"FORMULATION AND EVALUATION OF FAST DISINTEGRATING SUB LINGUAL TABLETS OF RIZATRIPTAN"

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Submitted by

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EVALUATION CERTIFICATE

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The work presented in this dissertation entitled, **"FORMULATION AND EVALUATION OF FAST DISINTEGRATING SUB LINGUAL TABLETS OF RIZATRIPTAN"** was carried out by me, under the direct supervision of **Dr. V. KAMALAKKANNAN, M.Pharm., Ph.D** Associate. Professor, Department of Pharmaceutics, J.K.K. Nattraja College of Pharmacy, Kumarapalayam.

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

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DEDICATED TO
MY BELOVED
FAMILY,
STAFFS AND
FRIENDS

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CONTENT

LIST OF FIGURES

LIST OF TABLES

LIST OF ABBREVATIONS

S.NO	Abbreviations	Expanded terminology
1.	FDDS	Fast dissolving drug delivery system
2.	ODT	Oral dispersible tablet
3.	L-HPC	Low substituted hydroxyl propyl cellulose
4.	Kg	Kilogarm
5.	mg	Milligram
6.	µg	Microgram
7.	RH	Relative humidity
8.	nm	Nano meter
9.	^{0}C	centigrade
10.	gm	Grams
11.	Q	Quantity
12.	mins	minute
13.	sec	seconds
14.	mm	Milli Meter
15.	gm	gram
16.	ml	Milli Liter
17.	rpm	Rotation per minute
18.	SD	Standard deviation
19.	Fig	Figure

20.	%	Percentage
21.	NDDS	Novel drug delivery systems
22.	HPMC	Hydroxy propyl methyl cellulose
23.	FDA	Food and drug administration
24.	NSAID	Non steroidal anti inflammatory drugs
25.	SLIT	Sublingual immunotherapy
26.	ACC	Allergen challenge chamber
27.	BUP	Buprenorphine
28.	EPPC	Epinerphine plasma concentrations
29.	RZT	Rizatriptan
30.	5-HT	5-Hydroxytriptamine
31.	MCC	Methyl crystalline cellulose
32.	OTF	Oral thin film
33.	LV	Low viscosity
34.	SSG	Sodium starch glycolate
35.	F	Formulation
36.	MAO-A	Monoamine oxidase A isoenzyme
37.	BP	British pharmacopeia
38.	WHO	World health organization
39.	ICH	International conference for harmonization
40.	API	Active pharmaceutical ingradient

1. INTRODUCTION

For the last twenty years, there has been an enhanced demand for more patient-compliant dosage forms. As a result, there are now approximately 350 drug delivery corporations and 1000 medical device companies. The demand for their technologies was approximately $14.20 billion in 1995 and, according to industry reports; this is expected to grow to $60 billion annually[1, 2].

Oral administration is the most popular route due to ease of ingestion, pain avoidance, versatility (to accommodate various types of drug candidates), and most importantly, patient compliance. Also, solid oral delivery systems do not require sterile conditions and are, therefore, less expensive to manufacture. Several novel technologies for oral delivery have recently become available to address the physicochemical and pharmacokinetic characteristics of drugs, while improving patient compliance. Electrostatic drug deposition and coating[3], and computer-assisted three-dimensional printing (3DP) tablet manufacture have also recently become available[4].

Fast-dissolving drug-delivery systems were first developed in the late 1970's as an alternative to tablets, capsules, and syrups for pediatric and geriatric patients who experience difficulties swallowing traditional oral solid-dosage forms. The novel technology of oral fast-dispersing dosage forms is known as fast dissolve, rapid dissolve, rapid melt and quick disintegrating tablets. However, the function and concept of all these dosage forms are similar.

By definition, a solid dosage form that dissolves or disintegrates quickly in the oral cavity, resulting in solution or suspension without the need for the administration of water, is known as an oral fast-dispersing dosage form. Difficulty in swallowing (dysphagia) is common among all age groups, especially in elderly, and is also seen in swallowing conventional tablets and capsules[5]. Dysphagia is associated with many medical conditions, including stroke, Parkinson's, AIDS, thyroidectomy, head and neck radiation therapy, and other neurological disorders, including cerebral palsy[6]. The most common complaint was tablet size, followed by surface, form and taste. The problem of swallowing tablets was more evident in

geriatric and pediatrics patients, as well as travelling patients who may not have ready access to water[7, 8].

Salient features of fast dissolving drug delivery systems[10]:

1. Ease of administration for patients who are mentally ill disabled and uncooperative.
2. Require no water
3. Over comes unacceptable taste of the drugs.
4. Can be designed to leave minimal or no residue in the mouth after administration and also provide a pleasant mouth feel.
5. Ability to provide advantages of liquid medication in the form of solid preparation.
6. Adaptable and amenable to existing processing and packaging
7. Cost effective

Need for fast dissolving drug delivery systems:

Fast dissolving drug delivery systems can improve acceptance and compliance in patients with dysphagia. Similarly, from market point of view, introduction of FDDS will assist life cycle management of drug especially if the drug is patent protected.

Dysphagia[11]:

Dysphagia, or difficulty in swallowing, is common among all age groups. According to a study dysphasia is common in about 35% of the general population, as well as an additional 30-40% of elderly and 18-20% of all persons in long term care facilities. Common complaints about the difficulty in swallowing tablets due to size, surface, form, and taste of tablets. Geriatric and pediatric patients and traveling patients who may not have ready access to water are in need of easy swallowing of dosage forms. These studies show an urgent need for a new dosage form like FDDS that make tablets disintegrate in the mouth without chewing or additional water intake and thus improve patient compliance.

Market view[12]:

The need for non invasive delivery systems continues due to poor patient compliance with existing delivery regimens, limited market size for drug companies and drug uses, coupled with high costs of disease management. Pharmaceutical marketing is one reason for the increase in available fast-dissolving /disintegrating products. As a drug entity reaches the end of its patent life, it is common for pharmaceutical manufacturers to develop a given drug entity in a new and improved dosage form. A dosage form allows the manufacturer to extend the market exclusivity, while offering its patient population a more convenient dosage form or dosing regimen. In this regard, fast dissolving /disintegrating formulations are similar to many sustained release formulations that are now commonly available. An extension of market exclusivity, which can be provided by a fast dissolving/ disintegrating dosage form, leads to increased revenue, while also targeting underserved and under-treated patient population.

HEADACHE[13]:

A headache or cephalalgia is pain anywhere in the region of the head or neck. It can be a symptom of a number of different conditions of the head and neck. The most common way to relieve a headache, is to look upside down for 3 minutes

Types of Headaches:

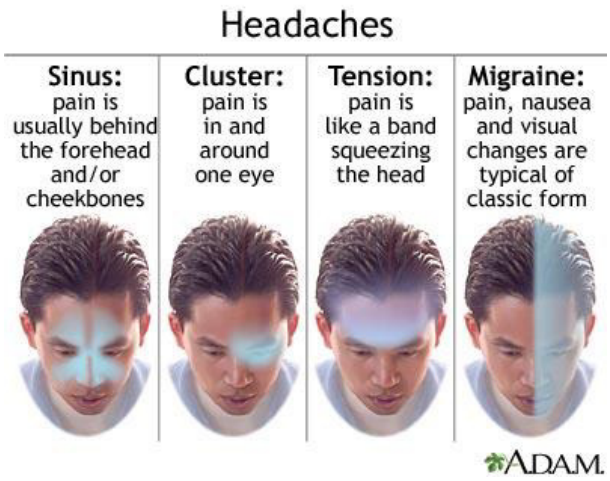


Fig:1Types of headaches and their symptoms

MIGRAINE[14]:

A migraine is a common type of headache that may occur with symptoms such as nausea, vomiting, or sensitivity to light. In many people, a throbbing pain is felt only on one side of the head.

