL [63]

Nonproprietary Names

BP: Mannitol

JP: D-Mannitol

PhEur: Mannitol

USP: Mannitol

Synonyms

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

Chemical Name and CAS Registry Number:

D -Mannitol [69-65-8]

Empirical Formula and Molecular Weight:

$C_6H_{14}O_6$, 182.17

Functional Category

Diluent; plasticizer; sweetening agent; tablet and capsule diluent; therapeutic agent; tonicity agent.

Description

Mannitol is D-mannitol. It is a hexahydric alcohol related to mannose and is isomeric with sorbitol. Mannitol occurs as a white, odorless, 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.

Solubility

Soluble in water, very slightly soluble in ethanol and practically insoluble in ether.

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 aluminum hydroxide (< 7% w/v). It has been suggested as a plasticizer in soft-gelatin capsules, as a component of sustained-release tablet formulations, and as a carrier in dry powder inhalers.

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 neither attacked by cold and dilute acids or alkalis nor by atmospheric oxygen in the absence of catalysts. Mannitol does not undergo Millard 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 aluminum, 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.

6.2.4. CHITOSAN LACTATE [63]

Nonproprietary Names

BP: Chitosan Hydrochloride

PhEur: Chitosan Hydrochloride

Synonyms

2-Amino-2-deoxy-(1,4)-b- D -glucopyranan; chitosani hydrochlori-dum; deacetylated chitin; deacetylchitin;b -1,4-poly-D-glucosamine;poly-D -glucosamine; poly-(1,4- b- D -glucopyranosamine).

Chemical Name and CAS Registry Number:

Poly-b -(1,4)-2-Amino-2-deoxy- D-glucose [9012-76-4]

Empirical Formula and Molecular Weight:

Partial deacetylation of chitin results in the production of chitosan, which is a polysaccharide comprising copolymers of glucosamine and N -acetylglucosamine. Chitosan is the term applied to deacetylated chitins in various stages of deacetylation and depolymeriza-tion and it is therefore not easily defined in terms of its exact chemical composition. A clear nomenclature with respect to the different degrees of N-deacetylation between chitin and chitosan has not been defined,and as such chitosan is not one chemical entity but varies in composition depending on the manufacturer. In essence, chitosan is chitin sufficiently deacetylated to form soluble amine salts. The degree of deacetylation necessary to obtain a soluble product must be greater than 80–85%. Chitosan is commercially available in several types and grades that vary in molecular weight by 10 000–1 000 000, and vary in degree of deacetylation and viscosity.

Description

Chitosan occurs as odorless, white or creamy-white powder or flakes. Fiber formation is quite common during precipitation and the chitosan may look ‘cottonlike’.

Solubility

Completely soluble in water at pH < 6.3 and precipitates at pH > 6.5

Functional Category

Coating agent; disintegrant; film-forming agent; mucoadhesive; tablet binder; viscosity increasing agent.

Applications in Pharmaceutical Formulation or Technology

Chitosan is used in cosmetics and is under investigation for use in a number of pharmaceutical formulations. The suitability and performance of chitosan as a component of pharmaceutical formulations for drug delivery applications has been investigated in numerous studies. These include controlled drug delivery applications, use as a component of mucoadhesive dosage forms, rapid release dosage forms, improved peptide delivery, colonic drug delivery systems, and use for gene delivery. Chitosan has been processed into several pharmaceutical forms including gels, films, beads, micro-spheres, tablets, and coatings for liposomes. Furthermore, chitosan may be processed into drug delivery systems using several techniques including spray-drying, coacervation, direct compression, and conventional granulation processes.

Stability and Storage conditions

Chitosan powder is a stable material at room temperature, although it is hygroscopic after drying. Chitosan should be stored in a tightly closed container in a cool, dry place. The PhEur 6.5 specifies that chitosan should be stored at a temperature of 2–88 C.

Incompatibilities

Chitosan is incompatible with strong oxidizing agents.

6.2.5. β – CYCLODEXTRIN [63]

Nonproprietary Names

BP : Betadex

Ph. Eur : Betadex

USP – NF : Betadex

Synonyms

Beta – cycloamylose; Beta – dextrin; Betadexum; Cacamax W7 pharma; Cyclohepta amylose; Cyclohepta glucan; Cyclomalto heptose; Kleptose

Chemical Name and CAS Registry Number:

β – Cyclodextrin & [585 -39- 9]

Empirical Formula and Molecular Weight:

$C_{42}H_{70}O_{35}$, 1135

Description

Cyclodextrins are oligosaccharides containing at least six D–(+)glucopyranose units attached by α(1→4) glucoside bonds. β – Cyclodextrin contains 7 glucose units. Cyclodextrins occur as white, practically odorless, fine crystalline powders, having a slightly sweet taste. Some cyclodextrin derivatives occur as amorphous powders.

Solubility

Soluble 1 in 200 parts of propylene glycol, 1 in 50 of water at 20^0C, 1 in 20 at 50^0C; practically insoluble in acetone, ethanol (95%), and methylene chloride.

Functional Category:

Solubilizing agent; stabilizing agent.

Applications in Pharmaceutical Formulation or Technology

Cyclodextrins are 'bucket like' or 'cone like' toroid molecules, with a rigid structure and a central cavity, the size of which varies according to the cyclodextrin type; The internal surface of the cavity is hydrophobic and outside of the torus is hydrophilic; this is due to the arrangement of hydroxyl groups within the molecule. This arrangement permits the cyclodextrin to accommodate a guest molecule within the cavity, forming an inclusion complex.

Cyclodextrins may be used to form inclusion complexes with a variety of drug molecules, resulting primarily in improvements to dissolution and bioavailability owing to enhanced solubility and improved chemical and physical stability. Cyclodextrin inclusion complexes have also been used to mask the unpleasant taste of active materials and to convert a liquid substance into a solid material.

β – Cyclodextrin is the most commonly used cyclodextrin, although it is the least soluble. It is the least expensive cyclodextrin; is commercially available from a number of sources; and is able to form inclusion complexes with a number of pharmaceutical interests. β – Cyclodextrin is primarily used in tablet and capsule formulations.

In oral tablet formulations, β – cyclodextrin may be used in both wet-granulation and direct-compression processes. The physical properties of β – Cyclodextrin vary depending on the manufacturer. However, β – Cyclodextrin tends to possess poor flow properties and requires a lubricant, such as 0.1%w/w Magnesium stearate, when it is directly compressed.

Stability and Storage conditions

β – Cyclodextrin and other cyclodextrins are stable in solid state if protected from high humidity. Cyclodextrins should be stored in a tightly sealed container, in a cool, dry place.

Incompatibilities

The activity of some antimicrobial preservatives in aqueous solution can be reduced in the presence of hydroxypropyl-β-cyclodextrin.

6.2.6. SODIUM LAURYL SULFATE [63]

Nonproprietary Names

BP: Sodium Lauryl Sulphate

JP: Sodium Lauryl Sulfate

PhEur: Sodium Lauril sulfate

USP-NF: Sodium Lauryl Sulfate

Synonyms

Dodecyl alcohol hydrogen sulfate, sodium salt; dodecyl sodium sulfate; dodecylsulfate sodium salt; Elfan 240; lauryl sodium sulfate; lauryl sulfate, sodium salt; monododecyl sodium sulfate; natrii lauril sulfas; sodium dodecyl sulfate; sodium n-dodecyl sulfate; sodium lauril sulfate; sodium monododecyl sulfate; sodium monolauryl sulfate; SDS; SLS; sulfuric acid monododecyl ester, sodium salt; Texapon K12P.

Chemical Name and CAS Registry Number:

Sulfuric acid monododecyl ester sodium salt (1: 1) [151-21-3]

Empirical Formula and Molecular Weight:

$C_{12}H_{25}NaO_4S$, 288.38

The USP32–NF27 describes sodium lauryl sulfate as a mixture of sodium alkyl sulfates consisting chiefly of sodium lauryl sulfate [$CH_3(CH_2)_{10}CH_2OSO_3Na$]. The PhEur 6.0 states that sodium lauryl sulfate should contain not less than 85% of sodium alkyl sulfates calculated as $C_{12}H_{25}NaO_4S$.

Description

SLS consists of white or cream to pale yellow-colored crystals, flakes or powder having a smooth feel, a soapy, bitter taste, and a faint odor of fatty substances.

Solubility

Freely soluble in methanol and DMSO; sparingly soluble in water, ethanol and acetone; partly soluble in alcohols.

Functional Category

Anionic surfactant; detergent; emulsifying agent; skin penetrant; tablet and capsule lubricant; wetting agent.

Applications in Pharmaceutical Formulation or Technology

Sodium lauryl sulfate is an anionic surfactant employed in a wide range of nonparenteral pharmaceutical formulations and cosmetics.

It is a detergent and wetting agent effective in both alkaline and acidic conditions. In recent years it has found application in analytical electrophoretic techniques: SDS (sodium dodecyl sulfate) polyacrylamide gel electrophoresis is one of the more widely used techniques for the analysis of proteins; and sodium lauryl sulfate has been used to enhance the selectivity of micellar electrokinetic chromatography (MEKC).

Stability and Storage conditions

Sodium lauryl sulfate is stable under normal storage conditions. However, in solution, under extreme conditions, i.e. pH 2.5 or below, it undergoes hydrolysis to lauryl alcohol and sodium bisulfate. The bulk material should be stored in a well-closed container away from strong oxidizing agents in a cool, dry place.

Incompatibilities

Sodium lauryl sulfate reacts with cationic surfactants, causing loss of activity even in concentrations too low to cause precipitation. Unlike soaps, it is compatible with dilute acids and calcium and magnesium ions. Sodium lauryl sulfate is incompatible with salts of polyvalent metal ions, such as aluminum, lead, tin or zinc, and precipitates with potassium salts. Solutions of sodium lauryl sulfate (pH 9.5–10.0) are mildly corrosive to mild steel, copper, brass, bronze and aluminum.

6.2.7. ASPARTAME [63]

Nonproprietary Names

BP: Aspartame

PhEur: Aspartame

USP-NF: Aspartame

Synonyms

(3 S)-3-Amino-4-[[(1S)-1-benzyl-2-methoxy-2-oxoethyl]amino]-4-oxobutanoic acid; 3-amino-N-(a -carboxyphenethyl)succinamic acid N-methyl ester; 3-amino- N-(a -methoxycarbonylphenethyl) succinamic acid; APM; aspartamum; aspartyl phenylamine methyl ester; Canderel ; E951; Equal; methyl N- L -a-aspartyl-L -phenylala-ninate; NatraTaste; NutraSweet; Pal Sweet; Pal Sweet Diet; Sanecta; SC-18862; Tri-Sweet.

Chemical Name and CAS Registry Number

N- L -a –Aspartyl -L- phenylalanine 1-methyl ester [22839-47-0]

Empirical Formula and Molecular Weight

$C_{14}H_{18}N_2O_5$, 294.30

Description

Aspartame occurs as a off white, almost odorless crystalline powder with an intensely sweet taste.

Solubility

Sparingly soluble in water and slightly soluble in ethanol.

Functional Category

Sweetening agent.

Applications in Pharmaceutical Formulation or Technology

Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It enhances flavor systems and can be used to mask some unpleasant taste characteristics; the approximate sweetening power is 180–200 times that of sucrose. Unlike some other intense sweeteners, aspartame is metabolized in the body and consequently has some nutritive value: 1 g provides approximately 17 kJ (4 kcal). However, in practice, a small quantity of aspartame consumed provides a minimal nutritive effect.

Stability and Storage conditions

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl- L-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine with a resulting loss of sweetness. A third-degradation product is also known, b- L -aspartyl-L-phenylalanine methyl ester. For the stability profile at 258^{o} C in aqueous buffers. Stability in aqueous solutions has been enhanced by the addition of cyclodextrins, and by the addition of polyethylene glycol 400 at pH 2. However, at pH 3.5–4.5 stability is not enhanced by the replacement of water with organic solvents. Aspartame degradation also occurs during prolonged heat treatment; losses of aspartame may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.

The bulk material should be stored in a well-closed container, in a cool, dry place.

Incompatibilities

Differential scanning calorimetry experiments with some directly compressible tablet excipients suggests that aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate. Reactions between aspartame and sugar alcohols are also known.

6.2.8. MAGNESIUM STEARATE [63]

Nonproprietary Names

BP : Magnesium stearate

JP : Magnesium stearate

Ph. Eur : Magnesium stearate

USP – NF: Magnesium stearate

Synonyms

Magnesium octadecanoate, Octadecanoic acid magnesium salt, Stearic acid.

Chemical Name and CAS Registry Number:

Octadecanoic acid magnesium salt & [557-04-0]

Empirical Formula:

$C_{36}H_{70}MgO_4$

Functional Category

Tablet and Capsule lubricant

Description

Magnesium stearate is a very fine, light, white, precipitated or milled, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.

Solubility

Practically insoluble in ethanol, ethanol (95%), ether and water, slightly soluble in warm benzene and warm ethanol (95%).

Applications in Pharmaceutical Formulations or Technology

It is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25 – 5.0%w/w. It is also used in barrier creams.

Stability and Storage conditions

Magnesium stearate is stable and should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Incompatible with strong acids, alkalis and iron salts. Avoid mixing with strong oxidizing materials. Magnesium stearate cannot be used in products containing Aspirin, some vitamins and most alkaloidal salts.

Methodology

6. 3. MATERIALS AND METHODS

The list of API, excipients and their manufacturers and their use in the present study are shown in Table 6.1.

Table 6.1: List of Materials Used

S.No	Drug/Excipient/Chemical	Manufacturer/ Supplier	Use in Formulation
1.	Rizatriptan benzoate	Aurobindo Pharma Ltd, Hyderabad	Active Pharmaceutical Ingredient
2.	β –Cyclodextrin	Madras Pharmaceuticals Ltd, Chennai	Permeation enhancer
3.	Chitosan (Water Soluble)	Panvo Organics Pvt Ltd, Chennai	Permeation enhancer
4.	Sodium lauryl sulphate	Vin Biotech Systems Ltd, Chennai	Permeation enhancer
5.	Avicel 102	Apex Laboratories Pvt Ltd, Chennai	Diluent
6.	Mannitol	Apex Laboratories Pvt Ltd, Chennai	Diluent
7.	Crospovidone	Apex Laboratories Pvt Ltd, Chennai	Super disintegrant
8.	Magnesium stearate	Apex Laboratories Pvt Ltd, Chennai	Lubricant
9.	Aspartame	Apex Laboratories Pvt Ltd, Chennai	Sweetening agent

The list of Instruments/Equipments used in the present study and their manufacturers are shown in Table 6.2.

Table 6.2: List of Instruments/Equipments

S.No	Instruments/Equipments	Manufacturer
1.	Electronic Weighing Balance	Asha Scientific Company, Mumbai
2.	Shifter	Pharma Spares, Mumbai
3.	10- Station Rotary Compression Machine	Rimek, India
4.	Vernier Caliper	Mitutoyo, Japan
5.	Monsanto Hardness Tester	Erweka, Mumbai
6.	Friabilator	Electrolab, India
7.	pH Meter	M C Dalal, Chennai
8.	Tablet Disintegration Apparatus	M C Dalal, Chennai
9.	Dissolution Test Apparatus	Veego, Mumbai
10.	UV-Visible Spectrophotometer	Shimadzu, Japan
11.	Fourier Transform Infra-Red Spectrophotometer	Nicolet

6.3.1. Physical Compatibility Study

The physical admixture of the drug and excipients expected to be present in the final product were taken in 2 ml glass vials and sealed, and the glass vials were kept at room temperature and at $40^0 \pm 2^0$C/75% ± 5% RH for 1 month. At the end of every ten days, the samples were withdrawn and analyzed for color change. [64]

6.3.2. Chemical Compatibility Study

Infrared spectroscopy was studied using FTIR spectrophotometry and the spectrum was recorded in wave number region of 4000 to 400cm^{-1}. The procedure consisted of dispersing the sample (drug alone, mixture of drug and the optimized formulation) in KBr and compressed into discs by applying a pressure of 5 Tons for 5 minutes in a hydraulic press. The pellet was placed in the light path and the spectrum was recorded. [65]

6.3.3. Preparation of Buffer and Reagents [66]

6.3.3.1 Preparation of Sodium hydroxide solution (0.2 M)

8 g of Sodium hydroxide was dissolved in about 700 ml of distilled water and volume was made up to 1000 ml with distilled water.

6.3.3.2 Preparation of Potassium dihydrogen phosphate solution (0.2 M)

Potassium dihydrogen phosphate (27.218 g) was dissolved in about 700 ml of distilled water and the volume was made up to 1000 ml with distilled water.

6.3.3.3 Preparation of Phosphate buffer solution (pH 6.8)

50.0 ml of 0.2 M Potassium dihydrogen phosphate was taken in a 100 ml volumetric flask, to which 22.4 ml of 0.2 M sodium hydroxide was added and volume was made up to the mark with distilled water.

6.3.4. Standard Curve for Rizatriptan benzoate [51]

6.3.4.1. Standard Curve in Phosphate buffer pH 6.8

100 mg of Rizatriptan benzoate was weighed and transferred to 100 ml standard flask. It was dissolved in phosphate buffer pH 6.8 and made up to the volume with phosphate buffer pH 6.8, to get a concentration of 1 mg/ml. From the stock solution, 10 ml was taken and diluted to 100 ml with phosphate buffer pH 6.8 to get a concentration of 100 µg/ml. The above solution was further diluted with phosphate buffer to get concentrations of 1, 2, 3, 4 and 5 µg/ml. The absorbance of the resulting solutions was measured at 226 nm using UV-Visible Spectrophotometer taking phosphate buffer pH 6.8 as blank.

6.3.5. Preformulation Parameters [39, 51]

The properties of the tablets like weight variation, hardness, friability, disintegration time, dissolution profile and content uniformity depends on the powder parameters. Properties of powder, which are of most importance, are Bulk density, Hausner ratio and Compressibility index etc. These parameters were evaluated on a laboratory scale for optimum production with respect to quality and quantity.

Prior to compression into tablets, the blend was evaluated for following properties.

6.3.5.1. Angle of Repose

Angle of repose was determined by using funnel method. Powder was poured from a funnel that can be raised vertically until a maximum cone height, h, was obtained. Diameter of heap, D, was measured. The angle of repose, θ, was calculated by formula

$$\tan \theta = h / r$$

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

Where, **θ** is the angle of repose

h is the height of pile

r is the radius of the pile

Table 6.3: Relationship between Angle of Repose and Flowability [67]

Angle of Repose	Flowability
25-30	Excellent
31-35	Good
36-40	Fair
41-45	Passable
46-55	Poor
56-65	Very Poor
>65	Very Very Poor

6.3.5.2. Bulk Density

Apparent bulk density was determined by pouring presieved drug excipient blend into a graduated cylinder and measuring the volume and weight "as it is". It is expressed in g/mL and is given by

$$D_b = M / V_0$$

Where, **M** is the mass of the powder

V_0 is the volume of the powder

6.3.5.3. Tapped Density

It was determined by placing a graduated cylinder, containing a known mass of drug- excipient blend, on mechanical tapping apparatus. The tapped volume was measured by tapping the powder to constant volume. It is expressed in g/mL and is given by

$$D_t = M / V_t$$

Where, **M** is the mass of powder

V_t is the volume of powder

6.3.5.4. Compressibility Index or Carr's Index

It is expressed in percentage and is calculated by using the formula,

$$\text{Carr's Index, CI} = [(D_t - D_b)/D_t] \times 100$$

Where, D_t is the Bulk density in g/mL

D_b is the Tapped density in g/mL

6.3.5.5. Hausner's Ratio

It is the ratio of tapped density to bulk density. It is calculated by the following formula:

$$\text{Hausner's Ratio, HR} = D_t / D_b$$

Where, D_b is the Bulk Density in g/mL

D_t is the Tapped Density in g/mL

Table 6.4: Values of Carr's Index, Hausner's Ratio [67]

Carr's Index	Flow Property	Hausner's Ratio
<10	Excellent	1.00 – 1.11
11 – 15	Good	1.12 – 1.18
16 -20	Fair	1.19 – 1.25
21 – 25	Passable	1.26 – 1.34
26 – 31	Poor	1.35 – 1.45
32 – 37	Very Poor	1.46 – 1.59
>38	Very, very Poor	>1.60

6.3.6. Formulation of Tablets [26, 27]

Direct Compression is the process by which tablets are compressed directly from mixtures of the drug and excipients without any preliminary treatment. In this process, directly compressible diluents like Mannitol and Microcrystalline Cellulose are mixed with the drug and other excipients to produce a uniform mixture and compressed into tablet. An important feature of direct compression diluents is their dilution potential.

Composition of sublingual tablet of Rizatriptan benzoate by direct compression is shown in table 6.5. All the ingredients were passed through 60# mesh sieve. Required

quantity of drug and excipient mixed thoroughly in a polythene bag. Finally the magnesium stearate was added and mixed thoroughly to get free flowing powder. The blend was compressed using rotary tablet compression machine with 8 mm punch.

Figure 6.1: Schematic representation of formulation development of Rizatriptan benzoate Sublingual Tablets [26, 27]

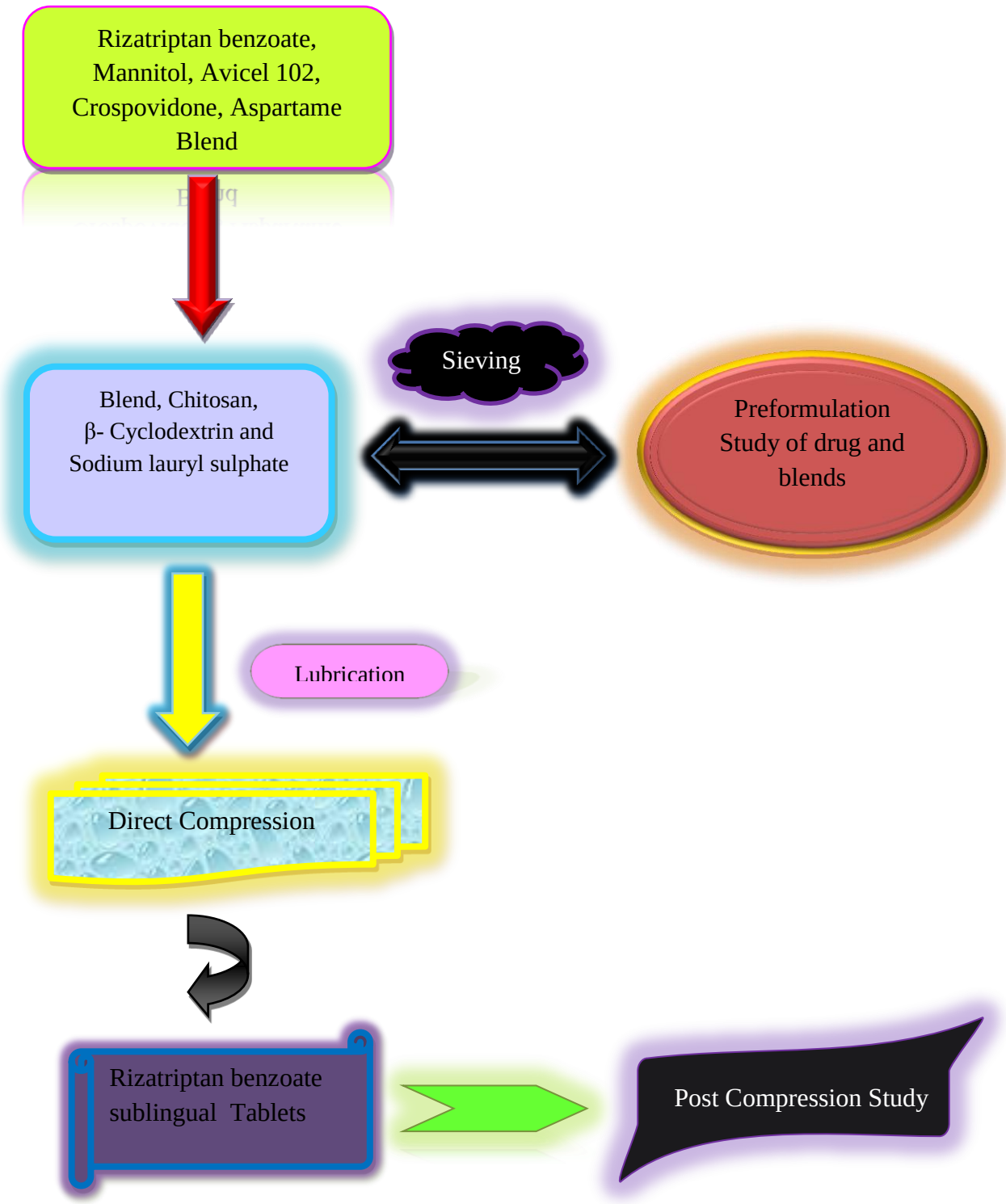


Table 6.5: Composition of Rizatriptan benzoate Sublingual Tablets [26, 27]

S.NO	INGREDIENTS	F-1*	F-2*	F-3*	F-4*	F-5*	F-6*	F-7*	F-8*	F-9*
1.	Rizatriptan benzoate**	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5	14.5
2.	Crospovidone	9	9	9	9	9	9	9	9	9
3.	Avicel 102	30.25	30.25	30.25	30.25	30.25	30.25	30.25	30.25	30.25
4.	Mannitol	92.5	91	89.5	92.5	91	89.5	92.5	91	89.5
5.	Beta-cyclodextrin	1.5	3	4.5	-	-	-	-	-	-
6.	Chitosan	-	-	-	1.5	3	4.5	-	-	-
7.	Sodium lauryl sulphate	-	-	-	-	-	-	1.5	3	4.5
8.	Aspartame	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75	0.75
9.	Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
	Total weight	150	150	150	150	150	150	150	150	150

* weight in mg ** Equivalent 10 mg Rizatriptan

6.3.7. Evaluation of Tablets [26, 27]

6.3.7.1. Description

Ten tablets were selected randomly and placed in a petridish. The tablets were observed from both the sides for colour, shape and appearance.

6.3.7.2. Uniformity of Weight

Twenty tablets were selected at random from each batch. The individual tablets were weighed and the average weight was determined. The individual weight was compared with the average weight. The variation in weight of tablets permissible is given in Table 6.6

Table 6.6: Uniformity of Weight [66, 67]

S.No	Average weight of a tablet	% Deviation
1.	80 mg or less	10
2.	More than 80 mg but less than 250 mg	7.5
3.	250 mg or more	5

6.3.7.3. Friability

20 tablets were weighed and placed in the Roche friabilator test apparatus, the tablets were exposed to rolling and repeated shocks, resulting from free falls within the apparatus. After 100 evolutions, the tablets were de-dusted and weighed again. The friability was determined as the percentage loss in weight of the tablets.

$$\text{Percentage Friability} = (1 - W/W_0) \times 100$$

Where,

W is the weight of the tablets after the test

$\mathbf{W_0}$ is the weight of the tablets before the test

6.3.7.4. Hardness

Hardness was measured using the Monsanto hardness tester. The pressure required to break diametrically placed matrix tablet, by a coiled spring was measured.

6.3.7.5. Dimensions

The thickness and diameter of the tablets were determined using a Vernier caliper. Three tablets from each formulation were used and average values were calculated.

6.3.7.6. *In-vitro* Disintegration Studies

Initially the disintegration time for sublingual tablets was measured using the conventional test for tablets as described in the pharmacopoeia. Tablets are placed in the disintegration tubes and time required for complete disintegration, that is without leaving any residues on the screen is recorded as disintegration time.

A modified method was also used to check the disintegration time. A about 6-8 mL of phosphate buffer 6.8 pH was taken in 10 mL of measuring cylinder .Tablet was placed in the cylinder and complete dispersion of tablet in the cylinder was recorded as the disintegration time.

6.3.7.7. Wetting Time [27]

A piece of tissue paper folded twice was placed in a small Petri dish (ID = 6.5 cm) containing 6 mL of simulated saliva pH, a tablet was put on the paper containing amaranth powder on the upper surface of the tablet, and the time required for formation of pink color was measured as wetting time. Three trials for each batch were performed and standard deviation was also determined.

6.3.7.8. Drug Content Uniformity

Twenty tablets were accurately weighed and finely powdered. A quantity equivalent to 20 mg of Rizatriptan benzoate was transferred to a 100 mL volumetric flask. To it, 50 mL of Phosphate buffer 6.8 was added and shaken to dissolve the drug. The solution was filtered and residue was washed with 25 mL of Phosphate buffer 6.8. The washing obtained was added to initial filtrate and volume was made upto 100 mL with Phosphate buffer 6.8. From the above solution 5 mL of stock solution was diluted to 100

mL. Again from second solution 10 mL of stock solution was diluted to 100 mL which gives 1 mcg/mL concentration. The drug content was determined spectrophotometrically at 226 nm.

6.3.7.9. *In vitro* Dissolution Studies [27]

Dissolution studies were carried out for all the formulations in USP paddle method (Apparatus 2) using Phosphate buffer 6.8, as the dissolution medium (900 mL) at 50 Rpm and 37 ± 0.5 ºC. Samples were periodically withdrawn at suitable time intervals and volume replaced with equivalent amounts of plain dissolution medium. The samples were analyzed spectrophotometrically at 226 nm.

6.3.7.10. *In vitro* Permeation study [26]

The open ended tube was used in the drug permeation study. The open ended tube enables *in vitro* analysis of drugs movement across a membrane using a two-compartment model. The donor compartment contains the formulation, a non-rate limiting membrane (semi permeable membrane) separates the compartments and supports the formulation. The samples were withdrawn from the beaker at regular intervals and the drug was quantified using UV spectrophotometer. The study was used to determine the rate and quantity of drug released from formulation containing Rizatriptan benzoate sublingual tablet.

6.3.7.11. *Ex vivo* permeation study [26]

i. Preparation of Excised Tissue

Goat buccal mucosa was obtained from the local slaughterhouse. The buccal mucosa was carefully removed from buccal cavity by cutting and pulling the mucosa from the cavity using forceps. The removed buccal mucosa was then immersed in Ringer's solution.

ii. Release Pattern of Drug from Sublingual Tablets

The open ended tube was used for release study. One side of the open ended tube one side was tightly tied with buccal mucosa and filled with drug solution. It acts as donor compartment. The open ended tube was immersed in receiver compartment beaker containing 200 mL of phosphate buffer pH 6.8 solution. The whole setup was maintained at 37^{o} C and stirrer was allowed to rotate at 50 rpm. At predetermined interval, 5 mL of sample was taken for 2

hours and simultaneously replaced with same volume of fresh buffer solution. Collected samples were suitably diluted and drug concentration was estimated using Shimadzu UV spectrophotometer at 226 nm.

Figure 6.2. *Ev-vivo* evaluation on goat sublingual mucosa

6.3.7.12. Stability Study [68]

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The storage conditions used for stability study was accelerated condition (40 ± 2 °C / 75 ± 5 %).

Stability study was carried out for the optimized formulations. Tablets of optimized formulation were striped packed and kept in humidity chamber for 90 days at the above mentioned temperature. Samples were withdrawn at monthly interval and analyzed for following parameters:

a. Dissolution and Permeability profile
b. Disintegration and Wetting time profile
c. Assay
d. Test for other physical parameters (Hardness, Thickness, Diameter and Friability).

Results and Discussion

7. RESULTS AND DISCUSSION

7.1. PREFORMULATION STUDIES

7.1.1. Solubility [66]

Rizatriptan benzoate is freely soluble in water, sparingly soluble in ethanol (96 per cent), slightly soluble in methylene chloride. It is also soluble in Phosphate Buffer pH-6.8.

7.1.2. Compatibility Study of Drug and Excipients

The compatibility between the drug and excipients was studied by FT-IR spectra. The position of peak in FT-IR spectra of pure Rizatriptan benzoate was compared with those in FT-IR spectra of Rizatriptan benzoate plus excipients. It was observed that, there was no disappearance or shift in peak position of Rizatriptan benzoate in any spectra of drug and excipients, which proved that the drug and excipients were compatible. Hence, it can be concluded that the drug can be used with the selected excipients without causing instability in the formulation. The data obtained is shown in Table 7.2 to 7.10. The spectra are reported in Figures 7.1 to 7.9.

Table 7.1: Physical compatibility study of drug and excipients

S.No	Drug and Excipients	Description and Conditions						
		Initial	Room temperature			40±2°C / 75±5%RH		
			10 Days	20 Days	30 Days	10 Days	20 Days	30 Days
1.	Rizatriptan benzoate	White Coloured Powder	NC	NC	NC	NC	NC	NC
2.	β -Cyclodextrin	White Crystalline Powder	NC	NC	NC	NC	NC	NC
3.	RZB + β - Cyclodextrin	White Yellow Coloured Powder	NC	NC	NC	NC	NC	NC
4.	Chitosan	Yellowish – White Powder	NC	NC	NC	NC	NC	NC

5.	RZB + Chitosan	Pale Yellow Coloured Powder	NC	NC	NC	NC	NC	NC
6.	Sodium lauryl sulphate	White Coloured Powder	NC	NC	NC	NC	NC	NC
7.	RZB + Sodium lauryl sulphate	White Coloured Powder	NC	NC	NC	NC	NC	NC
8.	Crospovidone	White Coloured Powder	NC	NC	NC	NC	NC	NC
9.	RZB + Crospovidone	White Coloured Powder	NC	NC	NC	NC	NC	NC
10.	Avicel 102	White Coloured Powder	NC	NC	NC	NC	NC	NC
11.	RZB + Avicel102	White Coloured Powder	NC	NC	NC	NC	NC	NC
12.	Mannitol	White Crystalline Powder	NC	NC	NC	NC	NC	NC
13.	RZB + Mannitol	White Coloured Powder	NC	NC	NC	NC	NC	NC
14.	Aspartame	white Coloured Powder	NC	NC	NC	NC	NC	NC
15.	RZB + Aspartame	White Coloured Powder	NC	NC	NC	NC	NC	NC
16.	Magnesium stearate	White Coloured Powder	NC	NC	NC	NC	NC	NC
17.	RZB + Magnesium stearate	White Coloured Powder	NC	NC	NC	NC	NC	NC

The physical compatibility study was performed and the results showed that there were no signs of incompatibility. The drug and the excipients are physically compatible.[65]

7.1.3. FTIR Study – Identification and Compatibility of Drug and Excipients

The identification of drug and the compatibility between the drug and excipients was carried out using FTIR. The FTIR spectra of the pure drug, drug excipient mixtures and tablet powder are shown in Figures 7.1 to 7.9 and Tables 7.2 to 7.10.

Figure 7.1: FTIR Spectrum of Rizatriptan benzoate

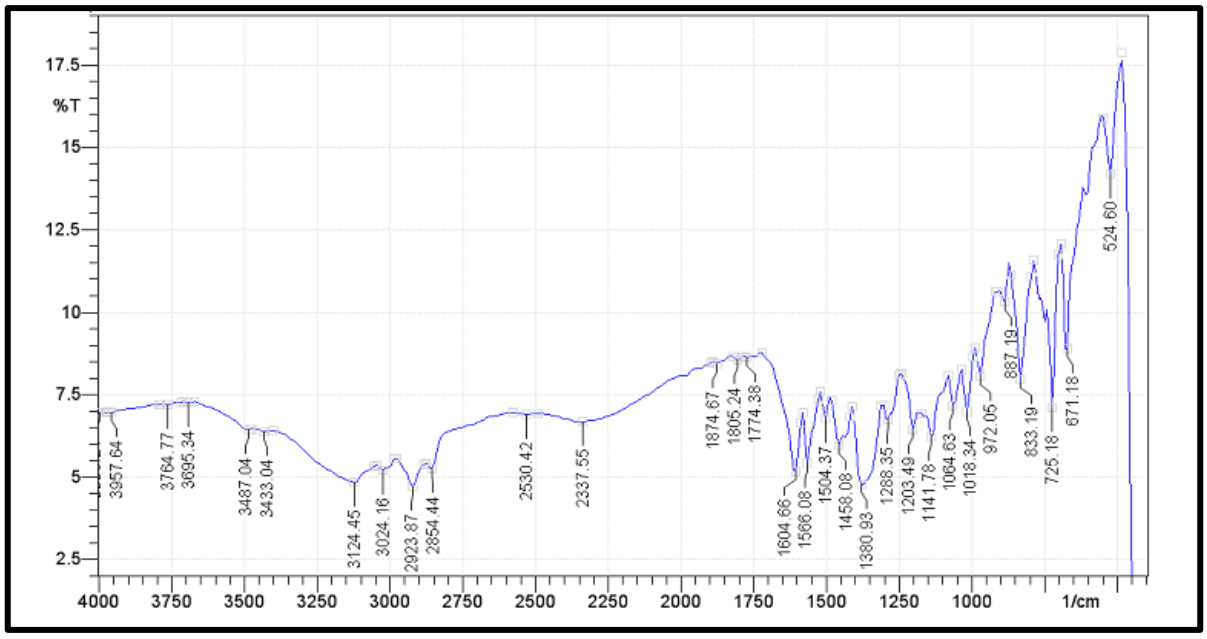


Table 7.2: FTIR Spectrum of Rizatriptan benzoate

Wave Number (cm^{-1})	Interpretation
3124	-OH Stretching (Carboxylic acid)
3024	-C-H Stretching (aliphatic)
2923	-C-H Stretching
1774	-C=O Stretching (Carboxylic acid)
1604	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1288	-C-C Stretching (Aliphatic)
1064	-C-N Stretching