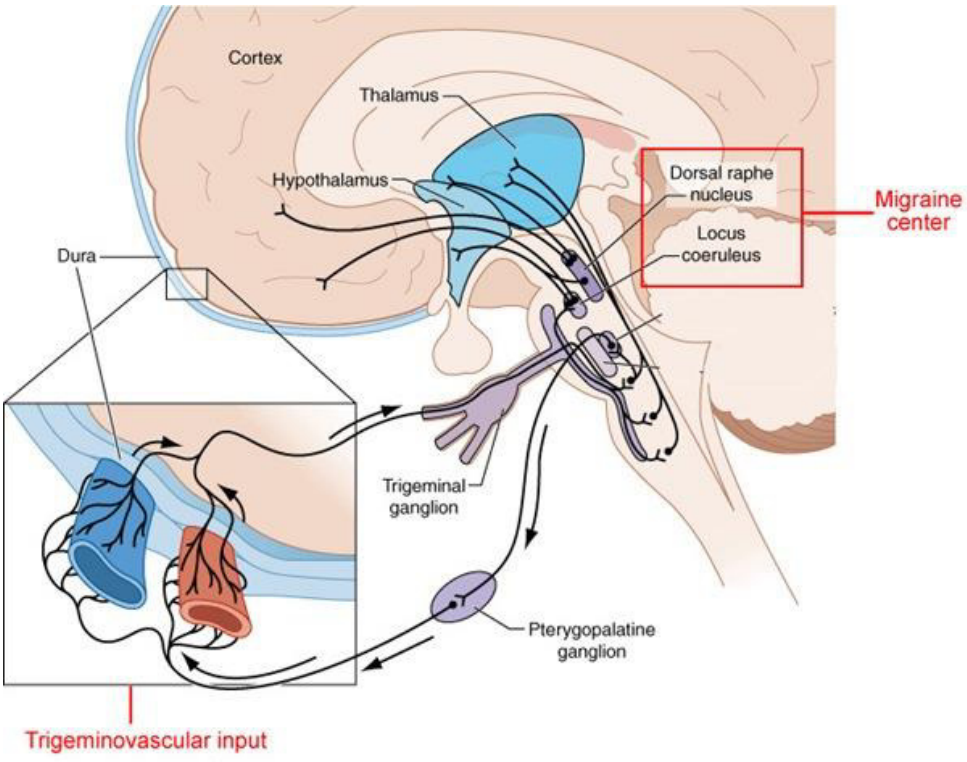


Fig :2 Migraine physiology

CLASSIFICATION:

- Migraine without aura
- Migraine with aura
    - Migraine with typical aura
    - Migraine with prolonged aura
    - Familial hemiplegic migraine
    - Basilar migraine
    - Migraine aura without headache
    - Migraine with acute onset aura
- Opthalmoplegic migraine
- Retinal migraine

- Childhood periodic syndromes that may be precursors to or associated with migraine
    - Benign paroxysmal vertigo of childhood
    - Alternating hemiplegia of childhood
- Complications of migraine
    - Status migrainous
    - Migrainous infarction
- Migrainous disorder not fulfilling above criteria

Symptoms:

Vision disturbances[15], or aura, are considered a "warning sign" that a migraine is coming. The aura occurs in both eyes and may involve any or all of the following:

- A temporary blind spot
- Blurred vision
- Eye pain
- Seeing stars or zigzag lines
- Tunnel vision

Treatment[16]:

There is no specific cure for migraine headaches. The goal is to treat your migraine symptoms right away, and to prevent symptoms by avoiding or changing your triggers[17].

Classification of anti-migraine drugs:

Antimigraine drugs or drugs that prevent migraine or cure migraine are classified as follows:

- Beta Blockers: The drugs prevent the widening of the arteries in your head by blocking the beta receptors.
- Anticonvulsants: These drugs treat seizures. Like many preventative migraine medications, they increase levels of an amino acid known as GABA, which may play an important in migraine development.

- Methysergide: This is one of the more toxic medications, and so is usually reserved for more serious cases.
- Calcium channel blockers: These medications have the ability to stop the spasm of the arteries, block the release of serotonin and inhibit platelet clumping.
- Antidepressants: It's believed that the anti-migraine effect of these medicines is a whole different reaction than what happens when treating depression.
- Clonidine: Clonidine is an alpha blocker that also protects the blood vessels.
- Cyproheptadine: It's most often prescribed to children, and seems to be only slightly effective for adults.
- NSAIDs[18]: Though primarily used to stop headaches once they start, they have also been used as a preventative medication.
- Combinations: Sometimes combinations of the above types of drugs will be prescribed.

TABLETS:

An ideal dosage regimen in the drug therapy of any disease is the one, which immediately attains the desire therapeutics concentration of drug in plasma (or at the site of action) and maintains it constant for the entire duration of treatment. This is possible through administration of conventional dosage form in a particular dose and at a particular frequency. Thus drug may be administered by variety of routes in a variety of dosage forms.

Drugs are more frequently taken by oral administration. Although a few drugs taken orally are intended to be dissolved within the mouth, the vast majority of drugs taken orally are swallowed. Compared with alternate routes, the oral route of drug administration is the most popular and has been successfully used for conventional delivery of drug. It is considered most natural, uncomplicated, convenient, safe means of administering drugs, greater flexibility in dosage form design, ease of production and low cost.

Drugs are administered by the oral route in a variety of pharmaceutical dosage forms. The most popular are tablets, capsules, suspensions, various

pharmaceutical solutions. Among the drugs that are administered orally, solid dosage form represent the preferred class of product. They are versatile, flexible in dosage strength, relatively stable, present lesser problem in formulation, packaging and it is convenient to manufacture, store, handle and use. Solid dosage form provides best protection to the drug against light, temperature, humidity, oxygen, and stress during transportation[19]. Amongst the solid oral dosage form tablets are widely used.

Tablets[20] may be defined as solid pharmaceutical dosage forms containing medicament with or without suitable excipients and prepared either by compression or moulding.

ADVANTAGES OF TABLETS:

Some of the potential advantages of tablets are as follows.

1. They are the unit dosage form having greatest capabilities amongst all the oral dosage form for the dose precision and least content variability.
2. Their cost is lowest amongst all the oral dosage forms.
3. They are the lightest and the most compact amongst all the oral dosage form.
4. They are easiest and cheapest for packaging and transportation.
5. They lend themselves to certain special release profile products such as enteric or delayed release products.
6. Tablets are better suited to large-scale production than other unit oral dosage forms.

They have the best-combined properties of chemical, mechanical, microbiological stability amongst all the oral dosage forms.

DISADVANTEGE OF TABLETS:

1. It is difficult to convert a high dose poorly compressible API into a tablet of suitable size for human use.
2. Difficult to formulate a drug with poor wettability, slow dissolution into a tablet.

3. Slow onset of action as compared to parenterals, liquid orals and capsules.
4. The amount of liquid drug (e.g. Vitamin E, Simethicone) that can be trapped into a tablet is very less.
5. Difficult to swallow for kids, terminally ill and geriatric patients.
6. Patients undergoing radiotherapy cannot swallow tablet.

CLASSIFICATION OF TABLETS:

Based on the route of administration or the function, the tablets are classified as follows.

1. Tablets ingested orally.

a) Compressed tablet
b) Multiple compressed tablet
    i) Layered tablet
    ii) Compression coated tablet
c) Repeat action tablet
d) Delayed action and enteric coated tablet
e) Sugar and chocolate coated tablet
f) Film coated tablet
g) Chewable tablet