Figure 7.2: FTIR Spectrum of Rizatriptan benzoate and β-cyclodextrin

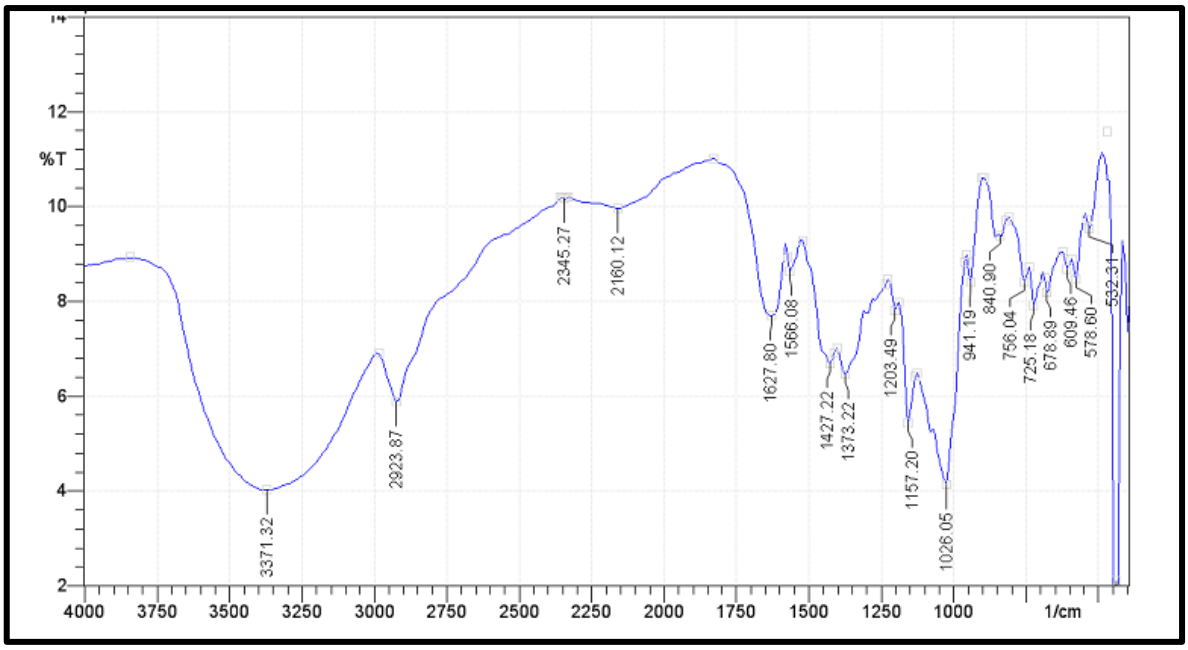


Table 7.3: FTIR Spectrum of Rizatriptan benzoate and β-cyclodextrin

Wave Number (cm^{-1})	Interpretation
3371	-OH Stretching (Carboxylic acid)
2923	-C-H Stretching
2160	-C=O Stretching (Carboxylic acid)
2160	-C=O Stretching (Carboxylic acid)
1627	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1157	-C-C Stretching (Aliphatic)
1064	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with β-cyclodextrin showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and β-cyclodextrin.[27]

Figure 7.3: FTIR Spectrum of Rizatriptan benzoate and Chitosan

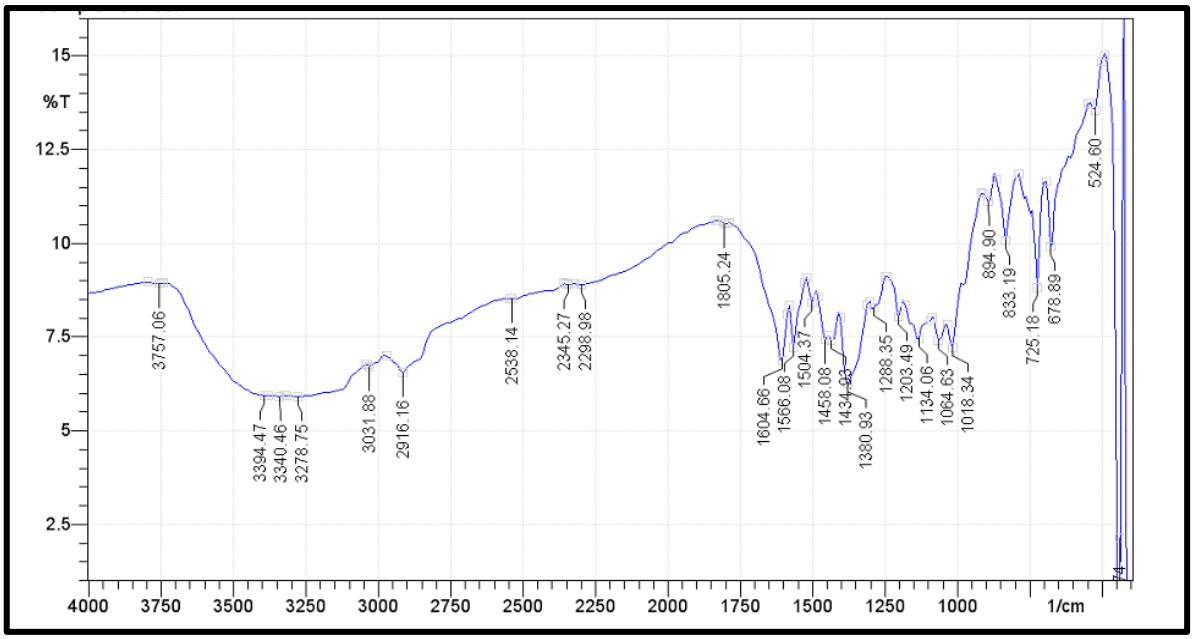


Table 7.4: FTIR Spectrum of Rizatriptan benzoate and β-cyclodextrin

Wave Number (cm^{-1})	Interpretation
3278	-OH Stretching (Carboxylic acid)
3031	-C-H Stretching (aliphatic)
2916	-C-H Stretching
1805	-C=O Stretching (Carboxylic acid)
1604	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1288	-C-C Stretching (Aliphatic)
1064	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Chitosan showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Chitosan. [27]

Figure 7.4: FTIR Spectrum of Rizatriptan benzoate and Sodium lauryl sulphate

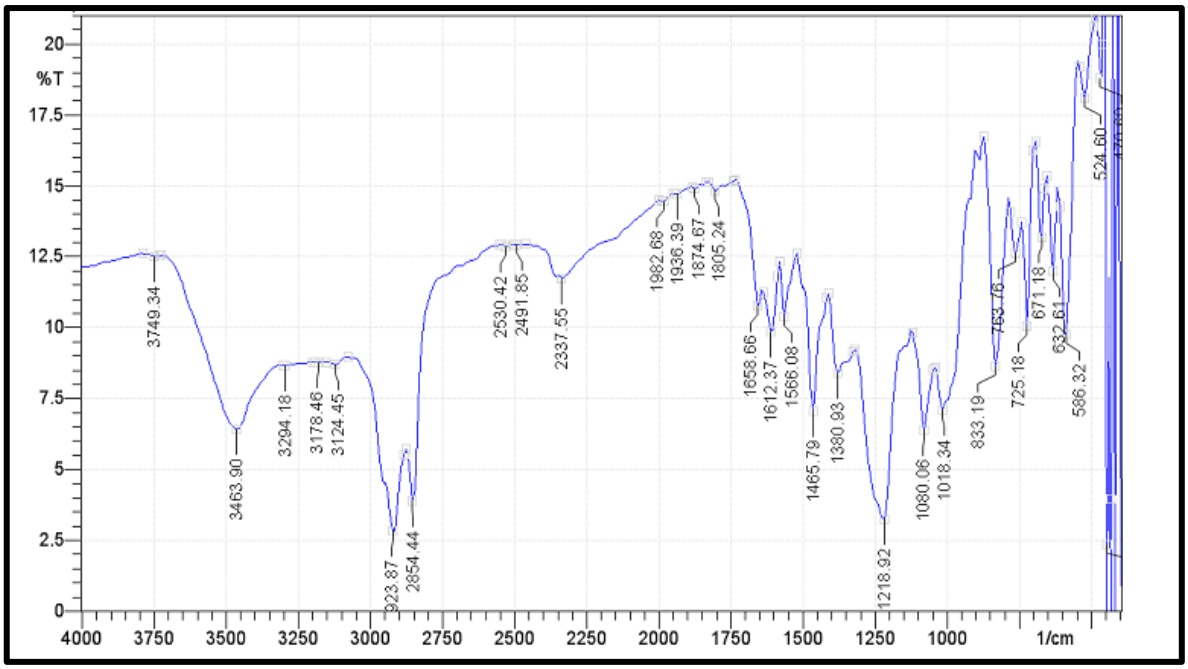


Table 7.5: FTIR Spectrum of Rizatriptan benzoate and Sodium lauryl sulphate

Wave Number (cm^{-1})	Interpretation
3124	-OH Stretching (Carboxylic acid)
2923	-C-H Stretching
1805	-C=O Stretching (Carboxylic acid)
1612	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1218	-C-C Stretching (Aliphatic)
1080	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Sodium lauryl sulphate showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Sodium lauryl sulphate. [27]

Figure 7.5: FTIR Spectrum of Rizatriptan benzoate and Avicel 102

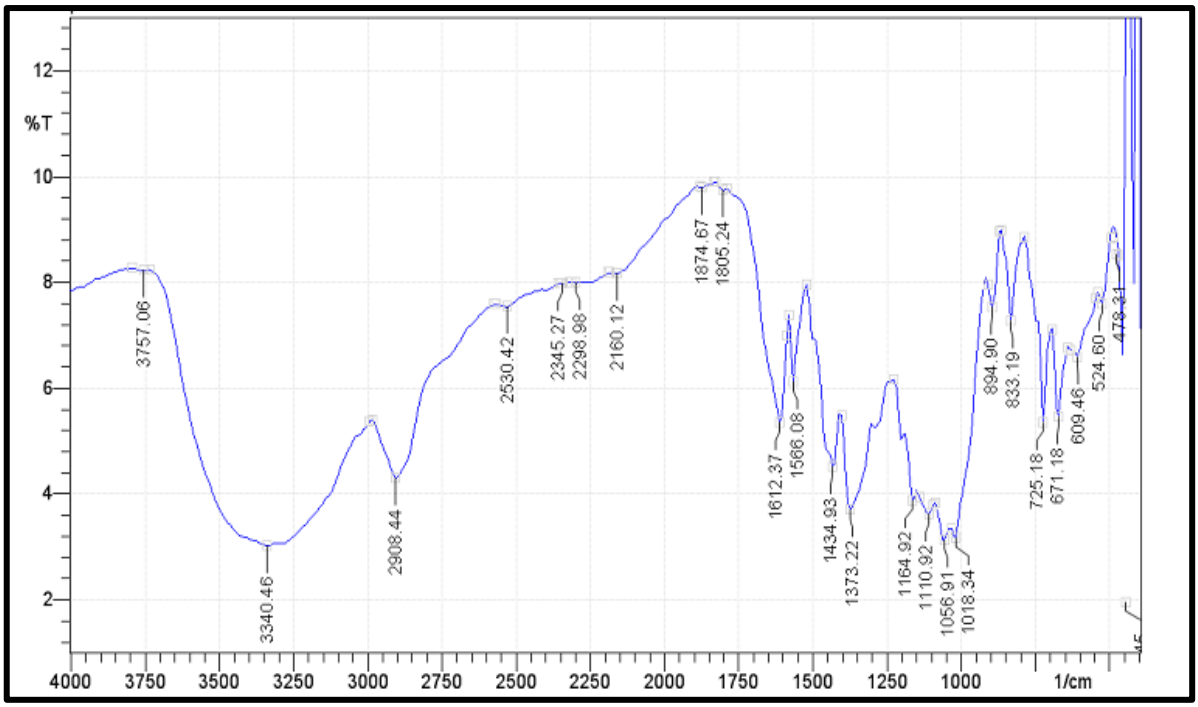


Table 7.6: FTIR Spectrum of Rizatriptan benzoate and Avicel 102

Wave Number (cm^{-1})	Interpretation
3340	-OH Stretching (Carboxylic acid)
2908	-C-H Stretching
1805	-C=O Stretching (Carboxylic acid)
1612	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1164	-C-C Stretching (Aliphatic)
1056	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Avicel 102 showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Avicel 102. [27]

Figure 7.6: FTIR Spectrum of Rizatriptan benzoate and Mannitol

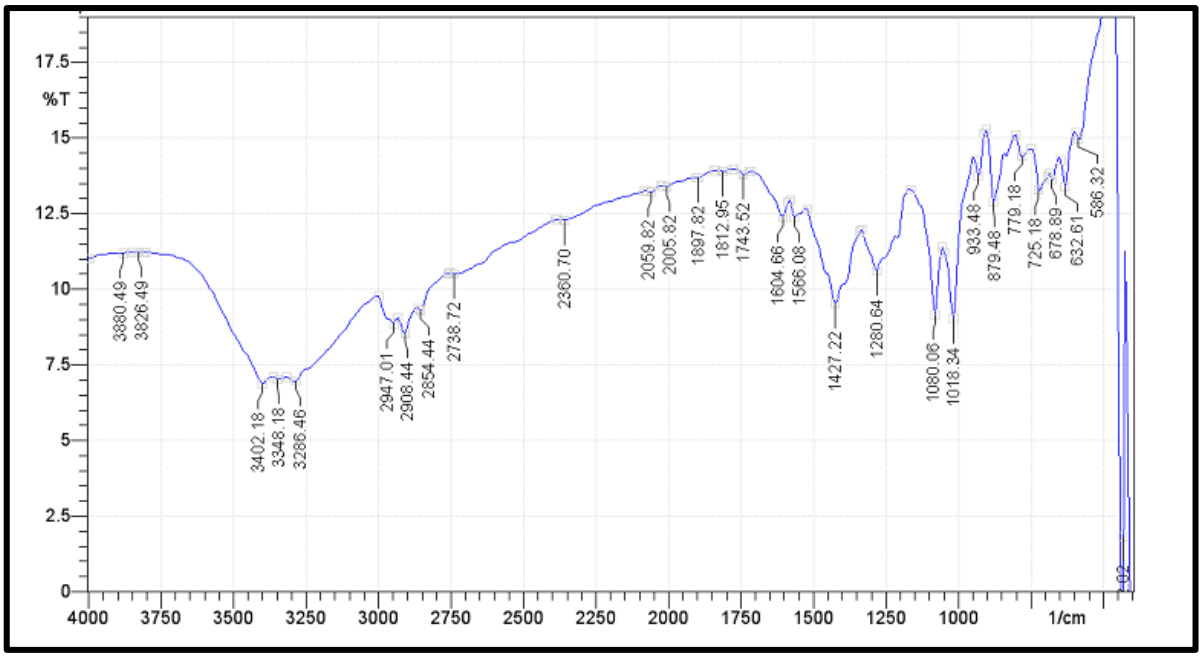


Table 7.7: FTIR Spectrum of Rizatriptan benzoate and Mannitol

Wave Number (cm^{-1})	Interpretation
3286	-OH Stretching (Carboxylic acid)
2947	-C-H Stretching (aliphatic)
2908	-C-H Stretching
1743	-C=O Stretching (Carboxylic acid)
1604	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1280	-C-C Stretching (Aliphatic)
1080	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Mannitol showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Mannitol. [27]

Figure 7.7: FTIR Spectrum of Rizatriptan benzoate and Crospovidone

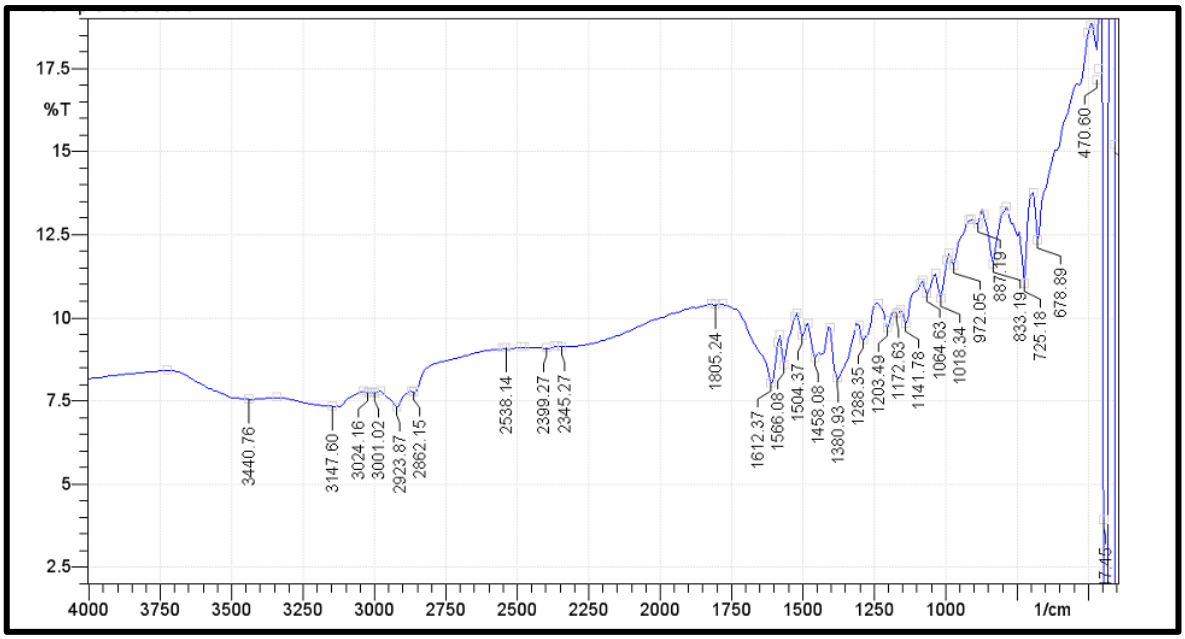


Table 7.8: FTIR Spectrum of Rizatriptan benzoate and Mannitol

Wave Number (cm^{-1})	Interpretation
3147	-OH Stretching (Carboxylic acid)
3024	-C-H Stretching (aliphatic)
2923	-C-H Stretching
1805	-C=O Stretching (Carboxylic acid)
1612	-C-C Stretching (Aromatic)
1566	-C=N Stretching (Hetero Aromatic)
1288	-C-C Stretching (Aliphatic)
1064	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Crospovidone showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Crospovidone. [27]

Figure 7.8: FTIR Spectrum of Rizatriptan benzoate and Aspartame

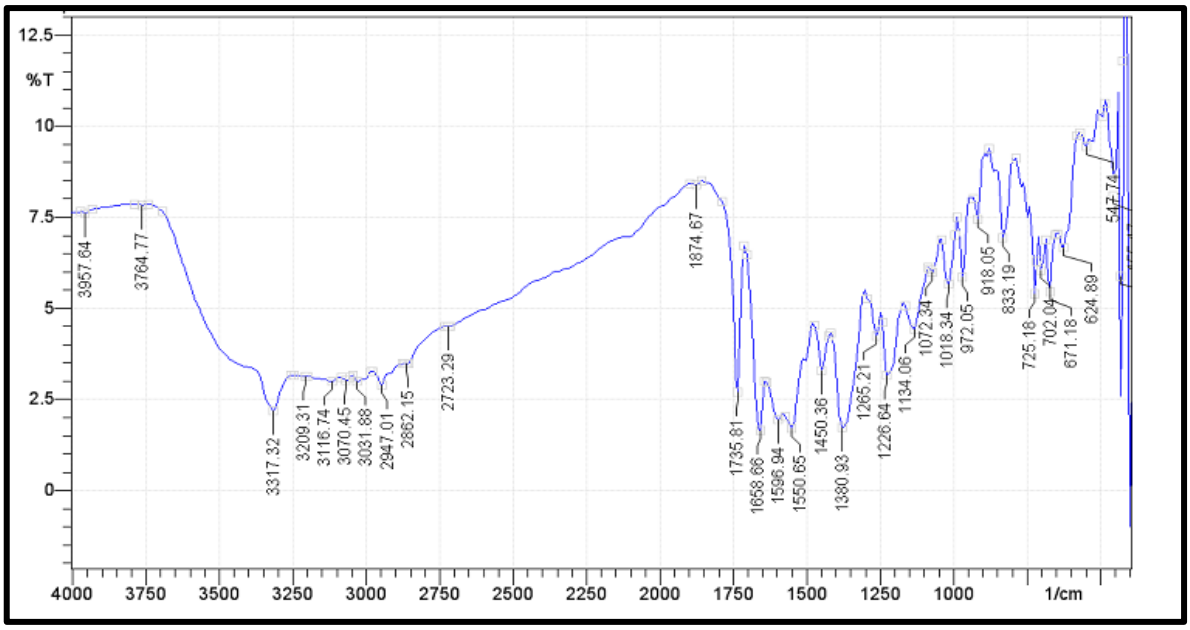


Table 7.9: FTIR Spectrum of Rizatriptan benzoate and Aspartame

Wave Number (cm^{-1})	Interpretation
3116	-OH Stretching (Carboxylic acid)
3031	-C-H Stretching (aliphatic)
2947	-C-H Stretching
1874	-C=O Stretching (Carboxylic acid)
1658	-C-C Stretching (Aromatic)
1550	-C=N Stretching (Hetero Aromatic)
1265	-C-C Stretching (Aliphatic)
1072	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Aspartame showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Aspartame. [27]

Figure 7.9: FTIR Spectrum of Rizatriptan benzoate and Magnesium stearate

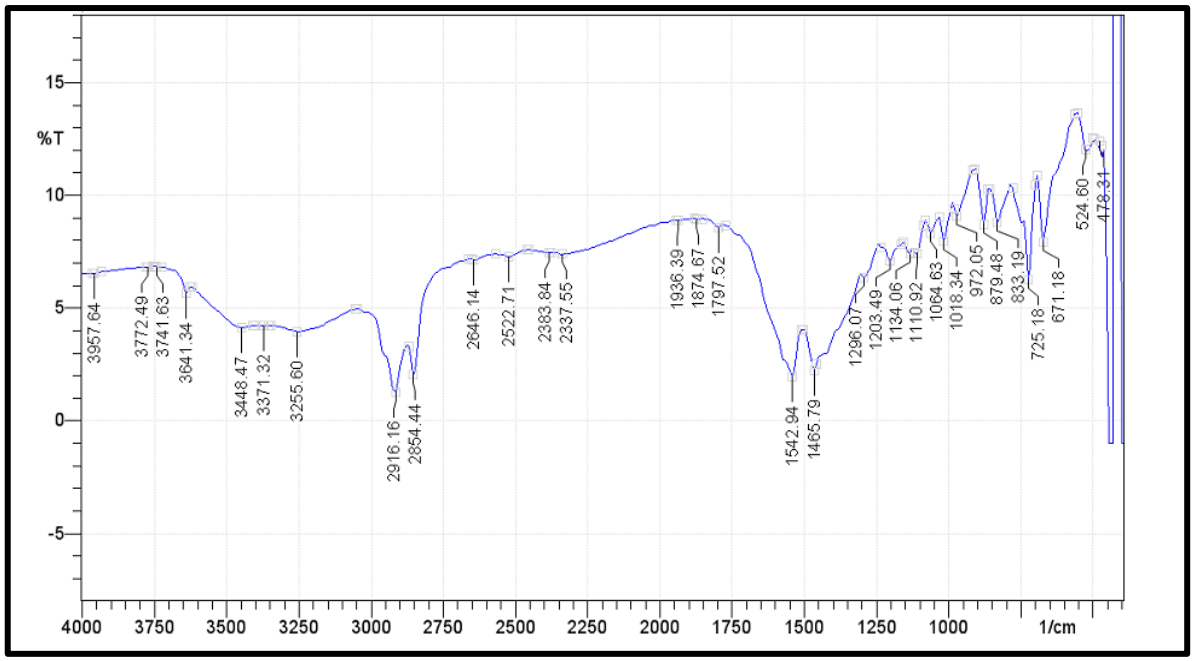


Table 7.10: FTIR Spectrum of Rizatriptan benzoate and Magnesium stearate

Wave Number (cm^{-1})	Interpretation
3255	-OH Stretching (Carboxylic acid)
3024	-C-H Stretching (aliphatic)
2916	-C-H Stretching
1797	-C=O Stretching (Carboxylic acid)
1542	-C-C Stretching (Aromatic)
1465	-C=N Stretching (Hetero Aromatic)
1296	-C-C Stretching (Aliphatic)
1064	-C-N Stretching

The peaks observed in the FTIR spectrum of Rizatriptan benzoate with Magnesium stearate showed no shift and no disappearance of characteristic peaks of drug. This suggests that there is no interaction between the drug and Magnesium stearate. [27]

7.1.4. Standard Curve of Rizatriptan benzoate [51]

The absorbance of the drug in different concentrations in phosphate buffer pH 6.8 was measured at a wavelength of 226 nm. The results are given in Table 7.11. The standard curves plotted using the absorbance of various concentrations is shown in Figure 7.10.

Table 7.11: Data for Standard curve of Rizatriptan benzoate

S.No	Concentration (mcg/ mL)	Absorbance			Mean ± SD
		SC-1	SC-2	SC-3	
1.	1	0.134	0.130	0.133	0.132 ± 0.0016996
2.	2	0.257	0.268	0.268	0.264 ± 0.0051854
3.	3	0.382	0.396	0.393	0.390 ± 0.0060184
4.	4	0.501	0.511	0.508	0.506 ± 0.0041899
5.	5	0.632	0.641	0.638	0.637 ± 0.0037416
	Regression	**0.99991**	**0.9995**	**0.9996**	**0.99967 ± 0.0001745**

Figure 7.10: Standard Curve of Rizatriptan benzoate in phosphate buffer pH 6.8

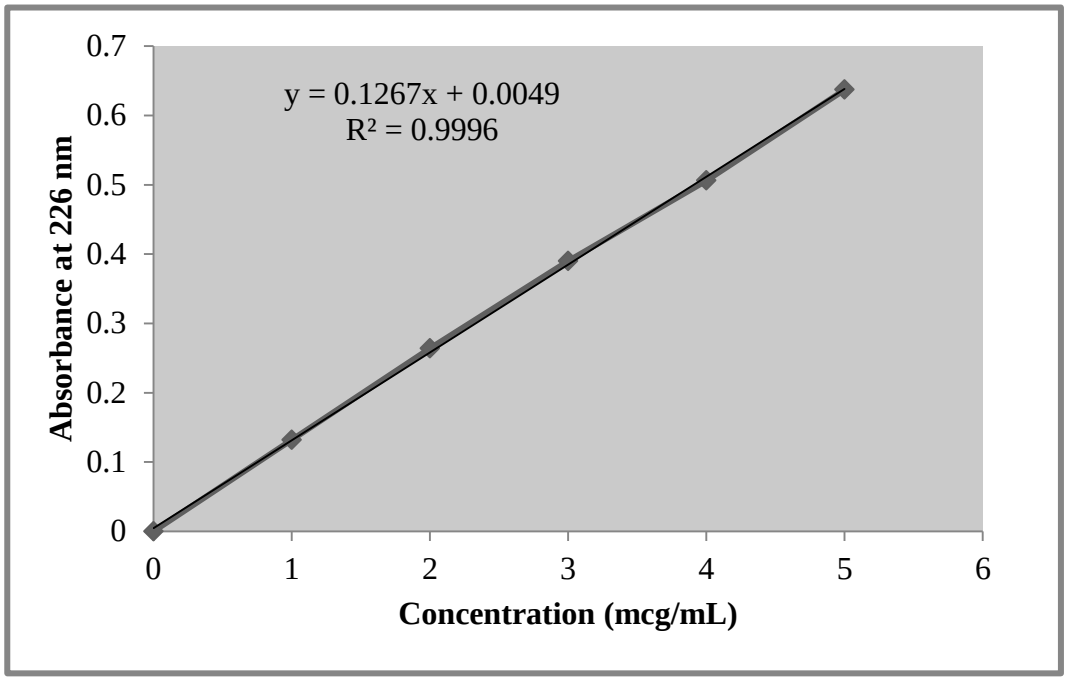


Figure 7.10. Standard curve of Rizatriptan benzoate

7.1.5. Pre-compression studies of the drug and powder blends [27, 67]

The results of the pre-compression study of the drug and the powder blends are given in Table 7.12 and Figures 7.11 to 7.15.

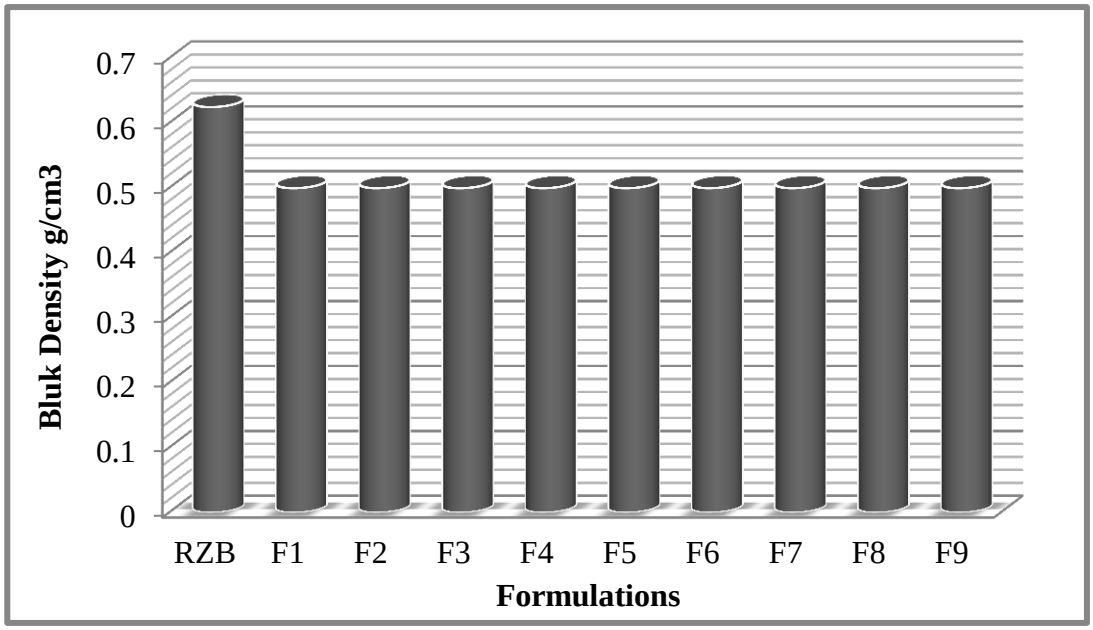
Table 7.12: Pre-compression study of drug and powder blends

Drug/ Powder blends	Bulk density* (g/cm^3)	Tapped density* (g/cm^3)	Compressibility index* (%)	Hausner's ratio*	Angle of Repose* (θ)
RZB	0.625±0.012	0.7142±0.024	12.14±0.045	1.142±0.063	33.05±0.047
F1	0.500±0.047	0.5555±0.015	10.00±0.024	1.111±0.017	29.75±0.054
F2	0.500±0.055	0.5454±0.032	08.3±0.038	1.099±0.009	29.30±0.026
F3	0.500±0.023	0.5395±0.067	07.33±0.016	1.079±0.025	28.89±0.054
F4	0.500±0.041	0.5454±0.052	08.33±0.037	1.079±0.052	29.00±0.035
F5	0.500±0.016	0.5357±0.043	06.66±0.021	1.071±0.038	28.89±0.062
F6	0.500±0.047	0.5319±0.068	05.99±0.059	1.063±0.027	29.17±0.028
F7	0.500±0.038	0.5260±0.016	05.00±0.028	1.052±0.045	29.40±0.063
F8	0.500±0.054	0.5357±0.047	06.66±0.015	1.071±0.029	29.29±0.037
F9	0.500±0.019	0.5261±0.035	05.00±0.012	1.052±0.053	29.67±0.046

*Mean±SD (n=3)

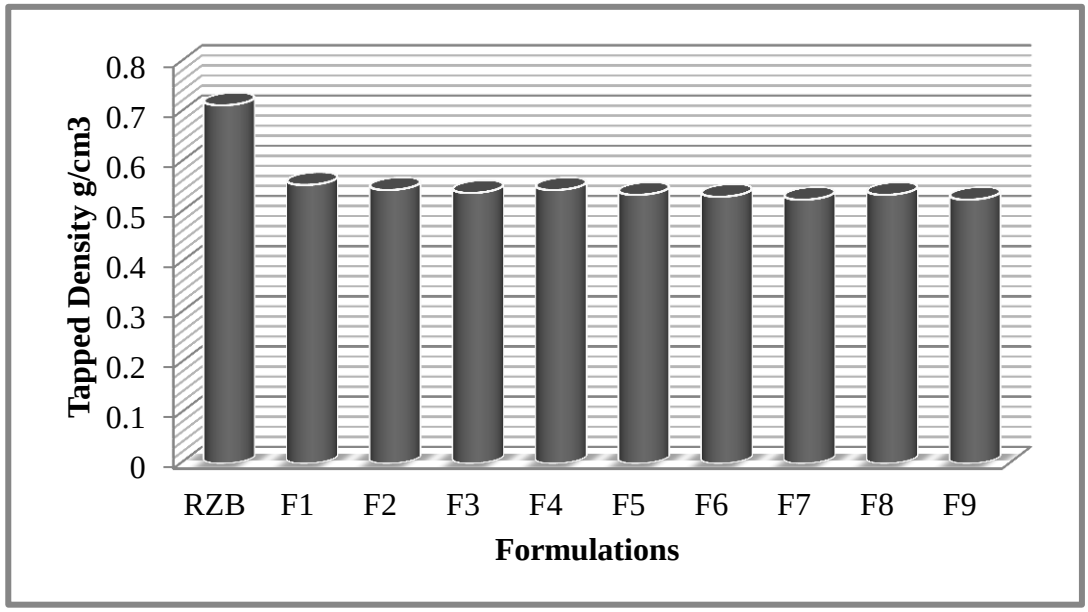
The drug has good flow property while the powder blends have excellent flow property.[4] Hence, the tablets were prepared by direct compression technique.

Figure 7.11: Bulk density of drug and powder blend



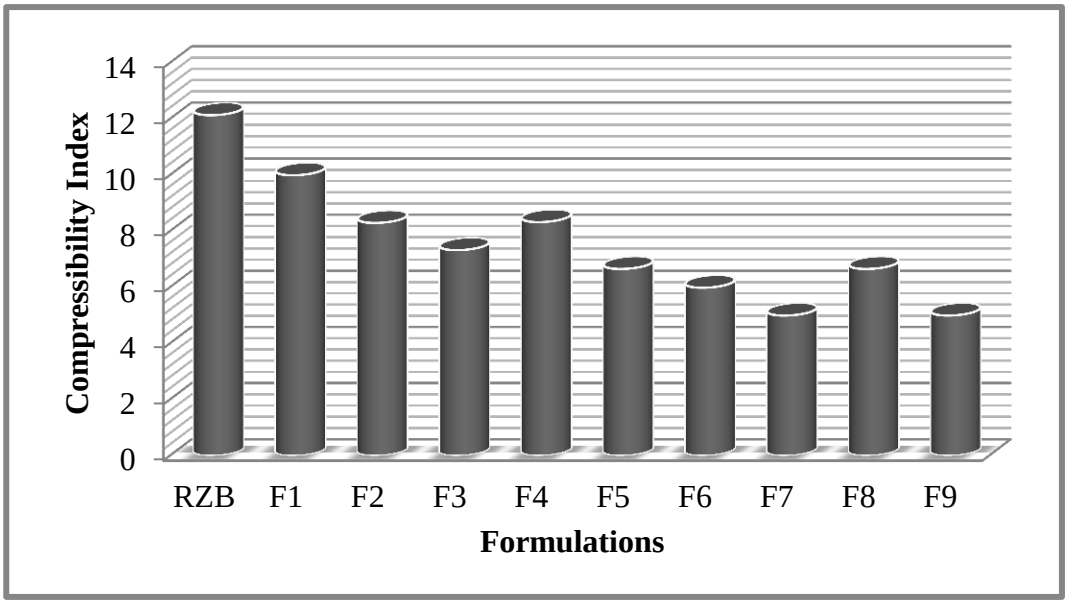
The bulk density of the drug was found to be 0.625 g/cm^3. The bulk density of the powder blend of various formulations ranged from 0.5013 g/cm^3 to 0.5 g/cm^3.