2. Tablets used in the oral cavity.

a) Buccal tablet
b) Sublingual tablet
c) Troches and lozenges
d) Dental cones

3. Tablets administered by other routes.

a) Implantation tablet
b) Vaginal tablets

4. Tablets used to prepare solution.

a) Effervescent tablet

b) Dispensing tablet

c) Hypodermic tablet

d) Tablets triturate

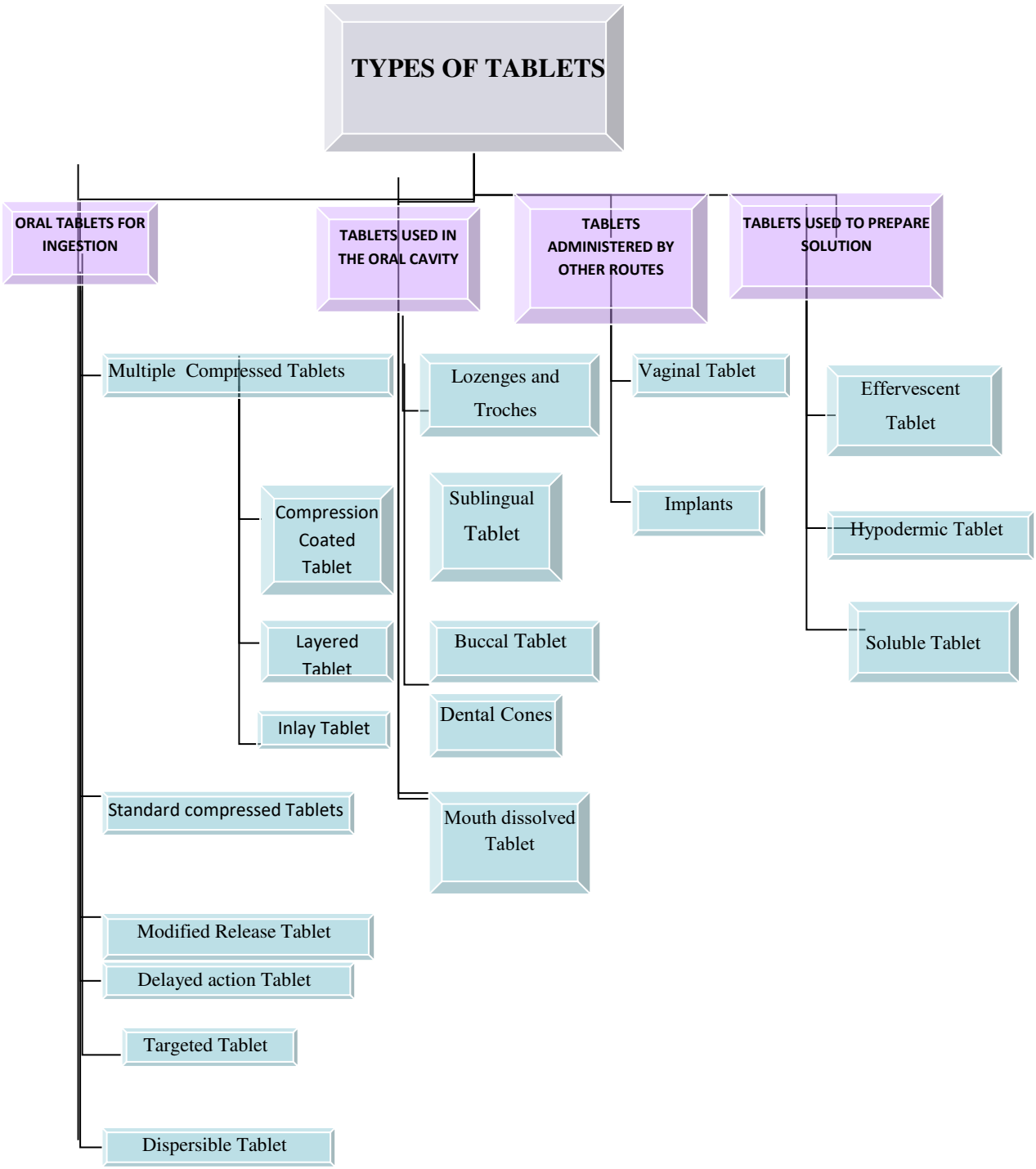


Fig 3: Classification of tablets

MOUTH DISPERSIBLE TABLET[21]

Recently pharmaceutical preparations used for elderly patients have been investigated to improve the treatment compliances and quality of life of patients.

Recent advances in Novel drug delivery system (NDDS) aims to enhance safety and efficacy of drug molecule by formulating a convenient dosage form for administration and to achieve better patient compliance. One such approach is "Mouth dissolving tablet" [22].

The concept of Mouth dissolving drug delivery system emerged from the desire to provide patient with conventional mean of taking their medication. Difficulty in swallowing (Dysphagia) is a common problem of all age groups, especially elderly and pediatrics, because of physiological changes associated with these groups of patients[23].

Other categories that experience problems using conventional oral dosage forms includes are the mentally ill, un co-operative and nauseated patients, those with conditions of motion sickness, sudden episodes of allergic attack or coughing. Sometimes it may be difficult to swallow conventional products due to unavailability of water. These problems led to the development of novel type of solid oral dosage form called "Mouth dissolving tablets". This tablet disintegrates instantaneously when placed on tongue, releasing the drug that dissolves or disperses in the saliva.

On placing mouth-dispersible tablet in the mouth, saliva serves to rapidly dissolve the dosage form. The saliva containing the dissolved or dispersed medicament is then swallowed and the drug is absorbed in the normal way. Some drugs are absorbed from the mouth, pharynx and esophagus as the saliva passes down into the stomach and it may produce rapid onset of action. In such a cases Bioavailability of drug is significantly greater than those observed from conventional tablet dosage form.

The dispersible tablets allows dissolution or dispersion in water prior to administration but the mouth dissolving tablet instead of dissolving or disintegrating

in water is expected to dissolve or disintegrate in oral cavity without drinking water. The disintegrated mass then slides down smoothly along the esophagus along with saliva.

SUBLINGUAL TABLETS:

Tablets that disintegrate or dissolved rapidly in the patients mouth are convenient for young children, the elderly and patients with swallowing difficulties and in situation where potable liquids are not available. For these formulations the small volume of saliva is usually sufficient to result in tablets disintegration in oral cavity. The medication can then be absorbed partially or entirely into the systemic circulation from blood vessels in the sublingual mucosa or it can be swallowed as a solution to be absorbed from gastrointestinal tract. The sublingual route usually produces a faster onset of action than orally ingested tablets and the portion absorbed through sublingual blood vessels bypass the hepatic first pass metabolic process.

Systemic drug delivery through the sublingual route had emerged from the desire to provide immediate onset of pharmacological action, dysphagia (Difficulty in swallowing) is a common problem of all age groups, especially elderly, children and patients who are mentally retarded, uncooperative, nauseated or on reduced liquid intake diets have difficulties in swallowing these dosage forms[24,25].

The sublingual administration of the drug means placement of drug under the tongue and drug reaches directly into the blood stream through the ventral surface of the tongue and floor of the mouth. The drug solutes are rapidly absorbed into reticulated vein which lies underneath the oral mucosa and transported through the facial veins, internal jugular vein and braclocephalic vein and then drained into systemic circulation.

The main mechanism for the absorption of the drug into oral mucosa via passive diffusion into the lipoidal membrane[26]. The absorption of the drug through the sublingual route is 3-10 times greater than oral route and is only surpassed by hypodermic injection. For these formulations, the small volume of saliva is usually sufficient to result in tablet disintegration in the oral cavity.

In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal (cheek) area, which in turn is more permeable than the palatal (Route of the mouth) area. The differences in permeability are based on the relative thickness, the blood supply and degree of keratinization of these membranes. In addition to the differences in the permeability of the various mucus membranes, the extent of drug delivery is also affected by the physiochemical properties of the drug to be delivered[27].

Sublingual products have been developed for numerous indications ranging from migraines(for which rapid onset of action is imporatant) to mental illness(for which patient compliance is important for treating chronic indications such as depression and Schizophrenia[28].

Sublingual glands:

Sublingual glands are also known as the salivary glands which are present in the floor of the mouth underneath the tongue. These glands produce mucin and help to promote the production of saliva. Because of the secretions of the glands the interior area of the mouth is kept lubricated which is necessary for chewing and swallowing.

Absorption means transfer of drug from its site of administration to the systemic circulation, so it is obvious that absorption is directly proportional to the membrane layer thickness.

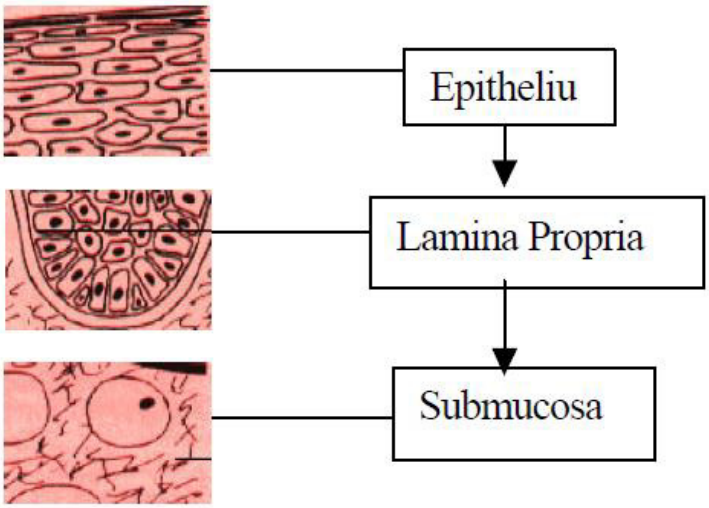
Sublingual > Buccal > Gingival > Palatal having mucosa thickness of 100-200, 200,250,500-600 respectively. Because of the high permeability and the rich blood supply, the sublingual route is capable of producing a rapid onset of action which makes it an appropriate route for drugs with short delivery period and frequent dosing regimen. The drug is released into saliva and its subsequent spreading may cause the drug to be absorbed across the oral cavity[29].

Structural features of oral mucosa structure:

The oral mucosa is composed of an outermost layer of stratified squamous epithelium (Fig 4). Below this lies a basement membrane, a lamina propria followed by the submucosa as the innermost layer. The epithelium is similar to stratified squamous epithelia found in the rest of the body in that it has a mitotically active

basal cell layer, advancing through a number of differentiating intermediate layers to the superficial layers, where cells are shed from the surface of the epithelium.

Fig 4: Different layers of oral mucosa



Mechanism of sublingual absorption:

The absorption potential of oral 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. Absorption of some drugs via oral mucosa is shown to increase by carrier pH is lowering (more acidic) and decrease with a lowering of pH(more alkaline)[30,31].