Figure 7.12: Tapped density of drug and powder blend



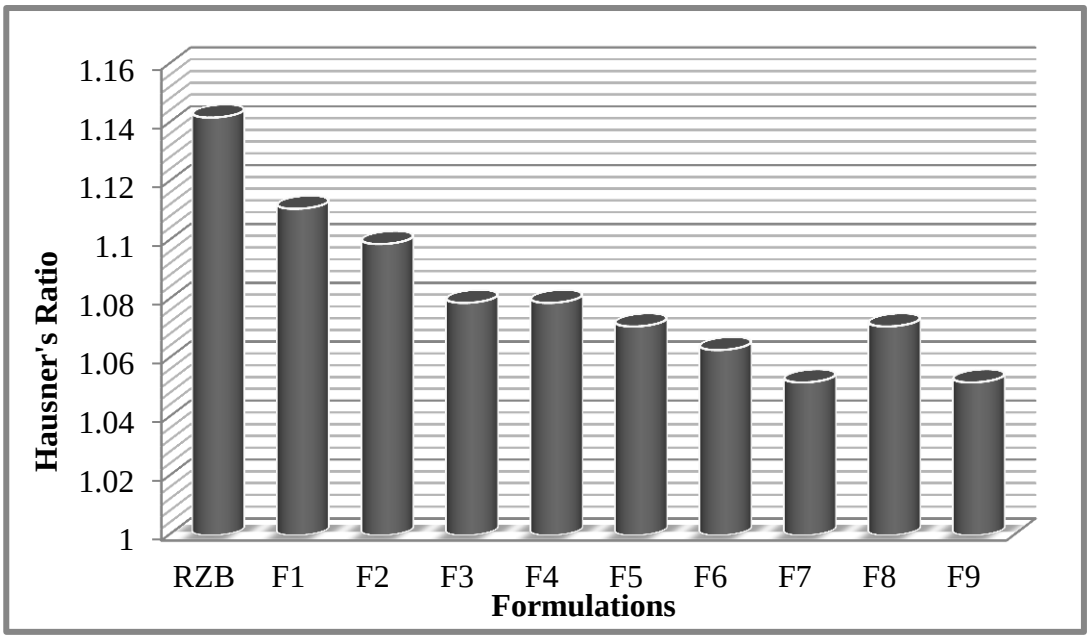
The tapped density of drug was found to be 0.7142 g/cm^3. The tapped density of various formulations ranged from 0.5555 g/cm^3 to 0.5261 g/cm^3.

Figure 7.13: Compressibility Index of drug and powder blend



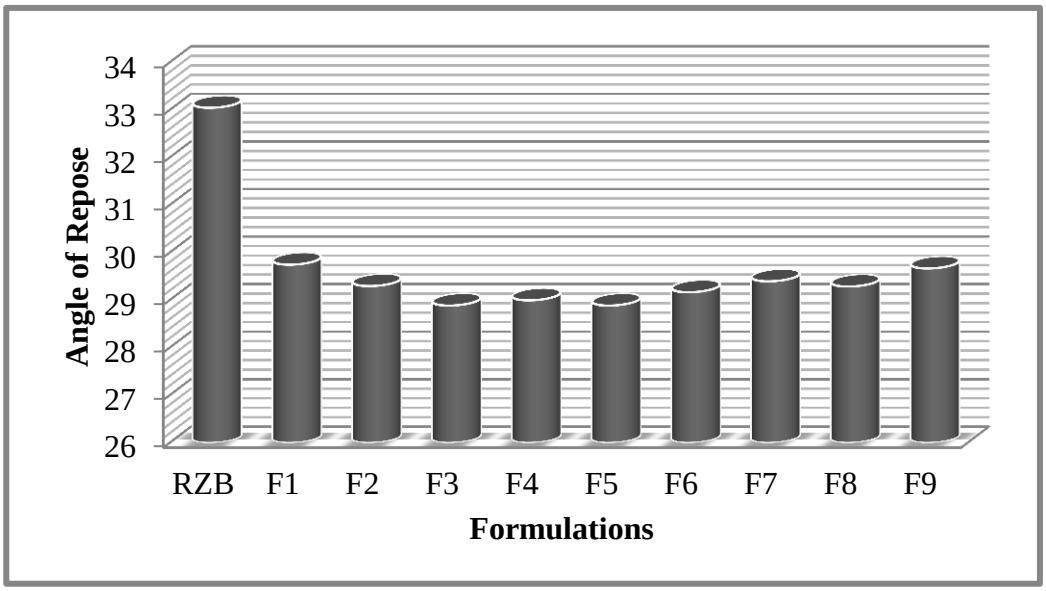
The compressibility index of the drug was found to be 12.14%. The compressibility index of various formulations ranged from 10% to 5%, showing excellent flow property.

Figure 7.14: Hausner's ratio of drug and powder blend



The Hausner's ratio of the drug was found to be 1.142. The Hausner's ratio of various formulations ranged from 1.111 to 1.052 showing excellent flow property.

Figure 7.15: Angle of repose of drug and powder blend



The angle of repose of the drug was found to be 33.05^{o}. The angle of repose of various formulations ranged from 29.75^{o} to 29.67^{o} showing excellent flow property.

7.2. POST-COMPRESSION EVALUATION OF SUBLINGUAL TABLETS

7.2.1. Description

The tablets were white coloured, round and flat faced with bevel edged bisect.

7.2.2. Thickness and Diameter [66]

Thickness and diameter of the nine formulations is given in Table 7.13.

The thickness and diameter of the tablets is 3.2 mm and 8mm respectively. The tablets (F-1 to F-9) have uniform thickness and diameter. [66]

7.2.3. Hardness

Hardness of the nine formulations is given in Table 7.13.

The hardness of the tablets ranged from 4.2 kg/cm^2 to 4.3 kg/cm^2. The tablets (F-1 to F-9) have sufficient hardness to withstand transport and handling. [66]

Table 7.13: Thickness, Diameter and Hardness of Sublingual tablets

Formulations	Thickness* (mm)	Diameter* (mm)	Hardness* kg/cm^2
F-1	3.2±0.0	8.0±0.0	4.3±0.2236
F-2	3.2±0.0	8.0±0.0	4.2±0.2236
F-3	3.2±0.0	8.0±0.0	4.3±0.1095
F-4	3.2±0.0	8.0±0.0	4.2±0.1414
F-5	3.2±0.0	8.0±0.0	4.2±0.0894
F-6	3.2±0.0	8.0±0.0	4.3±0.2236
F-7	3.2±0.0	8.0±0.0	4.2±0.3536
F-8	3.2±0.0	8.0±0.0	4.2±0.2739
F-9	3.2±0.0	8.0±0.0	4.2±0.2608

*Mean±SD (n=5)

7.2.4. Drug content

The content of active ingredient in various formulations is given in Table 7.14.

The percentage of drug content ranged from 95.20%w/w to 102.50%w/w. All the formulations comply with the official standards. [66]

7.2.5. Friability

The friability of various formulations is given in Table 7.14.

The percentage friability of various formulations ranged from 0.3123% to 0.9897%. The percentage friability is within the limit.[66]

7.2.6. Uniformity of Weight

The tablets were tested for uniformity of weight and the results are given in Table 7.14.

The weight of the tablets ranged from 0.152 g to 0.155 g. The tablets (F-1 to F-9) comply with the uniformity of weight test. [66, 67]

Table 7.14: Drug content, Uniformity of Weight and Friability of Sublingual tablets

Formulations	Drug content* (%w/w)	Friability* (%w/w)	Average Weight* (g)
F-1	098.24±0.0	0.7096±0.032	0.153±0.0015
F-2	095.20±0.0	0.9615±0.025	0.154±0.0053
F-3	101.41±0.0	0.9897.±0.016	0.153±0.0026
F-4	098.59±0.0	0.3123±0.027	0.152±0.0032
F-5	101.90±0.0	0.3838±0.014	0.152±0.0021
F-6	100.97±0.0	0.5727±0.035	0.153±0.0039
F-7	102.48±0.0	0.5692±0.022	0.154±0.0044
F-8	102.50±0.0	0.5832±0.011	0.155±0.0037
F-9	101.68±0.0	0.7690±0.018	0.155±0.0018

*Mean±SD (n=5)

7.2.7. Disintegration Time

The disintegration time of various formulations is given in Table 7.15.

The disintegration time ranged from 08 seconds to11 seconds. All the formulations comply with the official standards. [66]

7.2.8. Wetting Time

The wetting time of various formulations is given in Table 7.15.

The wetting time ranged from 03 to 05 seconds. [27]

Table 7.15: Drug content, Uniformity of Weight and Friability of Sublingual tablets

Formulations	Disintegration Time* (Sec)	Wetting Time* (Sec)
F-1	09.00±0.0	04.00±0.032
F-2	09.00±0.0	03.00±0.025
F-3	08.00±0.0	03.00.±0.016
F-4	11.00±0.0	05.00±0.027
F-5	09.00±0.0	04.00±0.014
F-6	09.00±0.0	04.00±0.035
F-7	10.00±0.0	04.00±0.022
F-8	09.00±0.0	03.00±0.011
F-9	08.00±0.0	03.00±0.018

*Mean±SD (n=5)

7.2.9. *In vitro* Dissolution study [27]

The results of *in vitro* dissolution study are shown in Table 7.16 to 7.19

Table 7.16: *In vitro* dissolution study of the sublingual tablets containing varying concentrations of β - Cyclodextrin

Time (Mins)	Cumulative Percentage Drug Release*		
	F-1	F-2	F-3
0	0	0	0
05	84.24±0.64	86.40±0.38	87.12±0.49
10	88.05±0.79	91.68±0.62	92.42±0.76
15	91.90±1.15	94.84±0.59	94.89±1.09
20	94.34±0.92	97.32±0.47	96.61±0.37
30	98.24±0.88	99.08±0.76	99.04±0.89
45	99.04±0.41	100.14±0.66	100.10±0.76
60	101.76±0.36	101.2±0.54	101.20±0.42

*Mean±SD (n=3)

Figure 7.16: Percentage cumulative drug release of formulation F-1, F-2 and F-3

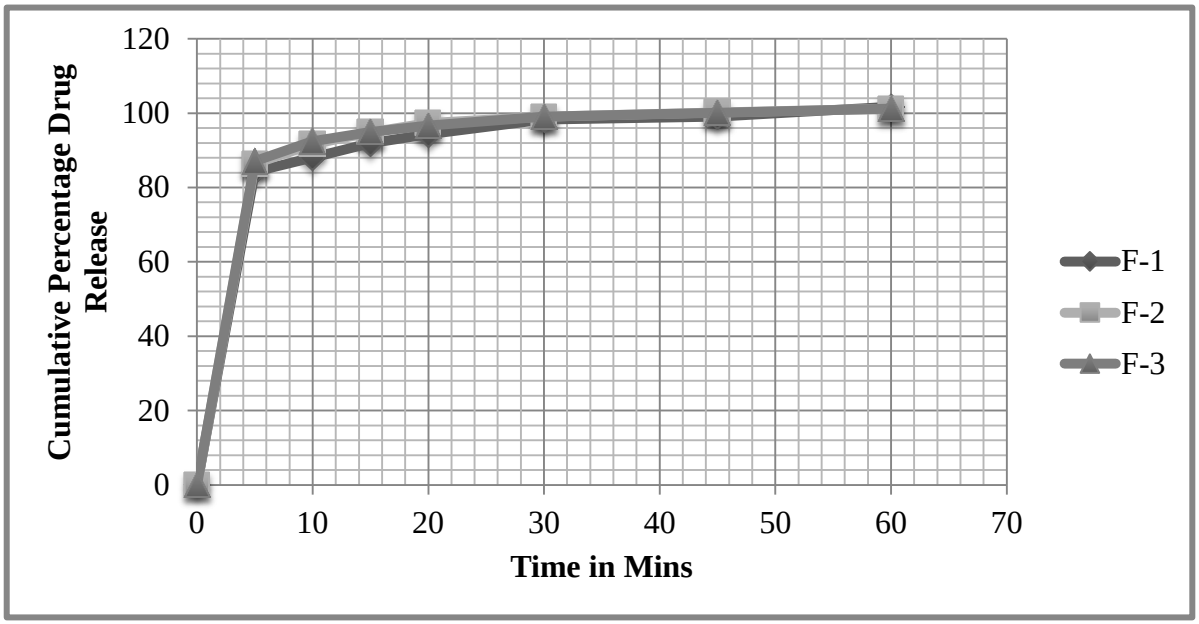


Table 7.17: *In vitro* dissolution study of the sublingual tablets containing varying concentrations of Chitosan lactate

Time (Mins)	Cumulative Percentage Drug Release*		
	F-4	F-5	F-6
0	0	0	0
05	83.72±0.64	84.24±0.38	85.68±0.49
10	88.32±0.79	87.33±0.62	88.07±0.76
15	91.16±1.15	90.45±0.59	90.48±1.09
20	93.59±0.92	93.60±0.47	92.90±0.37
30	96.79±0.88	97.44±0.76	96.78±0.89
45	98.52±0.41	99.25±0.66	98.53±0.76
60	100.20±0.36	101.00±0.54	100.90±0.42

*Mean±SD (n=3)

Figure 7.17: Percentage cumulative drug release of formulation F-4, F-5 and F-6

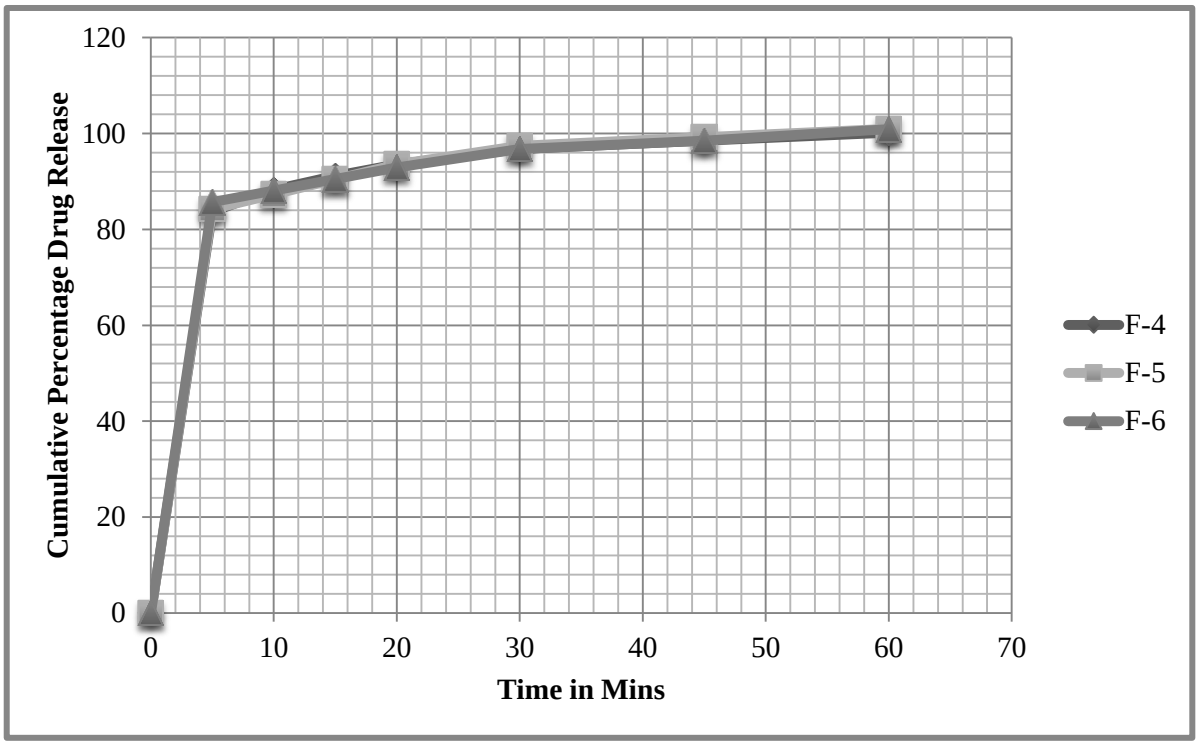


Table 7.18: *In vitro* dissolution study of the sublingual tablets containing varying concentrations of Sodium lauryl sulphate

Time (Mins)	Cumulative Percentage Drug Release*		
	F-7	F-8	F-9
0	0	0	0
05	84.96±0.64	85.68±0.38	86.40±0.49
10	87.34±0.79	89.51±0.62	90.24±0.76
15	90.74±1.15	91.93±0.59	92.67±1.09
20	92.88±0.92	94.37±0.47	95.12±0.37
30	96.76±0.88	96.11±0.76	96.86±0.89
45	98.51±0.41	97.85±0.66	98.61±0.76
60	99.55±0.36	99.60±0.54	100.30±0.42

*Mean±SD (n=3)

Figure 7.18: Percentage cumulative drug release of formulation F-7, F-8 and F-9

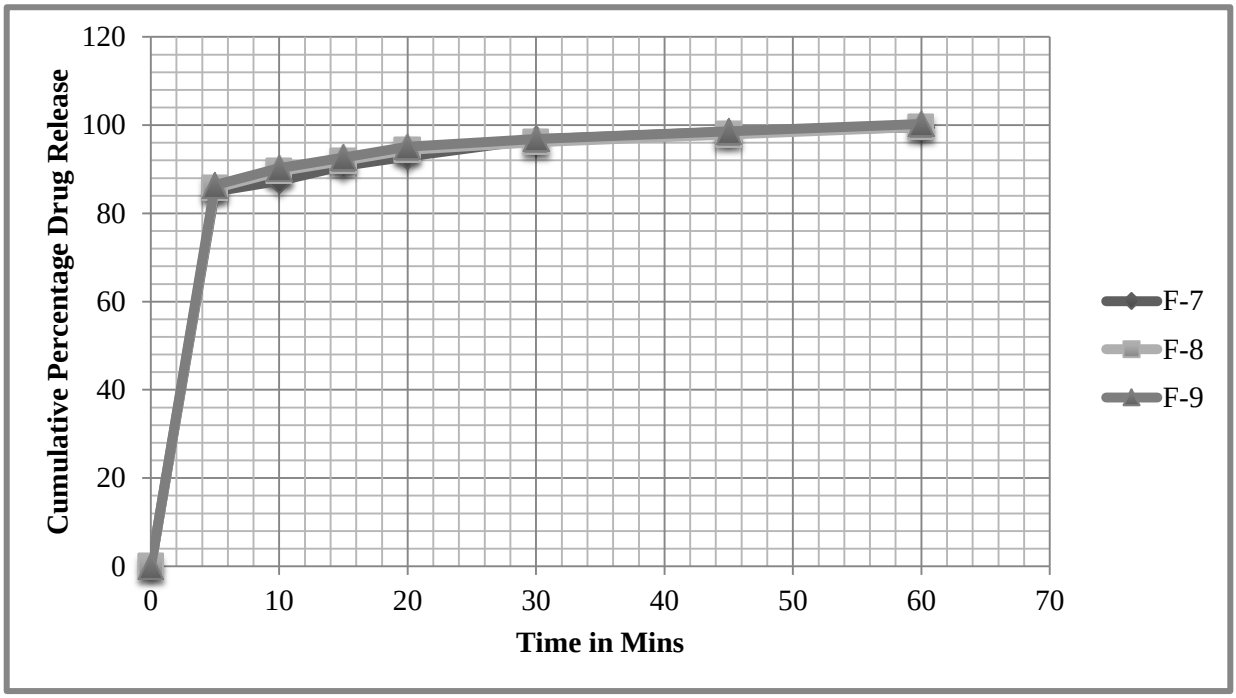
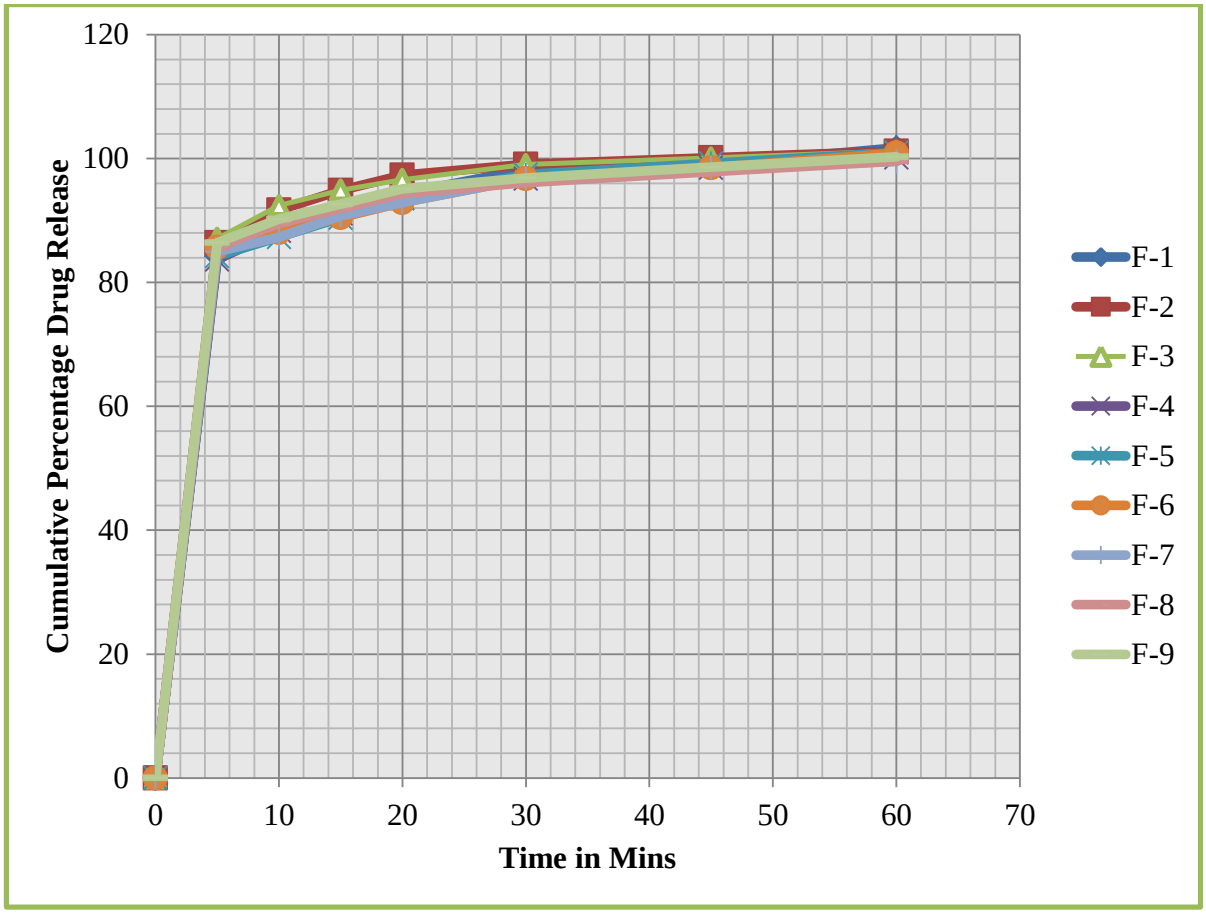


Table 7.19: *In vitro* dissolution study of the Rizatriptan benzoate Sublingual Tablets with various permeation enhancers

Time (Mins)	Cumulative Percentage Drug Release*								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
05	84.24±0.64	86.40±0.38	87.12±0.49	83.72±0.64	84.24±0.38	85.68±0.49	84.96±0.64	85.68±0.38	86.40±0.49
10	88.05±0.79	91.68±0.62	92.42±0.76	88.32±0.79	87.33±0.62	88.07±0.76	87.34±0.79	89.51±0.62	90.24±0.76
15	91.90±1.15	94.84±0.59	94.89±1.09	91.16±1.15	90.45±0.59	90.48±1.09	90.74±1.15	91.93±0.59	92.67±1.09
20	94.34±0.92	97.32±0.47	96.61±0.37	93.59±0.92	93.60±0.47	92.90±0.37	92.88±0.92	94.37±0.47	95.12±0.37
30	98.24±0.88	99.08±0.76	99.04±0.89	96.79±0.88	97.44±0.76	96.78±0.89	96.76±0.88	96.11±0.76	96.86±0.89
45	99.04±0.41	100.14±0.66	100.10±0.76	98.52±0.41	99.25±0.66	98.53±0.76	98.51±0.41	97.85±0.66	98.61±0.76
60	101.76±0.36	101.2±0.54	101.20±0.42	100.20±0.36	101.00±0.54	100.90±0.42	99.55±0.36	99.60±0.54	100.30±0.42

*Mean±SD (n=3)

Figure 7.19: Percentage cumulative drug release of formulation F-1 to F-9



All formulation showed maximum of 100% dissolution rate at the end of 60 minutes.

7.2.10. *In vitro* Permeation study [26]

The results of *in vitro* permeation study in egg membrane are shown in Table7.20-7.23

Table 7.20: *In vitro* permeation study in egg membrane of the sublingual tablets containing varying concentrations of β - Cyclodextrin

Time (Mins)	Cumulative Percentage Drug Release*		
	F-1	F-2	F-3
0	0	0	0
05	26.72±0.64	31.20±0.38	33.60±0.49
10	30.71±0.79	36.94±0.62	37.96±0.76
15	35.02±1.15	41.84±0.59	42.88±1.09
20	38.58±0.92	48.76±0.47	46.31±0.37
30	44.76±0.88	53.28±0.76	54.76±0.89
45	50.92±0.41	59.63±0.66	60.67±0.76
60	56.89±0.36	62.12±0.54	66.06±0.42

*Mean±SD (n=3)

Figure 7.20: Percentage cumulative drug release of formulation F-1, F-2 and F-3

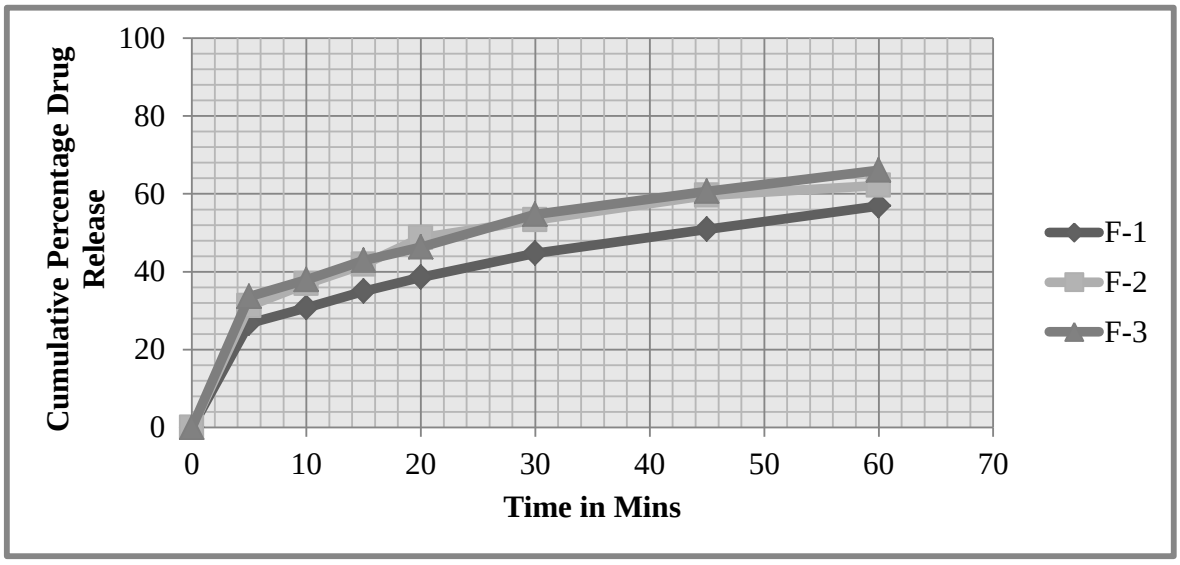


Table 7.21: *In vitro* permeation study in egg membrane of the sublingual tablets containing varying concentrations of Chitosan lactate

Time (Mins)	Cumulative Percentage Drug Release*		
	F-4	F-5	F-6
0	0	0	0
05	31.36±0.64	34.24±0.38	35.36±0.49
10	35.34±0.79	37.15±0.62	40.24±0.76
15	38.92±1.15	42.89±0.59	45.06±1.09
20	42.58±0.92	47.20±0.47	51.90±0.37
30	47.58±0.88	53.83±0.76	57.93±0.89
45	53.96±0.41	60.52±0.66	65.03±0.76
60	60.95±0.36	67.34±0.54	72.28±0.42

*Mean±SD (n=3)

Figure 7.21: Percentage cumulative drug release of formulation F-4, F-5 and F-6

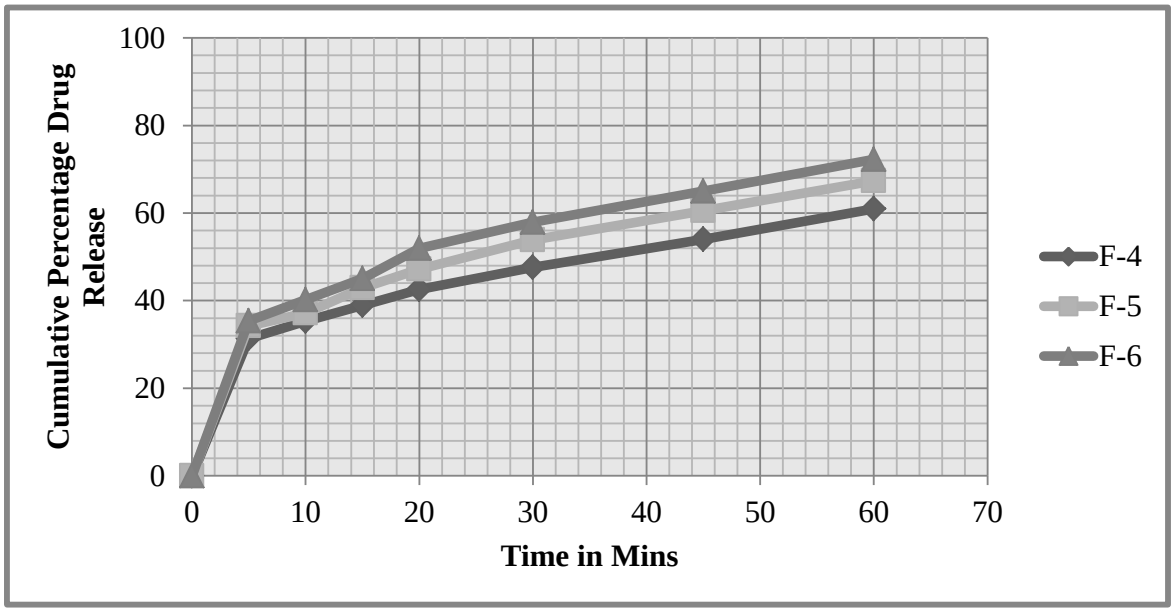


Table 7.22: *In vitro* permeation study in egg membrane of the sublingual tablets containing varying concentrations of Sodium lauryl sulphate

Time (Mins)	Cumulative Percentage Drug Release*		
	F-7	F-8	F-9
0	0	0	0
05	24.32±0.64	25.44±0.38	28.32±0.49
10	28.44±0.79	27.83±0.62	32.38±0.76
15	32.34±1.15	31.55±0.59	37.40±1.09
20	37.28±0.92	36.31±0.47	41.00±0.37
30	41.04±0.88	42.28±0.76	43.87±0.89
45	45.19±0.41	49.35±0.66	52.87±0.76
60	52.14±0.36	56.24±0.54	62.06±0.42

*Mean±SD (n=3)

Figure 7.22: Percentage cumulative drug release of formulation F-7, F-8 and F-9

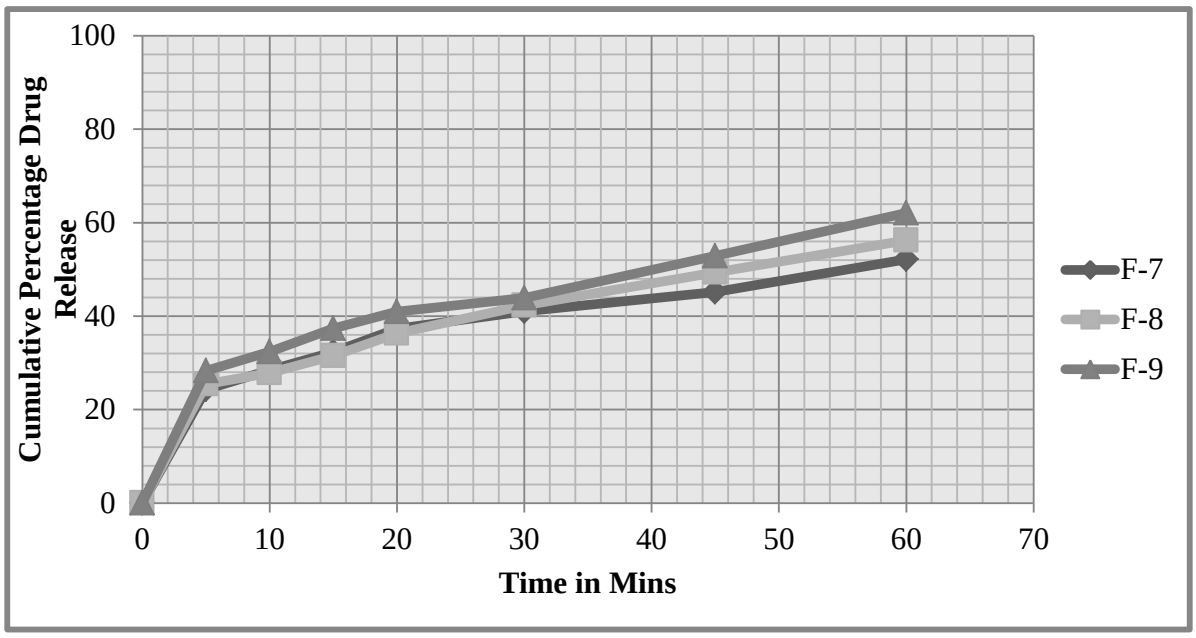
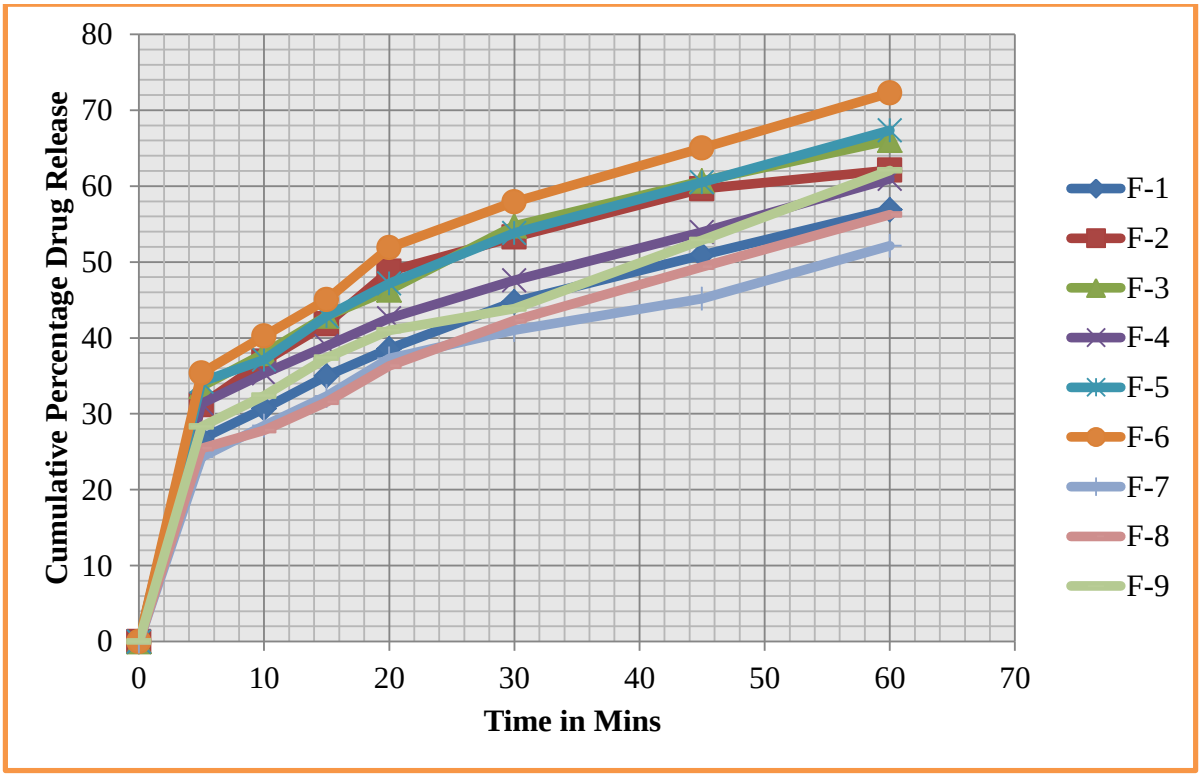


Table 7.23: *In vitro* permeation study on egg membrane of the Rizatriptan benzoate sublingual tablets with various permeation enhancers

Time (Mins)	Cumulative Percentage Drug Release*								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
05	26.72±0.64	31.20±0.38	33.60±0.49	31.36±0.64	34.24±0.38	35.36±0.49	24.32±0.64	25.44±0.38	28.32±0.49
10	30.71±0.79	36.94±0.62	37.96±0.76	35.34±0.79	37.15±0.62	40.24±0.76	28.44±0.79	27.83±0.62	32.38±0.76
15	35.02±1.15	41.84±0.59	42.88±1.09	38.92±1.15	42.89±0.59	45.06±1.09	32.34±1.15	31.55±0.59	37.40±1.09
20	38.58±0.92	48.76±0.47	46.31±0.37	42.58±0.92	47.20±0.47	51.90±0.37	37.28±0.92	36.31±0.47	41.00±0.37
30	44.76±0.88	53.28±0.76	54.76±0.89	47.58±0.88	53.83±0.76	57.93±0.89	41.04±0.88	42.28±0.76	43.87±0.89
45	50.92±0.41	59.63±0.66	60.67±0.76	53.96±0.41	60.52±0.66	65.03±0.76	45.19±0.41	49.35±0.66	52.87±0.76
60	56.89±0.36	62.12±0.54	66.06±0.42	60.95±0.36	67.34±0.54	72.28±0.42	52.14±0.36	56.24±0.54	62.06±0.42

*Mean±SD (n=3)

Figure 7.23: Percentage cumulative drug release of formulation F-1 to F-9



Formulation F-1, F-2, and F-3 showed 56.89%, 62.12% and 66.06% drug release at the end of 60 minutes. The formulation F-4, F-5 and F-6 showed 60.95%, 67.34% and 72.28% drug release at the end of 60 minutes. Formulation F-7, F-8 and F-9 showed 52.14%, 56.24% and 62.06% at the end of 60 minutes. Among these, F-6 showed 72.28% at the end of 60 minutes with high permeability.