The cells of the oral epithelium and epidermis are also capable of absorbing by endocytosis (the uptake of particles by a cell as if they hollowly wrapping itself around it. These engulfed particles are usually too large to diffuse through its wall). It is unlikely that this mechanism is used across the entire stratified epithelium. It is also unlikely that active transport process operate with in the oral mucosa. However it is believed that acidic stimulation of the salivary glands with the accompanying vasodilation, facilitates absorption and uptake into the circular system.

The mouth is lined with a mucus membrane which is covered with squamous epithelium and contains mucus glands. The sublingual mucosal tissue is similar to that of buccal mucosa[32].

The salivary glands consists of lobules of cells which secretes saliva through the salivary ducts into the mouth. The three pairs of salivary glands are the Parotid, Submandibular and sublingual which lies on the floor of the mouth. The more acid the taste, the greater the stimulation of salivary output; serving to avoid potential harm to acid-sensitive tooth enamel by bathing the mouth in copious neutralizing fliud.

The sublingual artery travels forward to the sublingual gland, it supplies the gland and branches to the neighboring muscles and to the mucus 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 submental branches of the facial artery. The sublingual artery stems from the lingual artery-the bodies 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 acess to its routes applying the greater part of the cerebral hemisphere[33,34].

Criteria to formulate sublingual tablets:

- No bitter taste
- Dose lowers than 20mg
- Small to moderate molecular weight
- Good stability in water and saliva
- Partially non-ionised at the oral cavities pH
- Undergoing first pass effect

Factors affecting the sublingual absorption[35]:

1. Lipophilicity of drug
2. Solubility in salivary secretion
3. pH and pka of the saliva
4. Binding to oral mucosa
5. Thickness of oral epithelium
6. Oil-water partition coefficient

1.Lipophilicity of drug: For a drug to be absorbed completely through sublingual route the drug must behave slightly higher lipid solubility than that required for GI absorption is necessary for passive permeation.

2.Solubility in salivary secretion: In addition to high lipid solubility the drug should be soluble in aqueous buccal fluids i.e., biphasic solubility of drug is necessary for absorption.

3. pH and pka of the saliva: As the mean pH of the saliva is 6.0, this pH favours the absorption of drug which remain unionized. Also, the absorption of the drugs through the oral mucosa occurs if the pka is greater than 2 for an acid and less than for a base.

4. Binding to oral mucosa: Systemic availability of drugs that bind to oral mucosa is poor.

5. Thickness of oral epithelium: As the thickness of sublingual epithelium is 100-200µm which is less as compared to buccal thickness. So the absorption of the drug is faster due to thinner epithelium and also the immersion of drug in smaller volume of saliva.

6. Oil- water Partition coefficient: Compounds with favourables O/W partition coefficients are readily absorbed through the oral mucosa. An O/W partition coefficient range of 40-2000 is considered optimal for the drugs to be absorbed sublingually.

Advantages:

- A relatively rapid onset of action can be achieved compared to the oral route, and the formulation can be removed if therapy is required to be discontinued.
- Liver is bypassed and also drug is protected from degradation due to pH and digestive enzymes of the middle gastro intestinal tract.
- Improved patient comlliance due to the elimination of associated pain with injections; administration of drugs in unconscious are incapacitated patients; convenience of administration as compared to injections are oral medications.

- Low dosage gives high efficacy as hepatic first pass metabolism is avoided and also reduces the risk of side effects.
- The large contact surface of the oral cavity contributes to rapid and extensive drug absorption.
- Due to rapidity in action these sublingual dosage forms are widely used in emergency conditions.
- Rapid absorption and higher blood levels due to high vascularisation of the region and therefore particularly useful for administration of anti- angina drugs.
- They also present the advantage of providing fast dissolution or disintegration in the oral cavity, without the need for water or chewing.

Disadvantages:

- Since sublingual administration of drugs interferes with eating, drinking and talking, this route is generally considered unsuitable for prolonged administration.
- Although this site is not well suited to sustain-delivery systems.
- Sublingual medications cannot be used when a patient is uncooperative or unconscious.
- The patient should not smoke while taking sublingual medication, because smoking causes vasoconstriction of the blood vessels. This will decrease the absorption of the medication.

SUPERDISINTEGRANTS[36]:

There has been a considerable demand for faster disintegrating formulations and faster dissolution; hence the need to formulate modified disintegrants with still higher efficacies has lead to the new generation of "super disintegrants" in addition to the disintegrants discussed earlier. **Superdisintegrants** are effective at low concentration and have greater disintegrating efficiency. They are more effective intragranular and exert less effect on compressibility and flow ability. But superdisintegrants have some drawbacks - they are hygroscopic therefore not used

with moisture sensitive drugs, functionality is not as desired at higher concentrations and some are anionic and may cause some slight *in-vitro* binding with cationic drugs.

These superdisintegrants act by swelling and due to swelling pressure exerted in the outer direction or radial direction, it causes tablet to burst or the accelerated absorption of water leading to an enormous increase in the volume of granules to promote disintegration.

Fig:5 Mechanism of superdisintegrants by swelling

Three major groups of compounds have been developed which swell to many times their original size when placed in water while producing minimal viscosity effects:

1. *Modified Starches***-** Sodium carboxymethyl starch (Chemically treated potato starch)

i.e. Sodium starch glycolate (Explotab, Primogel)

Mechanism of action: Rapid and extensive swelling with minimal gelling.

2. *Cross-linked polyvinylpyrrolidone-* water insoluble and strongly hydrophilic.

i.e. crospovidone (Polyplasdone XL, Kollidon CL)

Mechanism of action: Water wicking, swelling and possibly some deformation recovery.

3. *Modified cellulose-* Internally cross-linked form of Sodium carboxymethyl cellulose, Crosscaramellose i.e. Ac-Di-Sol (Accelerates dissolution), Nymcel.

Table No:1 List of superdisintegrants

Category	Superdisintegrants	Mechanism of action	Special comment
Cross linked cellulose	Crosscarmellose® Ac-Di-Sol® Nymce ZSX® Primellose® Solutab® Vivasol® L-HPC	- Swells 4-8 folds in < 10 seconds. - Swelling and wicking both.	- Swell in two dimensions. - Direct compression or granulation - Starch free
Crosslinked PVP	Crospovidone Crosspovidon M® Kollidon® Polyplasdone®	- Swells very little and returns to original size after compression but act by capillary action	- Water insoluble and spongy in nature so get porous tablet
Crosslinked starch	Sodium starch glycolate Explotab® Primogel®	- Swells 7-12 folds in < 30 seconds	- Swells in three dimensions and high level serve as sustain release matrix
Crosslinked alginic acid	Alginic acid NF Satialgine®	- Rapid swelling in aqueous medium or wicking action	- Promote disintegration in both dry or wet granulation
Natural superdisintegrant	Soy polysaccharides Emcosoy®		- Does not contain any starch or sugar.

Table No: 2 Drugs used in the formulation of sublingual dosage forms

Drug	Category	Dosage Form
Physostigmine salicylate	Anti-alzheimers	Tablet[36]
Scopolamine	Opioid analgesic	Spray[37]
Captopril	Antihypertensive	Tablet[38]
Furosemide	Diuretic	Tablet[39]
Nifedipine	Anti angina	Tablet[40]
Nitro gycerine	Anti angina	Tablet[41]
Vinpocetine	Neurotropic agent	Tablet[42]
Terbutaline sulphate	Bonchodilator	Tablet[43]
Amlodipine besylate	Antihyperttensive	Tablet[44]
Salbutamol sulphate	Antiasthmatic agent	Film

Table No: 3 List of some marketed sublingual tablets

Brand Name	Drug	Category
Abstral	Fentanyl citrate	Opioid analgesic
Subutex	Buprenorphine	Opioid analgesic
Avitan	Lorazepam	Anti anxiety
Edular	Zolpidem tartarate	Sedatives/ Hypnotics
Isordill	Isosorbide dinitrate	Vasodilators
Nitrostat	Nitrroglycerin	Antianginal

2. LITERATURE REVIEW

Sindhu Abraham et.al[45]., has developed and optimized sublingual tablets of Rabeprazole sodium which is effective in the treatment of acid peptic disorders. The tablets were prepared by wet granulation method using polymers Crospovidone and Croscamellose sodium while the response variables include quantity determined were wetting time and in vitro Dispersion time.tha hardness of all the formulations was in the range of 3-4kg/cm^2. The percentage friability of all the formulations was found to be not more than 0.6%. In all the formulations the drug content was found to be uniform among the different batches of tablets and ranged from 97.37% to 100.51% of the theoretical value. The results were indicated that the amount of Crospovidone and Croscamellose sodium significantly affected the dependent variables wetting time and disintegration time.

Vineet Bharadwaj et. al[46]., has prepared fast disintegration 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. The super disintegrants used in this study were Kollidon CL, Ac-Di-Sod and Sodium starch glycolate in varying concentration(2%, 4%, 6%). From the results it is 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 super disintegrants used in the study.

Rajat Sharma et.al[47]., has formulated and evaluated the fast dissolving sublingual tablet of Glipizide. The super disintegrant used in this study was Crospovidone. The tablets were evaluated for weight variation, hardness, friability, wetting time, water absorption ratio and disintegration time and dissolution study. The tablets were prepared by wet granulation procedure. Sublimation of Naphthalene from tablets resulted in better tablets as compared to the tablets prepared from granules that were exposing to vaccum.

Bhanja et.al[48]., has developed and optimized a sublingual tablet of Perindopril which is an effective drug in the treatment of Hypertendion.Perindopril containing tablets were prepared by direct compression method using different ingredients such as Crospovidone, Sodium saccharin, Mannitol, Microcrystalline cellulose, Talc and

Magnesium stearate. An optimized formulation f4 was found which provided short wetting time of 45 sec, water absorption ratio 55 and in vitro disintegration time of 98sec. The super disintegrant Crospovidone was found to be effective with 99.88% drug availability in 12 min.

Neha Narang et.al[49]., has described about the drug delivery via the oral mucous membrane is more promising to the oral route. Sublingual route is a useful when rapid onset of action is desired with better patient compliance than orally ingested tablets. In terms of permeability, the sublingual area of the oral cavity is more permeable than the buccal area which inturn is more permeable than the palatal bioavailability.

Noushin bolourchian et.al[50]., has reported aimed to design and optimize a sublingual tablet formulation of Physostigmine salicylate, an effective drug in Alzheimer's disease and nerve gas poisoning, by means of the D-optimal experimental design methodology. Polyvinyl pyrrolidone, lactose, starch 1500 and Sodium starch glycolate were used in the formulations as independent variables. Tablets were prepared by the direct compression method and evaluated for their physical properties (tablet hardness, disintegration time and friability), which were regarded as responses in a D-optimal design. Due to the significance of the special cubic model for data fitted, compared to other models, it was used to examine the obtained results. Response surface plots were plotted to study the tablet properties and the optimized overlay plot was generated based on the results and targets considered for the responses. After verification of the optimum checkpoint formulations, an optimized formulation was chosen due to its desirable physical properties and closely observed and predicted values. Drug assay, content uniformity of the dosage unit, drug dissolution and accelerated stability studies were done on the optimum formulation as further experiments. All the obtained results complied with the requirements of a sublingual tablet formulation.

:**Friedrich Horak, MD et.al[51].,** has reported the efficacy and safety of a 5-grass-pollen sublingual immunotherapy (SLIT) tablet have been evaluated in clinical studies during the pollen season. The allergen challenge chamber (ACC) has been

developed as a pharmacodynamic assessment tool to control the environmental allergens and to avoid all problem associated with unpredictable pollen seasons sought to evaluate the onset of action and efficacy of 300-IR (index of reactivity) SLIT tablets by using an ACC : Patients with grass pollen–induced rhino conjunctivitis were randomized into the active or placebo groups. A standardized allergen challenge with grass pollen and symptom evaluation every 15 minutes was performed at baseline, 1 week, and 1, 2, and 4 months of treatment. The primary end point was the average rhino conjunctivitis total symptom score (ARTSS). Allergen-specific basophil activation T-cell proliferation, and plasmatic IgE and IgG responses were assessed before and after treatment In the intention-to-treat population (n 589) a significant treatment effect was achieved after the first month (P 5.0042) and second month (P 5.0203) and was maintained through to the fourth month (P 5.0007). In the active group the ARTSS (means 6 SDs) decreased at each challenge: week 1 7.40 6 2.682; month 1, 5.89 6 2.431; month 2, 5.09 6 2.088 and month 4, 4.85 6 1.999. An improvement (Vs placebo) of 29.3% for the mean ARTSS (median, 33.3%) was observed at end point. Furthermore, the induction of grass pollen allergen specific IgGs was associated with clinical response. The most frequent adverse reactions were local: oral pruritus, ear pruritus, and throat irritation. In this ACC study the 300-IR 5-grass-pollen SLIT tablets had a significant effect on rhino conjunctivitis symptoms (Vs placebo) from the first month of treatment onward.

Ronald Dahl,MD et.al[52]., has reported that allergen immunotherapy (desensitization) by injection is effective for seasonal allergic rhinitis and has been shown to induce long-term disease remission. The sublingual route also has potential, although definitive evidence from large randomized controlled trials has been lacking. A longitudinal, double-blind, placebo-controlled, parallel-group study that included 51 centers from 8 countries. Subjects were randomized (1:1) to receive a grass allergen tablet or placebo once daily. A total of 634 subjects with a history of grass pollen–induced rhino conjunctivitis for at least 2 years and confirmation of IgE sensitivity (positive skin prick test and serum-specific IgE) were included in the study The primary efficacy analysis showed a reduction of 30% in rhino conjunctivitis symptom score (P < .0001) and a reduction of 38% in rhino

conjunctivitis medication score (P <.0001) compared with placebo. Side effects mainly comprised mild itching and swelling in the mouth that was in general well tolerated and led to treatment withdrawal in less than 4% of participants. There were no serious local side effects and no severe systemic adverse events. Sublingual immunotherapy with grass allergen tablets was effective in grass pollen–induced rhinoconjunctivitis. The tablet was well tolerated with minor local side effects.

Jaymin Upadhyay et.al[53]., has reported Buprenorphine (BUP) is a partial agonist at μ-, δ- and ORL1 (Opioid receptor-like)/nociceptin receptors and antagonist at the κ-opioid receptor site. BUP is known to have both analgesic as well as antihyper analgesic effects via its central activity, and is used in the treatment of moderate to severe chronic pain conditions. Recently, it was shown that intravenous (IV) administration of 0.2 mg/70 kg BUP modulates the blood oxygenation level-dependent (BOLD) functional magnetic resonance imaging (FMRI) response to acute noxious stimuli in healthy human subjects. The present study extends these observations by investigating the effects of BUP dose and route of administration on central nervous system (CNS) pain circuitry. Specifically, the modulation of evoked pain BOLD responses and resting state functional connectivity was measured following IV (0.1 and 0.2 mg/70 kg) and sublingual (SL) (2mg) BUP administration in healthy human subjects. While 0.1 mg/70 kg IV BUP is sub-analgesic, both 0.2 mg/70 kg IV BUP and 2.0 mg SL BUP are analgesic doses of the drug. Evoked BOLD responses were clearly modulated in a dose-dependent manner. The analgesic doses of BUP by both routes of administration yielded a potentiation in limbic/mesolimbic circuitry and attenuation in sensorimotor/sensory-discriminative circuitry. In addition, robust decreases in functional connectivity between the putamen and the sensorimotor/sensory-discriminative structures were observed at the two analgesic doses subsequent to measuring the maximum plasma BUP concentrations (Cmax).

Mutasem M. Rawas-Qalaji et.al[54]., has reported Epinephrine autoinjectors are underused in the emergency treatment of anaphylaxis in the community, perhaps in part because of fear of needles. Objectives: To determine the sublingual Epinephrine dose from a novel fast-disintegrating tablet required to achieve Epinephrine plasma concentrations (EPPCs) similar to those obtained after Epinephrine 0.3 mg

intramuscular injection. Methods: In a prospective 5-way crossover study, sublingual tablets containing Epinephrine 0, 10, 20, and 40 mg, and epinephrine 0.3 mg intramuscular in the thigh (EpiPen) were compared in a validated rabbit model. Blood samples were collected before dosing and 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, and 180 minutes afterward. EPPCs were measured by using high-performance liquid chromatography–electrochemical detection. Pharmacokinetic parameters were calculated by using WinNonlin.

Kory J. Schuh et.al[55]., has reported Buprenorphine is an opioid partial agonist being developed as a treatment for opioid dependence. Buprenorphine, usually administered as a sublingual liquid, is now being developed as a sublingual tablet for clinical use. The present study compared participants' plasma concentrations after daily maintenance on three Buprenorphine liquid doses (2, 4 and 8 mg) and one tablet dose (8 mg). Fourteen opioid-dependent individuals (11 males, three females) participated. Plasma samples were collected over a 24-h period after at least 7 days of maintenance on each dose. Results showed that the liquid doses produced dose-related increases in plasma concentrations. The 8-mg tablet produced mean plasma concentrations significantly lower than those of the 8-mg liquid, although there was substantial individual variability. Thus, the Buprenorphine tablet dose might have to be adjusted to produce plasma concentrations equivalent to those of the liquid.