7.2.11. *Ex vivo* Permeation study [26]

The results of *ex vivo* permeation study in goat sublingual mucosa are in Table 7.24-7.27

Table 7.24: *Ex vivo* permeation study in goat sublingual mucosa of the sublingual tablets containing varying concentrations of β - Cyclodextrin

Time (Mins)	Cumulative Percentage Drug Release*		
	F-1	F-2	F-3
0	0	0	0
05	27.52±0.64	32.64±0.38	37.60±0.49
10	31.08±0.79	37.93±0.62	39.98±0.76
15	35.84±1.15	43.98±0.59	44.95±1.09
20	40.06±0.92	50.64±0.47	48.43±0.37
30	46.13±0.88	55.19±0.76	57.24±0.89
45	51.84±0.41	61.59±0.66	63.37±0.76
60	57.99±0.36	64.28±0.54	68.34±0.42
90	65.00±0.59	71.80±0.88	75.00±0.38
120	71.60±0.47	78.35±0.41	83.01±0.62

*Mean±SD (n=3)

Figure 7.24: Percentage cumulative drug release of formulation F-1, F-2 and F-3

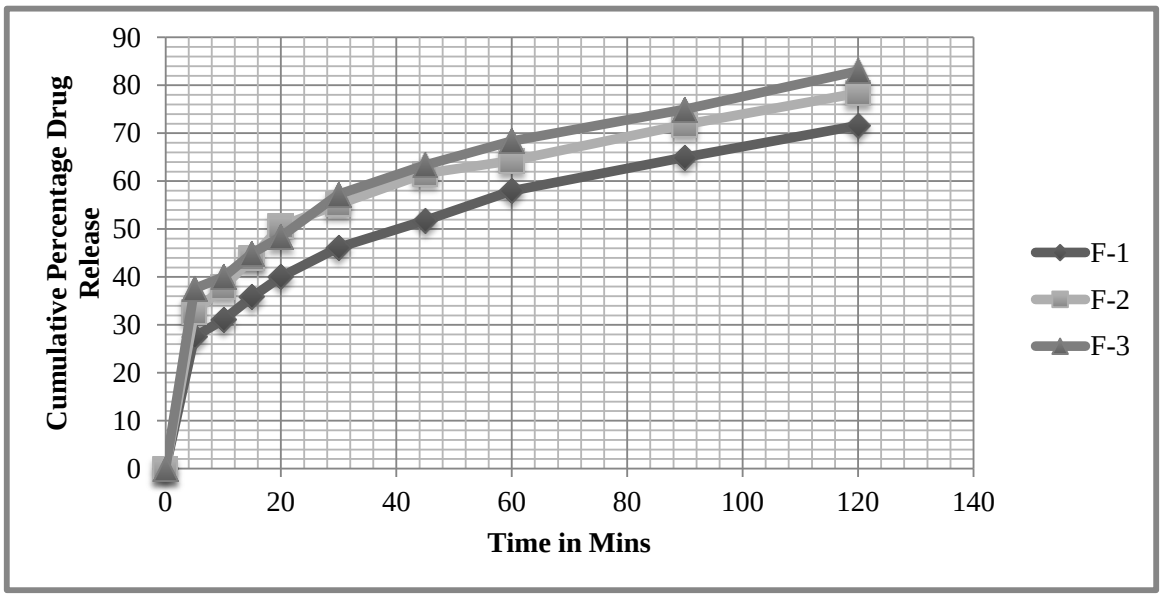


Table 7.25: *Ex vivo* permeation study in goat sublingual mucosa of the sublingual tablets containing varying concentrations of Chitosan lactate

Time (Mins)	Cumulative Percentage Drug Release*		
	F-4	F-5	F-6
0	0	0	0
05	33.12±0.64	35.68±0.38	36.48±0.49
10	36.98±0.79	39.29±0.62	42.19±0.76
15	40.61±1.15	45.37±0.59	45.12±1.09
20	44.62±0.92	50.13±0.47	53.95±0.37
30	49.51±0.88	55.64±0.76	60.18±0.89
45	56.41±0.41	62.21±0.66	67.18±0.76
60	62.98±0.36	69.07±0.54	74.79±0.42
90	68.24±0.59	74.94±0.88	80.32±0.38
120	75.36±0.47	81.96±0.41	86.42±0.62

*Mean±SD (n=3)

Figure 7.25: Percentage cumulative drug release of formulation F-4, F-5 and F-6

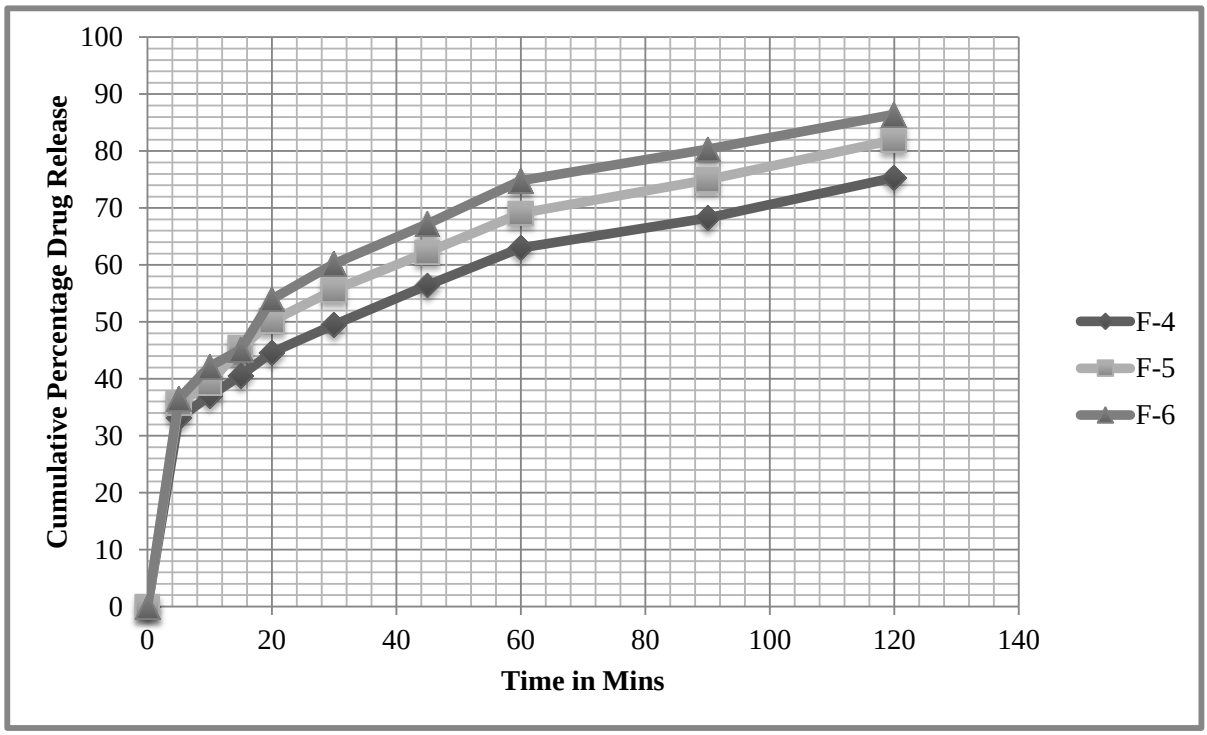


Table 7.26: *Ex vivo* permeation study in goat sublingual mucosa of the sublingual tablets containing varying concentrations of Sodium lauryl sulphate

Time (Mins)	Cumulative Percentage Drug Release*		
	F-7	F-8	F-9
0	0	0	0
05	24.64±0.64	28.16±0.38	33.12±0.49
10	29.41±0.79	30.46±0.62	37.62±0.76
15	36.32±1.15	34.88±0.59	42.54±1.09
20	38.00±0.92	38.76±0.47	46.60±0.37
30	42.73±0.88	44.79±0.76	51.22±0.89
45	48.68±0.41	55.96±0.66	56.88±0.76
60	54.44±0.36	57.74±0.54	63.82±0.42
90	60.63±0.59	64.64±0.88	70.21±0.38
120	67.11±0.47	70.73±0.41	77.05±0.62

*Mean±SD (n=3)

Figure 7.26: Percentage cumulative drug release of formulation F-7, F-8 and F-9

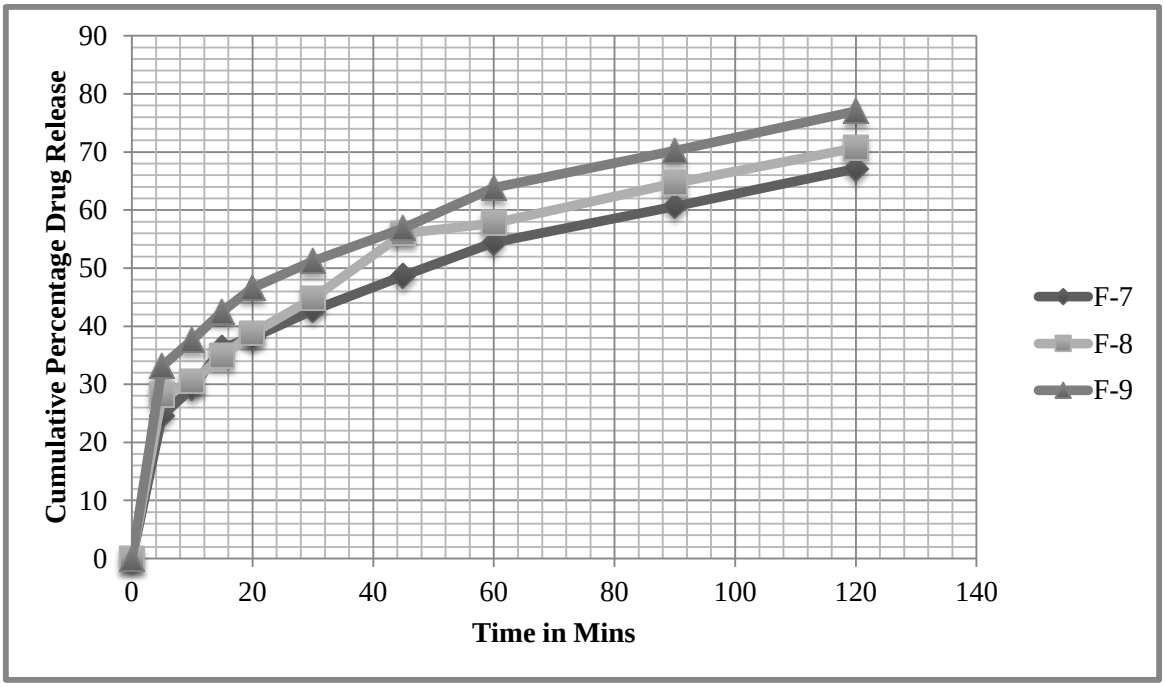
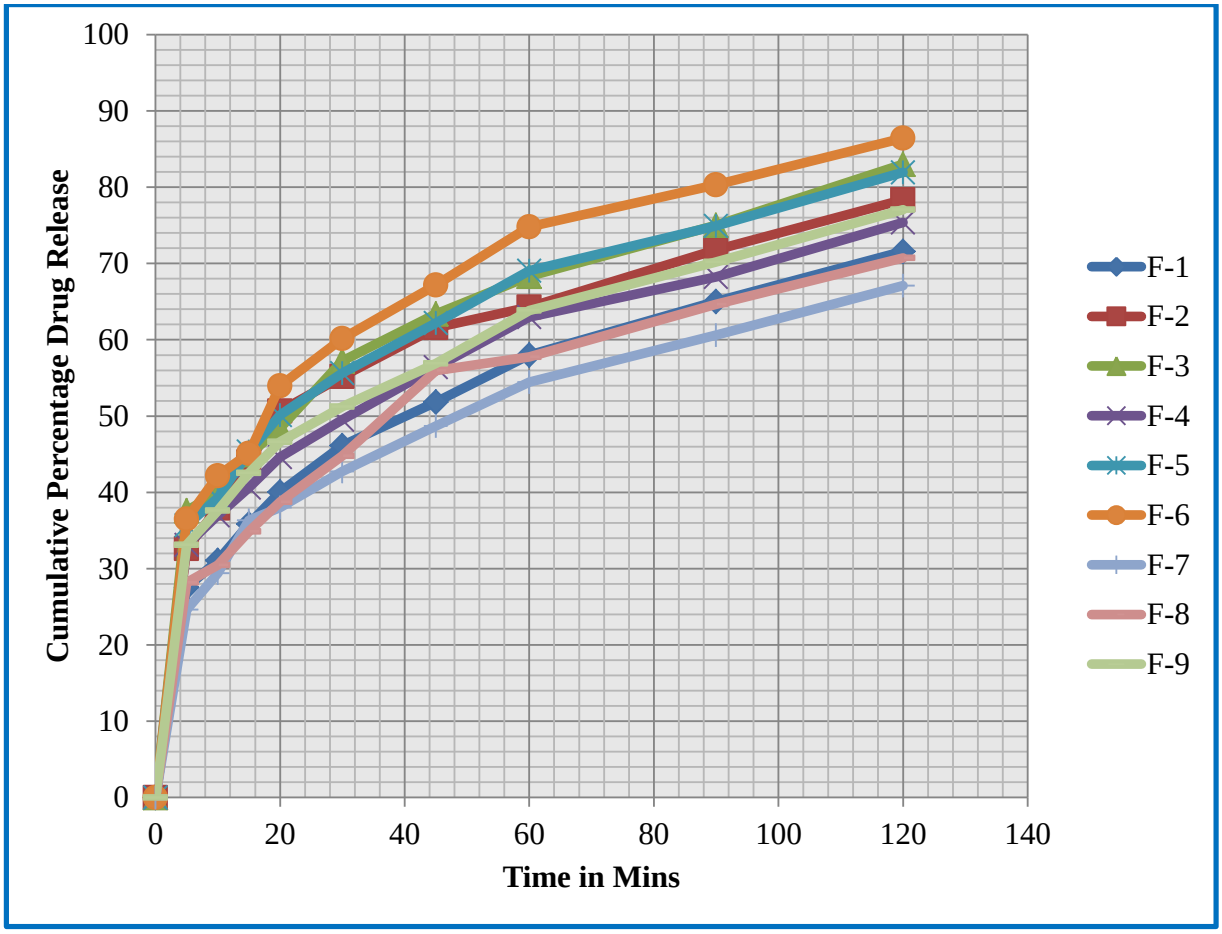


Table 7.27: *Ex vivo* permeation study on goat sublingual mucosa of the Rizatriptan benzoate sublingual tablets with various permeation enhancers

Time (Mins)	Cumulative Percentage Drug Release*								
	F-1	F-2	F-3	F-4	F-5	F-6	F-7	F-8	F-9
0	0	0	0	0	0	0	0	0	0
05	27.52±0.64	32.64±0.38	37.60±0.49	33.12±0.64	35.68±0.38	36.48±0.49	24.64±0.64	28.16±0.38	33.12±0.49
10	31.08±0.79	37.93±0.62	39.98±0.76	36.98±0.79	39.29±0.62	42.19±0.76	29.41±0.79	30.46±0.62	37.62±0.76
15	35.84±1.15	43.98±0.59	44.95±1.09	40.61±1.15	45.37±0.59	45.12±1.09	36.32±1.15	34.88±0.59	42.54±1.09
20	40.06±0.92	50.64±0.47	48.43±0.37	44.62±0.92	50.13±0.47	53.95±0.37	38.00±0.92	38.76±0.47	46.60±0.37
30	46.13±0.88	55.19±0.76	57.24±0.89	49.51±0.88	55.64±0.76	60.18±0.89	42.73±0.88	44.79±0.76	51.22±0.89
45	51.84±0.41	61.59±0.66	63.37±0.76	56.41±0.41	62.21±0.66	67.18±0.76	48.68±0.41	55.96±0.66	56.88±0.76
60	57.99±0.36	64.28±0.54	68.34±0.42	62.98±0.36	69.07±0.54	74.79±0.42	54.44±0.36	57.74±0.54	63.82±0.42
90	65.00±0.59	71.80±0.88	75.00±0.38	68.24±0.59	74.94±0.88	80.32±0.38	60.63±0.59	64.64±0.88	70.21±0.38
120	71.60±0.47	78.35±0.41	83.01±0.62	75.36±0.47	81.96±0.41	86.42±0.62	67.11±0.47	70.73±0.41	77.05±0.62

*Mean±SD (n=3)

Figure 7.27: Percentage cumulative drug release of formulation F-1 to F-9



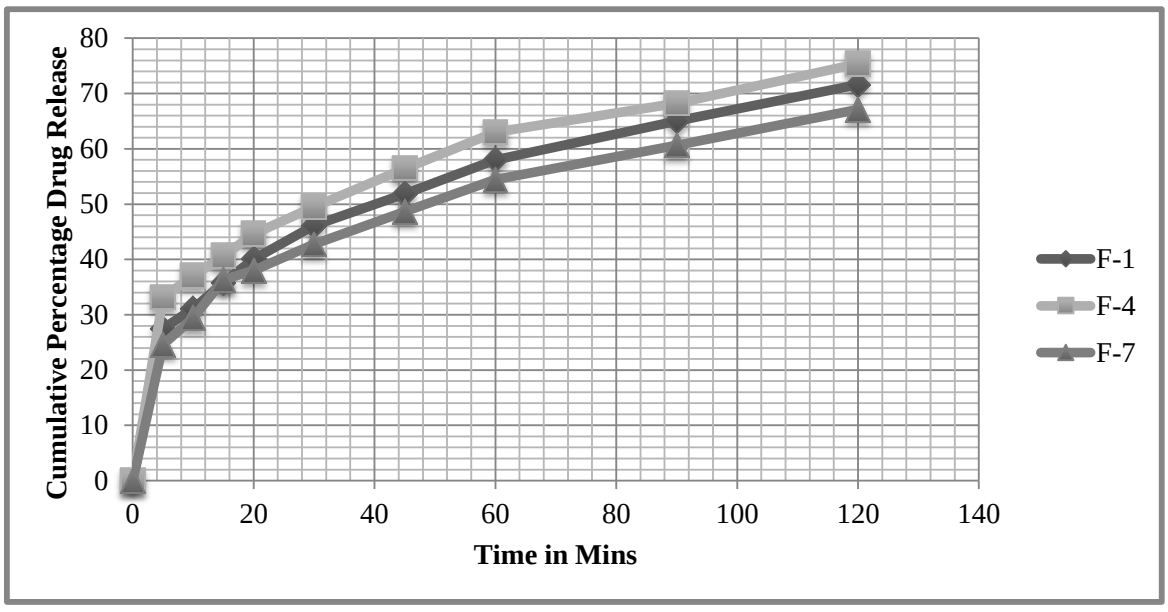
Formulation F-1, F-2, and F-3 showed 71.60%, 78.35% and 83.01% drug release at the end of 120 minutes. The formulation F-4, F-5 and F-6 showed 75.36%, 81.96% and 86.42% drug release at the end of 120 minutes. Formulation F-7, F-8 and F-9 showed 67.11%, 70.73% and 77.05% at the end of 120 minutes. Among these F-6 showed 86.42% at the end of 120 minutes with high permeability.