Susanne Bredenberg et.al[56]., has reported Oro-mucosal delivery of drugs promotes rapid absorption and high bioavailability, with subsequent almost immediate onset of pharmacological effect. However, many Oro-mucosal delivery systems are compromised by the possibility of the patient swallowing the active substance before it has been released and absorbed locally into the systemic circulation. This paper introduces 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 bio-adhesive component was also added to the carrier particles. Tablets containing 100, 200 and 400 g of fentanyl were tested both in vitro and in vivo. The tablets disintegrated rapidly and dissolution tests revealed that fentanyl citrate was dissolved from the formulation almost instantly. Plasma

concentrations of fentanyl were obtained within 10min, with no second peak. These results indicated that the bio-adhesive component prevented the fentanyl from being swallowed (the fraction swallowed was considered smaller compared to other mucosal delivery systems), without hindering its release and absorption. This new sublingual tablet formulation may also hold potential for other substances where a rapid onset of effect is desirable.

Noushin Bolourtchian,et.al[57]., has developed and optimized a 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. Meanwhile linear model was best fitted with hardness data. The obtained results were used to generate optimized overlay plot. 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.

Carl G.H. Dahlof, MD,et.al[58]., has reported Rizatriptan is a selective 5hydroxytriptammem receptor agonist that was launched in 1998 for the acute treatment of migraine in adults. Based on data from 6 large clinical trials in patients 218 years of age in whom migraine was diagnosed according to International Headache Society criteria, the marketed l0-mg and 5-mg oral doses of Rizatriptan are effective in relieving headache pain and associated migraine symptoms. The l0-mg dose is more effective than the 5-mg dose. At 2 hours after dosing, up to 77% of patients taking Rizatriptan 10 mg had pain relief compared with 37% of those taking placebo, up to 44% were completely pain free

compared with 7% of those taking placebo, and up to 77% were free of nausea compared with 58% of those taking placebo (P < 0.05 for all 3 comparisons). Both doses of Rizatriptan are generally well tolerated. In placebo-controlled studies involving treatment of a single migraine attack, the most common side effects (incidence 22%) occurred in <l0% of patients, typically were transitory (2 to 3 hours), and were mild or moderate. Rizatriptan is an effective and well-tolerated acute treatment for migraine.

Seymour Solomon,et al[59]., has reported the 5-hydroxytryptamine in, in agonists, or triptans, are the newest class of drugs to become available for the acute treatment of migraine. The class currently includes Sumatriptan, Zolmitriptan, Naratriptan, and Rizatriptan. The efficacy of rizatriptan in the acute treatment of migraine has been established against placebo and other oral triptans in controlled comparative trials. Methods: At enrollment, 216 patients completed a questionnaire describing their responses to their current Nontriptan medications. They were then given specially packaged samples of 4 standard IO-mg Rizatriptan tablets and 4 orally disintegrating lo-mg Rizatriptan tablets (wafers) and were asked to take a different formulation for each of their next 2 attacks, the sequence to be at their discretion. Within -24 hours after taking Rizatriptan, patients were to call a toll-free number to report their responses to Rizatriptan using an interactive voice-response system.

E Loder et.al[60]., has reported data from seven randomized, placebo-controlled, double-blind phase III clinical trials were analysed to further evaluate the efficacy of Rizatriptan 10 mg (n=2068) in comparison with placebo (n=1260) and Rizatriptan 5 mg (n=1486) for the acute treatment of a migraine attack. Migraine was diagnosed according to International Headache Society criteria. Headache severity, associated migraine symptoms and functional disability were measured immediately before dosing and at 0.5, 1, 1.5 and 2 h. Headache recurrence (return of moderate or severe headache after an initial response) was also recorded. In addition to conventional pain relief (reduction of moderate or severe headache to mild or none) and pain free measures, the analysis looked at the elimination of associated migraine symptoms and disability in patients who had symptoms or disability at baseline. Maintenance of pain relief or pain-free status over24 h was also analysed. At 2 h, Rizatriptan 10

mg was significantly more effective than placebo for pain relief (71% vs. 38%, P<0.001), and for elimination of pain, nausea, photophobia, phonophobia and functional disability. The benefit was maintained over 24 h; 37% of patients on Rizatriptan 10 mg had sustained pain relief vs. 18% for placebo (P<0.001).

Sunita A Chaudhary et.al[61]., has reported RZT is potent anti migraine drug having agonist activity at the 5-hydroxytryptamine (5-HT) 1B and 5-HT 1D receptor. It commonly used for relief of headaches in treatment of migraine. Conventional tablets of RZT are not capable of rapid action, which is required for immediate relief from migraine pain. Marketed freeze dried tablet of RZT is available. Freeze drying is cumbersome and it yields a fragile and hygroscopic product. Thus, the aim of the present investigation is to formulate orally disintegrating tablets (ODTs) of Rizatriptan using simple and cost effective dosage forms. Approach used was use of superdisintegrants to prepare tablets. Tablets were prepared by direct compression using superdisintegrants such Crospovidone, Croscarmellose sodium, and Sodium starch glycolate with incorporation of diluents like Lactose, MCC and Mannitol. Tablets of RZT prepared using Crospovidone with MCC exhibited the least friability and disintegration time (sec). To decrease the disintegration time further, modified diluents like spray dried lactose, Avicel pH 102 and Orocell 200.used along with the superdisintegrants for the preparation of ODTs. Tablet prepared using orocell showed good disintegration but shows less dispersion. Further trial was done in combinations of Orocell with Avicel pH 102. Among them Avicel pH 102 and orocell in 35:65 ratio showed less time of disintegration and rapid dissolution.

Kiran Kumar S, et.al[62]., has reported in view to enhance patient compliance an attempt has been made in the present work, Rizatriptan Benzoate Rapimelt tablets and oral Thin Films (OTFs) were prepared by effervescence technique and solvent casting technique respectively. The motive of study is to provide a dosage form that can quickly disintegrate upon contact with the saliva. The excipients used in the preparation of Rapimelt tablets were effervescence agents (sodium bicarbonate & citric acid) along with superdisintegrants, such as Croscarmellose Sodium (2-4%), Crospovidone (2-4%), and Sodium Starch Glycolate (4-8%). The low viscosity hydrophilic polymer, HPMC E5 LV (1-5%) used in the preparation of Oral Thin Films. Sweetener and flavors were added to enhance the mouth feel in both dosage

forms. The prepared tablets were evaluated for Thickness, Weight variation, Hardness, Friability, Assay, Content uniformity, in- vitro disintegration time, Simulated Wetting Time, and Dissolution. The Oral thin films were evaluated for physical appearance, thickness, folding endurance, assay, content uniformity, in-vitro disintegration time, and dissolution. Based on the in- vitro disintegration time and dissolution results the best formulations were selected in each dosage form type.

T. Satyanarayana, et.al[63]., has reported oral disintegrating tablets have emerged as an alternative to the conventional oral dosage forms to improve the patient compliance. Due to problem in swallowing ability with age, the pediatric and geriatric patients complain of difficulty to take conventional solid dosage forms. The ODT's are solid dosage forms that dissolve or disintegrate rapidly in the oral cavity. This results in solution or suspension without the need of water. The main objective of this work is to formulate and evaluate Rizatriptan Benzoate ODT's using different concentration of super disintegrating agents like Croscarmellose , Sodium starch glycolate (SSG),Crospovidone. Tablets were prepared by direct compression method and evaluated for hardness, thickness, friability, disintegration time, and percentage of drug release.. The results indicated that formulation prepared with Crospovidone was found to be optimised which provides maximum drug release (100%) and minimum disintegration time (less than 10 second).

R. V. KENY,et.al[64]., has investigated development of mouth disintegrating tablets of Rizatriptan benzoate to produce the intended benefits. Mouth disintegrating tablets of Rizatriptan benzoate were prepared using superdisintegrants Crospovidone, Carboxymethylcellulose 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±2o/75%±5% RH for 1 mo showed non significant drug loss. The formulation containing combination of

Crospovidone and Indion 234 was found to give the best results. Apart from fulfi lling all official and other specifications, the tablets exhibited higher rate of release.

Chavan Jyotsna D.et.al[65]., has reported microparticulate drug delivery systems provides numerous advantages like, increased surface area, modified release pattern, improved bioavailability etc. In the present work, attempt has been made to use Chitosan, natural polymer for the preparation of microparticles by spray drying and evaluate them for size, shape, dissolution, mucoadhesion strength studies etc. For preparation of microparticles, model drug Rizatriptan benzoate has been used. It has been observed that, all drug loaded microparticles were spherical in nature with narrow size distribution. Spray drying induced drug amorphousiation, which contributed for dissolution enhancement of drug. Also the loading of Rizatriptan benzoate into Chitosan microparticles led to an improvement of its dissolution/release rate. The rate of dissolution increases with increase in proportion of Chitosan. In fact about 90–100% of drug release was achieved in less than 2 hr from the spray-dried microparticles. With the increase in proportion of chitosan in formulation (F1-F5) it has been observed that mucoadhesive strength of microparticles was increased due to decreasing mucocilliary clearance which increases residence time of drug in nasal cavity thus increasing absorption.