Table 7.28: Comparative *ex vivo* permeation study in goat sublingual mucosa of F-1, F-4 and F-7

Time (Mins)	Cumulative Percentage Drug Release*		
	F-1	F-4	F-7
0	0	0	0
05	27.52±0.64	33.12±0.64	24.64±0.64
10	31.08±0.79	36.98±0.79	29.41±0.79
15	35.84±1.15	40.61±1.15	36.32±1.15
20	40.06±0.92	44.62±0.92	38.00±0.92
30	46.13±0.88	49.51±0.88	42.73±0.88
45	51.84±0.41	56.41±0.41	48.68±0.41
60	57.99±0.36	62.98±0.36	54.44±0.36
90	65.00±0.59	68.24±0.59	60.63±0.59
120	71.60±0.47	75.36±0.47	67.11±0.47

*Mean±SD (n=3)

Figure 7.28: Percentage cumulative drug release of formulation F-7, F-4 and F-7



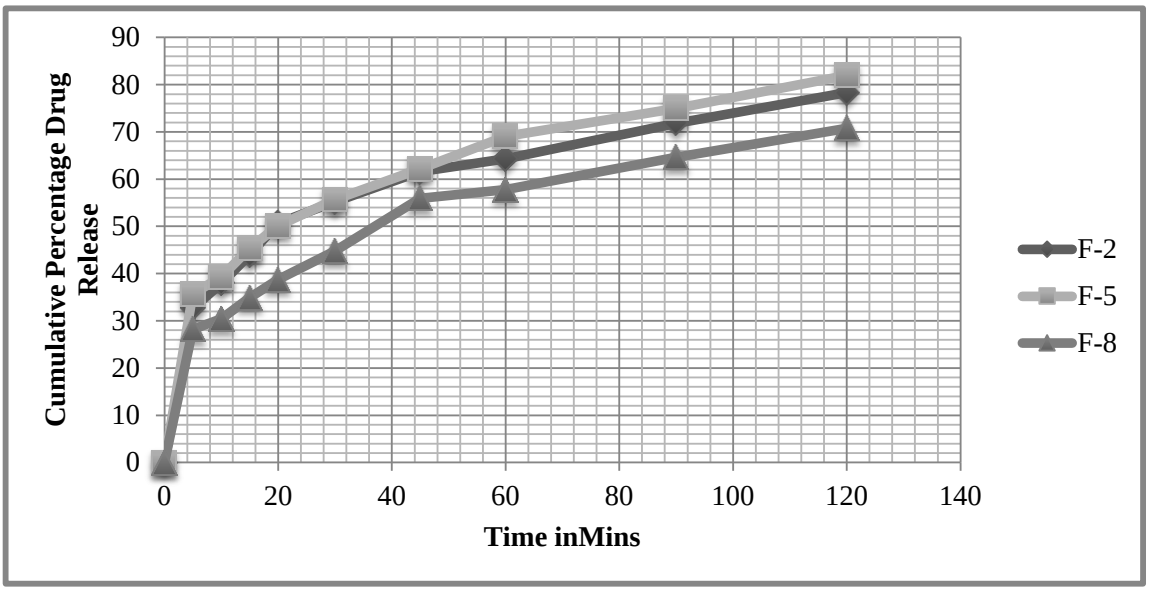
F-4 showed good permeability compared to F-1 and F-7.

Table 7.29: Comparative *ex vivo* permeation study in goat sublingual mucosa of F-2, F-5 and F-8

Time (Mins)	Cumulative Percentage Drug Release*		
	F-3	F-6	F-9
0	0	0	0
05	32.64±0.38	35.68±0.38	28.16±0.38
10	37.93±0.62	39.29±0.62	30.46±0.62
15	43.98±0.59	45.37±0.59	34.88±0.59
20	50.64±0.47	50.13±0.47	38.76±0.47
30	55.19±0.76	55.64±0.76	44.79±0.76
45	61.59±0.66	62.21±0.66	55.96±0.66
60	64.28±0.54	69.07±0.54	57.74±0.54
90	71.80±0.88	74.94±0.88	64.64±0.88
120	78.35±0.41	81.96±0.41	70.73±0.41

*Mean±SD (n=3)

Figure 7.29: Comparative percentage cumulative drug release of F-2, F-5 and F-8



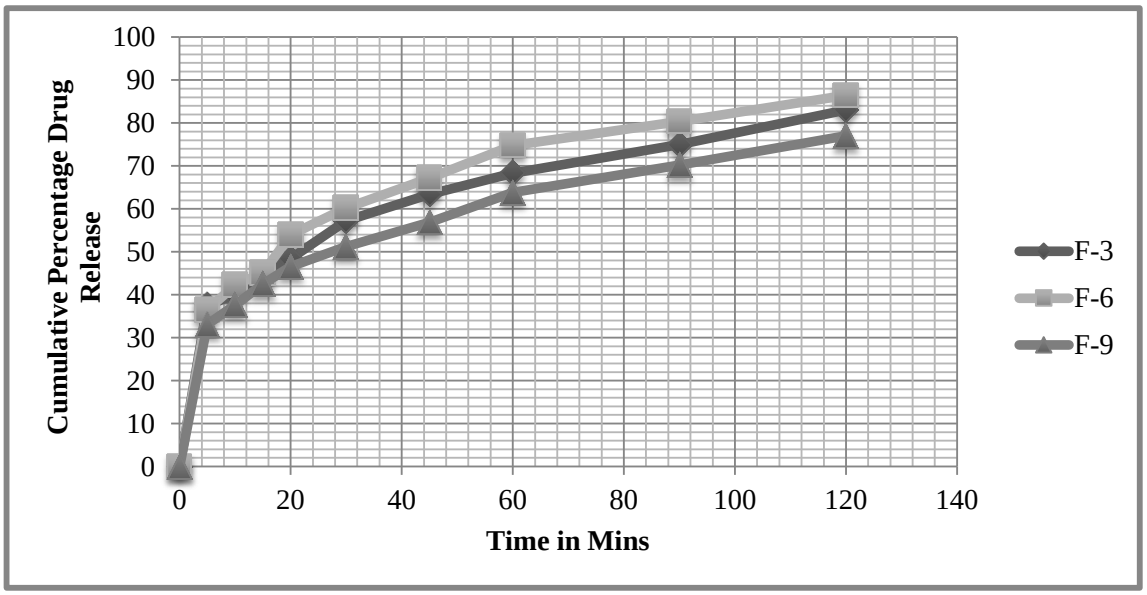
F-5 showed good permeability compared to F-1, F-2, F-4, F-7 and F-8.

Table 7.30: Comparative *ex vivo* permeation study in goat sublingual mucosa of F-3, F-6 and F-9

Time (Mins)	Cumulative Percentage Drug Release*		
	F-3	F-6	F-9
0	0	0	0
05	37.60±0.49	36.48±0.49	33.12±0.49
10	39.98±0.76	42.19±0.76	37.62±0.76
15	44.95±1.09	45.12±1.09	42.54±1.09
20	48.43±0.37	53.95±0.37	46.60±0.37
30	57.24±0.89	60.18±0.89	51.22±0.89
45	63.37±0.76	67.18±0.76	56.88±0.76
60	68.34±0.42	74.79±0.42	63.82±0.42
90	75.00±0.38	80.32±0.38	70.21±0.38
120	83.01±0.62	86.42±0.62	77.05±0.62

*Mean±SD (n=3)

Figure 7.30: Comparative percentage cumulative drug release of F-3, F-6 and F-9



F-5 showed good permeability compared to all other formualtions.

7.3. OPTIMIZED FORMULATION

7.3.1. PREFORMULATION STUDIES

Table 7.31: Preformulation Parameters of the Optimized Formulation F-6

S.No	Parameters	F-6
1.	Bulk density* (g/cm^3)	0.500±0.047
2.	Tapped density* (g/cm^3)	0.5319±0.068
3.	Compressibility index* (%)	05.99±0.059
4.	Hausner's ratio*	1.063±0.027
5.	Angle of Repose* (θ)	29.17±0.028

*Mean±SD (n=5)

7.3.2. POST COMPRESSION STUDIES

Table 7.32: Post-Compression Parameters of the Optimized Formulation F-6

S.No	Parameters	F-6
1.	Thickness* (mm)	3.2±0.0
2.	Diameter* (mm)	8.0±0.0
3.	Hardness* kg/cm^2	4.3±0.2236
4.	Drug content* (%w/w)	100.97±0.0
5.	Friability* (%w/w)	0.5727±0.035
6.	Average Weight* (g)	0.153±0.0039
7.	Disintegration Time* (Seconds)	09.00±0.0
8.	Wetting Time* (Seconds)	04.00±0.035

*Mean±SD (n=3)

7.3.3. *IN VITRO* DISSOLUTION STUDY

Table 7.33: *In-vitro* Dissolution Study of the Optimized Formulation F-6

S.No	Time (Mins)	Absorbance	Concentration (mcg/mL)	Concentration (mg/mL)	Cumulative Concentration (mg/mL)	Adjusted Cumulative Concentration (mg/mL)	Percentage drug release
1.	05	0.131	0.944	0.0944	0.0944	8.4960	84.96
2.	10	0.133	0.960	0.0960	0.1940	8.7344	87.34
3.	15	0.135	0.976	0.0976	0.2880	8.9744	89.74
4.	20	0.137	0.992	0.0992	0.3872	9.2760	92.76
5.	30	0.141	1.024	0.1024	0.4896	9.6032	96.03
6.	45	0.142	1.032	0.1032	0.5928	9.7760	97.76
7.	60	0.143	1.040	0.1040	0.6968	9.9528	99.52

7.3.4. *IN VITRO* PERMEATION STUDY ON EGG MEMBRANE

Table 7.33: *In-vitro* Permeation Study on Egg Membrane of the Optimized Formulation F-6

S.No	Time (Mins)	Absorbance	Concentration (mcg/mL)	Concentration (mg/mL)	Cumulative Concentration (mg/mL)	Adjusted Cumulative Concentration (mg/mL)	Percentage drug release
1.	05	0.238	1.800	0.0900	0.0900	3.3600	36.60
2.	10	0.265	2.016	0.1008	0.1908	4.1220	41.22
3.	15	0.287	2.192	0.1096	0.3004	4.5748	45.74
4.	20	0.323	2.480	0.1240	0.4244	5.2604	52.60
5.	30	0.353	2.720	0.1360	0.5604	5.8644	58.64
6.	45	0.388	3.000	0.1500	0.7104	6.5604	65.60
7.	60	0.424	3.288	0.1644	0.8748	7.2864	72.86
8.	90	0.444	3.448	0.1724	1.0472	7.7708	77.70
9.	120	0.471	3.664	0.1832	1.2304	8.3752	83.75

7.3.5. *EX VIVO* PERMEATION STUDY ON GOAT SUBLINGUAL MUCOSA

Table 7.34: *Ex-vivo* Permeation Study on Goat Sublingual Mucosa of the Optimized Formulation F-6

S.No	Time (Mins)	Absorbance	Concentration (mcg/mL)	Concentration (mg/mL)	Cumulative Concentration (mg/mL)	Adjusted Cumulative Concentration (mg/mL)	Percentage drug release
1.	05	0.247	1.824	0.0912	0.0912	3.6480	36.48
2.	10	0.271	2.064	0.1032	0.1944	4.2196	42.19
3.	15	0.295	2.256	0.1128	0.3072	4.5120	45.12
4.	20	0.331	2.544	0.1272	0.4344	5.3952	53.95
5.	30	0.362	2.792	0.1396	0.5740	6.0184	60.18
6.	45	0.397	3.072	0.1536	0.7276	6.7180	67.18
7.	60	0.435	3.376	0.1688	0.8964	7.4796	74.79
8.	90	0.459	3.568	0.1784	1.0748	8.0320	80.32
9.	120	0.486	3.784	0.1892	1.2640	86.6428	86.42

8. STABILITY STUDY [68]

The optimized sublingual tablet formulation was subjected to stability study and results are given in table 7.35.

Table 7.34: Stability study of optimized formulation- Evaluation parameters

S.No	Parameters	Initial	First Month	Second Month	Third Month
1.	Thickness* (mm)	3.2±0.0	3.2±0.0	3.2±0.0	3.2±0.0
2.	Diameter* (mm)	8.0±0.0	8.0±0.0	8.0±0.0	8.0±0.0
3.	Hardness* kg/cm^2	4.3±0.2236	4.3±0.2176	4.3±0.2146	4.3±0.2196
4.	Drug content* (%w/w)	100.97±0.910	99.57±0.857	99.23±0.987	99.03±0.868
5.	Friability** (%w/w)	0.5727±0.035	0.5802±0.075	0.5828±0.069	0.5879±0.060
6.	Average Weight** (g)	0.153±0.0039	0.153±0.0058	0.153±0.0067	0.153±0.0088
7.	Disintegration Time$^{\#}$ (Sec)	09.00±0.0	09.00±0.0	09.00±0.0	09.00±0.0
8.	Wetting Time$^{\#}$ (Sec)	04.00±0.035	04.00±0.029	04.00±0.033	04.00±0.031
9.	In vitro dissolution study $^{\#}$ (% cumulative release)	99.52±0.935	99.22±0.894	99.05±0.867	99.14±0.899
10.	In vitro permeation study (% cumulative release) $^{\#}$	83.75±0.789	82.92±0.806	83.76±0.878	83.06±0.897
11.	Ex vivo permeation study (% cumulative release) $^{\#}$	86.42±0.698	86.97±0.912	86.03±0.654	86.47±0.807

*Mean±SD (n=10) **Mean±SD (n=20) $^{\#}$Mean±SD (n=6)

Summary and Conclusion

8. SUMMARY AND CONCLUSION

8.1. SUMMARY

In this work an attempt was made to design sublingual drug delivery system containing an Antimigraine drug. The main objective of the present research work was to overcome the hepatic first pass metabolism, provide controlled release and to enhance the permeability.

The conventional dosage forms available are associated with low bioavailability problems due to extensive first pass metabolism where in antimigraine agents are also characterized by highly soluble nature with low permeability, due to which frequency of dosing is increased, which results in patient incompliance. In order to overcome these drawbacks, drugs can be developed in form of sublingual drug delivery system. Sublingual drug delivery systems provide additional advantages over conventional tablets including termination of drug action in case of toxicity by removing the dosage form from the buccal cavity.

The scheme of work has been divided into various parts. The collection of theoretical and technical data by extensive literature survey, review of literature and drug profile is presented in chapter 3 and 4 respectively. This was followed by procurement of materials and standardization of all materials used in the formulation of sublingual tablets.

Sublingual tablets were prepared by direct compression method using Rizatriptan benzoate and different permeation enhancers like β-Cyclodextrin, Chitosan lactate and Sodium lauryl sulphate in different ratios and Crospovidone as superdisintegrant in order to release the drug in immediate manner.

The tablets were evaluated for Disintegration time, Weight variation, Thickness, Hardness, Percentage friability, Wetting Time, Drug Content and *In vitro* dissolution studies, *In vitro* permeation study on egg membrane and *Ex-vivo* permeation study on goat sublingual mucosa. The resulting tablets were evaluated considering the disintegration time as well as permeation as the main criteria. Disintegration time of all batches was found to be between 08– 12 sec. Friability and hardness were also good in all batches. *Ex-vivo* as well as *In vitro* permeation study of Batch F-6 was found to be high with good disintegration time, friability and hardness. Batch F-6 showed rapid dissolution rate and complete dissolution was achieved within 60 min. Formulation F-6 was considered as the best formulation.

The results obtained have been discussed in chapter 7. Results of FT-IR

revealed that there was no chemical interaction between the drug and the permeation enhancers used. The prepared tablets showed good disintegration time. The release pattern of the formulations was good.

Stability studies of the selected formulation was carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation. The stability studies were carried out at 40 ºC/75% RH for 90 days. There was no significant change in the physical property and drug content during the study period.

From the above the results, formulation F-6 was found to be the best formulation for the sublingual delivery of Rizatriptan benzoate that complied with all the parameters. However, *in vivo* experiments need to be carried out to know the absorption pattern and bioavailability of drug from the sublingual tablets and thus enabling us to establish *in vitro – in vivo* correlation.

8.2. CONCLUSIONS

The concept of sublingual tablets containing Rizatriptan benzoate offers a suitable and practical approach in serving the desired objective of management of Migraine. Most of the excipients used in the formulation are water-soluble and hence have better patient acceptability. The present work of formulating a sublingual tablet containing Rizatriptan benzoate was successful in terms of reducing manufacturing difficulties, cost and providing better patient compliance with effective medication.

It has been observed from the above study that excipients like Mannitol, Microcrystalline cellulose, Crospovidone, Aspartame, Chitosan lactate, Beta-Cyclodextrin and Sodium lauryl sulphate etc. were ideal excipients and effective for formulating sublingual tablets. Sublingual tablets provide several advantages especially when administered to children and elderly patients. Rapid absorption into the systemic circulation within short time period may be achieved. The batch F-6 was considered to be the best among all other batches since it exhibited good dissolution profile, disintegration time, uniformity of drug content and further good stability and *ex- vivo* as well as *in-vitro* permeation profile. The following parameters were obtained for optimized batch F-6

- Disintegration time -09 seconds
- *In-vitro* permeation study on egg membrane- 83.75% at the end of 120 minutes
- *Ex-vivo* permeability study on goat sublingual mucosa- 86.42% at the end of 120

minutes

From the overall results, it is clear that the formulation F-6 containing 3% of Chitosan lactate is the optimal formulation among the other formulations, as it produced better drug permeability than other formulations.

8.3. SCOPE OF THE STUDY

- The research work may be extended by using different permeation enhancers of natural or synthetic origin in various ratios for the formulation of sublingual tablets.
- *In vivo* studies need to be undertaken to establish *in-vitro* and *in-vivo* correlation.
- *In vivo* study using gamma scintillography method.
- Pharmacokinetic and toxicity study.
- Scale up studies for the optimized formulation.

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