H. Elshafeey, et.al[66]., has reported the bioequivalence of two commercial 10mg tablet formulations of Rizatriptan, a selective 5-hydroxytryptamine1B/1D (5-HT1B/1D) receptor agonist indicated for the acute treatment of migraine attacks using a newly developed and validated LC-MS/MS assay. Intraday and Intraday assay precision was acceptable. The lower limit of quantification was 0.1mg/ml. Accuracy was observed over a linear range of 0.1-100 mg/ml. The differences between the two products did not reach statistical significance with 90% CIs of 91.3-112.6, 101.6-111.2 and 102.0-111.6 for Cmax, AUC0-12 and AUC0-inf respectively. The test/reference ratio of these parameters was within the acceptance range of the FDA criterion for bioequivalence. Both formulations were apparently well absorbed from the gastrointestinal tract (i.e., no specific gastrointestinal tract-related adverse events were reported).

3. AIM AND OBJECTIVE

Aim of the study:

The aim of present study is to design and evaluation of fast disintegrating sublingual tablets of Rizatriptan using different super-disintegrants.

Objective:

Migraine is a common type of headache that may occur with symptoms such as nausea, vomiting, or sensitivity to light. In many people, a throbbing pain is felt only on one side of the head. The oral dispersible dosage forms are less effective as it undergoes first pass metabolism and because of its low bioavailability (45%). Compared with ODT the onset of action produced by sublingual tablets is faster.

Triptans are the widely used drugs for the treatment of migraine. Among these Sumatriptan is mostly used drug. Rizatriptan is more advantageous than Sumatriptan as 10mg of Rizatriptan is equipotent to 100mg of Sumatriptan.

The objective of the present study was to develop fast disintegrating sublingual tablets of Rizatriptan. Hence an attempt was made to develop fast disintegrating sublingual tablet dosage with the following objectives:

1. To design the formula for fast disintegrating sublingual tablets of Rizatriptan.
2. To evaluate the formulated tablets.
3. To study the in vitro dissolution profile of prepared tablets.
4. Stability study of prepared tablet at certain conditions as per ICH guidelines.
5. To get patient compliance and acceptable taste in the oral cavity.
6. To reduce bitterness of the drug by using different sweeteners.

4. PLAN OF WORK

The study was proposed to carry out in the following stages:

Preformulation studies:

The calibration curve is done with Phosphate buffer pH 6.8 since the maximum dissolution was found in this medium.

In order to indicate the absence of interaction between the drug and excipients FTIR studies were conducted.

Formulation and evaluation of drug and drug excipients mixture for direct compression:

Evaluation of powder mixture by

- Angle of repose
- Bulk density
- Tapped density
- Compressibility index
- Haurn's ratio

Formulation and evaluation of fast disintegrating sublingual tablets:

To study the influence of different excipients, excipient concentrations on the physiochemical and *in vitro* release behavior of fast disintegrating sublingual tablets the following steps were conducted:

- Compression of drug and its excipients into a tablet.
- Evaluation of fast disintegrating sublingual tablets by

1. Thickness
2. Hardness
3. Friability
4. Weight variation
5. Drug content
6. Wetting time
7. Disintegration test
8. In vitro release studies
9. Stability studies

5. DRUG PROFILE& EXCIPIENTS PROFILE

5.1 DRUG PROFILE

RIZATRIPTAN:

Name of drug : Rizatriptan

Molecular formula : $C_{15}H_{19}N_5$

Molecular weight : 269.345 g/mol

Chemical name : *N*,*N*-dimethyl-2-[5-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-indol-3-yl]ethanamine

Chemical structure :

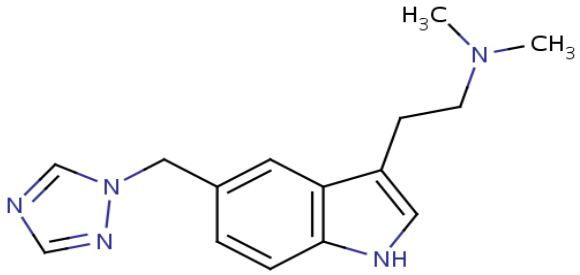


Fig 6: Chemical structure of Rizatriptan

Category : Anti-migraine Agent

Vasoconstrictor Agent

Selective Serotonin Agonist

Serotonin Agonist

Anti-inflammatory Agent

Bioavailability : 45%

Protein binding : 14%

Half life : 2-3hrs

Melting Point : 170-180°C

BCS Classification : Class-III (High Solubility & Low Permeability)

Mechanism of action: Three distinct pharmacological actions have been implicated in the antimigraine effect of the triptans:

- stimulation of presynaptic 5-HT1D receptors, which serves to inhibit both dural vasodilation and inflammation.
- direct inhibition of trigeminal nuclei cell excitability via 5-HT1B/1D receptor agonism in the brainstem.
- vasoconstriction of meningeal, dural, cerebral or pial vessels as a result of vascular 5-HT1B receptor agonism.

Pharmacokinetics:

Absorption: Rapid 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.

Metabolism: 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.

Excretion: 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.

Adverse effects: Coronary artery vasospasm, Transient myocardial ischemia, Myocardial Infraction, Ventricular Tachycardia, Phonophobia, Photophobia, Myalgia, Diarrhoea.

Advantage: 10mg of Rizatriptan Benzoate is equipotent to a 100mg of Sumatriptan.

5.3 EXCIPIENT REVIEW

MANNITOL:

Synonyms: Cordycepic acid; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.

Structure:

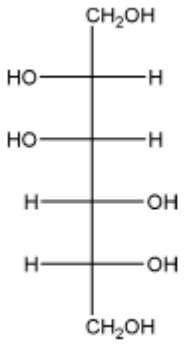


Fig No: 7 Structure of Mannitol

Empirical formula : $C_6H_{14}O_6$

Molecular weight : 182.17.

Chemical name : D-Mannitol

Functional category : Diluent; diluent for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.

Applications: As a diluent in tablets (10-90% w/w). It is non-hygroscopic and can be used with moisture sensitive active ingredients. In the manufacture of chewable tablet formulation because of its negative heat of solution, sweetness and mouth feel. Therapeutically, mannitol is administered parenterally as an osmotic diuretic, as a diagnostic agent for kidney function, as an adjunct in the treatment of acute renal failure, and as an agent to reduce intracranial pressure, treat cerebral edema, and reduce intraocular pressure.

Description: 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. It shows polymorphism.

Melting point: 166–168^{o} C.

Solubility: Freely soluble in water, practically insoluble in ether.

Stability and storage conditions: Mannitol is stable in the dry state and in aqueous solutions. In solution, it is not attacked by cold, dilute acids or alkalis, nor by atmospheric oxygen in the absence of catalysts. It should be stored in a well-closed container in a cool, dry place.

Incompatibilities: 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.

CROSPOVIDONE

Nonproprietary names:

BP Crosspovidone, PhEur: Crospovidonum, USPNF: Crospovidone

Synonyms:

Crosslinked povidone, E1202 Kollidon CL, Polyplasdone XL-10, polyvinyl polypyrrolidone PVP, 1-vinyl 2 pyrrolidone homopolymer.

Chemical name : 1- Etheny1-2 pyrrolidinone homopolymer

Empirical formula : $[C_6H_9NO]n$

Molecular weight : > 1000000

Functional category : Tablet disintegrant

Description : Crospovidone is white to creamy white, finely divided free flowing. Practically tasteless, odorless or nearly odorless, hygroscopic powder.

Solubility :Practically insoluble in water and most common organic solvents.

Typical properties:

Acidity / Alkalinity pH :5.0-8.0(1%w/v aqueous slurry)

Density : 1.22 g/cm^3

Bulk density : Polyplasdone XL10 – 0.416 g/cm^3

Moisture content : maximum moisture sorption is approximately 60% Polyplasdone XL-10- 5.0 % Maximum 45.

Compressibility (Carr index) :Polyplasdone XL -10-30%

Particle size distribution :Less than 74 μm for Polyplasdone XL-10

Specific surface Area :Polyplasdone XL-10 1.2-1.4m^2/g

Stability and storage conditions:

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

Application in pharmaceutical formulation or technology:

Crosspovidone 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, It rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels. The particle size of Crospovidone strongly influences disintegration of tablets. Larger particle provide a faster disintegration than smaller particles. Crosspovidone can also be used as solubility enhancer.

Incompatibilities:

Crosspovidone is compatible with most organic and inorganic pharmaceutical ingredients. When exposed to a high water level, Crospovidone may form molecular adduct with some materials.

MAGNESIUM STEARATE

Nonproprietary names	**:**	BP:Magnesium stearate PhEur: magnesii stearas USPNF; Magnesium stearate.
Synonyms	**:**	E572, Hyqual, magnesium octadecanoate stearic acid
Chemical name	**:**	Octadecanoic acid magnesium Salt
Empirical formula	**:**	$C_{36}H_{70}MgO_4$
Structural formula	**:**	$[CH3\ (H_2)_{16}COO]_2\ Mg$
Molecular weight	**:**	591.27
Functional category	**:**	Tablet and capsule lubricant
Flow ability	**:**	Poorly flowing, cohesive powder
Melting point	**:**	88.5C
Moisture content	**:**	3.85%.

Applications in pharmaceutical formulation or technology:

Magnesium stearate is widely used in cosmetics food and pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.2-5.0percent.

Description:

Magnesium stearate is a fine, white, precipitated or milled, impaltable powder of low bulk density having a faint, characteristic odour and taste the powder is greasy to touch and readily adheres to the skin.

Polymorphism:

A trihydrate, acicular form and a dihydrate lamellar form have been isolated with the latter processing the better lubricating properties.

Solubility:

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

HYDROXY PROPYL CELLULOSE, LOW SUBSTITUTED

Non proprietary names **:** JP,USPNF: Low substituted hydroxyl propyl cellulose

Synonyms **:** Hyprolose, low substituted; L-HPC

Chemical name **:** Cellulose, 2-hydroxy propyl ether (low substituted)

CAS registry No **:** [78214-4-2]

Functional category:

- Tablet and capsule disintegrant
- Tablet binder

Description:

L-HPC occurs as a white to yellowish white powder or granules. It is odourless or has a slight, characteristic odour and it is tasteless.

Pharmacopeial specification:

Test	*JP'01*	*USPNF 23*
1. Chloride	≤ 0.335%	≤ 0.36
2. Heavy metals	≤ 10 ppm	≤ 0.001 %

3. Arsenic	≤ 2 ppm	- - -
4. pH	5.0-7.5	- - -
5. Loss on drying	≤ 6.0%	≤ 5.0%
6. Residue on ignition	≤1.0%	≤ 0.5%
7. Assay	5.0-16.0%	5.0-16.0%

Typical properties:

Acidity/alkalinity*:* pH = 5.0-7.5 for 1%w/v aq. Suspension

Angle of repose*:*

LH-11 49^0

LH-21 45^0

Ash value: 0.3-0.4%

Density*:*

	Bulk	*Tapped*
LH-11	0.32	0.56
LH-21	0.36	0.62

Melting point *:* Decomposition at 275°C

Moisture content*:*

8% at 33% RH

38% at 95%RH

Specific gravity*:* 1.46

Solubility*:*

Practically insoluble in ethanol (95%) and in ether

Dissolves in a solution of sodium hydroxide (1 in 10)

Insoluble but swells in water.

Stability and Storage condition:

L-HPC is a stable, though hygroscopic, material. The powder should be stored

in a well closed container.

Incompatibilities:

Alkaline substances may interact. If a tablet formulation contains such a material, its disintegration may be extended after storage.

Safety:

L-HPC is generally regarded as a non-toxic and non-irritant material.

Handling precautions:

Excessive dust generation should be avoided to minimize the risk of explosions

Applications in pharmaceutical formulations:

It is primarily used in tableting as a disintegrant and as a binder in wet granulation. In addition, it has been used to delay the release of drug from a tablet matrix.LH-11 has the medium substitution level and the larger particle size, and is typically used as an anticapping agent and disintegrant for direct compression.

LH-21 is used as a binder and disintegrant for tablets through the direct compression process.

The typical content of L-HPC in a formulation is approx. 5-25%.

Regulatory status:

Approved for use in pharmaceuticals in Europe, Japan, USA and other countries.

CROSCARMELLOSE SODIUM

Non propreitary names:

BP,USPNF: Croscarmellose sodium

PhEur: Carmellosum natricum conexum

Synonyms:

Crosslinked carboxy methyl cellulose sodium (Ac-di-sol), modified cellulose gum (pharmacel XL; Primellose; Solutab)

Chemical name and CAS registry NO:

Cellulose, Carboxymethyl ether, Sodium salt crosslinked

Emperical formula and molecular weight:

Functional category: Disintegrant

- Tablet disintegrant 0.5-5.0
- Capsule disintegrant 10-25

Description:

Croscarmellose sodium occurs as an odourless, white or grayish-white powder.

Pharmacopeial specifications:

Test	PhEur'05	USPNF 23
pH (1%w/v dispersion)	5.0-7.0	5.0-7.0
Loss on drying	≤ 10.0%	≤ 10.0%
Heavy metals	≤ 10 ppm	≤ 0.001%
Sulphated ash	14.0-28.0%	------
Sodium chloride and sodium glycolate	≤ 0.5%	≤ 0.5%
Water soluble material	≤ 10.0%	1.0-10.0%

Typical properties:

Acidity/alkalinity : pH = 5.0-7.0 in aq.dispersion

Density (bulk) : 0.529 g/cm^3

Density (tapped) : 0.819 g/cm^3

Density (true) : 1.543 g/cm^3

Solubility : Practically insoluble in acetone, ethanol, and toluene. It rapidly swells to 4-8 times it's original volume on Contact with water.

Stability and storage conditions:

Croscarmellose sodium is a stable though hygroscopic material. It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Croscarmellose sodium isn't compatible with strong acids or with soluble salts

of iron and some other metals such as aluminium, mercury, and zinc.

Safety:

It is generally regarded as an essentially non-toxic and non-irritant material.

Handling precautions:

Croscarmellose sodium may be irritant to the eyes; eye protection is recommended.

Regulatory status:

Included in the FDA Inactive Ingredients Guide (oral capsules, granules, sublingual tablets and tablets).

ASPARTAME

Non proprietary names:

BP;USPNF: Aspartame

PhEur: Aspartamum

Synonyms:

3-amino-N- (α- carboxyphenethyl) succinic acid N-methyl ester; 3-amino-N-(α-methoxycarbonylphenethyl) succinamic acid; APM; aspartyl phenylamine methyl ester; methyl N-α-L-aspartyl-L-phenylalaninate

Chemical name and CAS registry NO:

N-α-L-aspartyl-L-phenylalanine 1- methyl ester [22839-47-0]

Empirical formula and molecular weight:

$C_{14}H_{18}N_2O_5$ 294.31

Functional category:

Sweetening agent

Description:

Aspartame occurs as an off-white, almost odourless crystalline powder with an intensely sweet taste.

Pharmacopeial specification:

Test	PhEur'05	USPNF 23
Heavy metals	≤ 10 ppm	≤ 0.001%
Loss on drying	≤ 4.5%	≤ 4.5%
Sulphated ash	≤ 0.2%	≤ 0.2%
Assay	98.0-102.0%	98.0-102.0%

Typical properties:

Acidity/alkalinity : pH = 4.5-6.0 (0.8% w/v aq.solution)

Density (bulk) : 0.17 g/cm^3

Density (tapped) : 0.29 g/cm^3

Density (true) : 1.347 g/cm^3

Melting point : 246-247°C

Solubility : Slightly soluble in ethanol (95%); sparingly soluble in water

Solubility increases upto 10%w/v at temp. 20°C and at pH 2.

Stability and storage conditions:

Aspartame is stable in dry conditions. In the presence of moisture, hydrolysis occurs to form the degradation products L-aspartyl-phenylalanine and 3-benzyl-6-carboxymethyl-2,5-diketopiperazine. Aspartame degradation may be minimized by using processes that employ high temperatures for a short time followed by rapid cooling.

Aspartame should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Aspartame is incompatible with dibasic calcium phosphate and also with the lubricant magnesium stearate.

Safety:

It is generally regarded as a non-toxic material. In normal healthy individuals aspartame should be avoided by those persons with phenylketourea. The WHO has set

an acceptable daily intake for aspartame at upto 40 mg/kg body weight.

Applications in pharmaceutical formulations:

Aspartame is used as an intense sweetening agent in beverage products, food

products, and table-top sweetners and in pharmaceutical preparations including tablets, powder mixes and vitamin preparations.

Therapeutically, aspartame has also been used in the treatment of sickle cell anemia.

Regulatory status:

Included in the FDA Inactive Ingredients Guide (oral powder for reconstitution, buccal batch, granules, film-coated, and tablets).

TALC

Non proprietary names:

JP;USP: Talc

BP: Purified talc

PhEur: Talcum

Synonyms:

Hydrous magnesium calcium silicate; hydrous magnesium silicate; magnesium

hydrogen metasilicate; powdered talc; purified French talc; soapstone; steatite.

Empirical formula: $Mg_6(Si_2O_5)_4(OH)_4$

Functional category	**Concentration (%)**
➢ Tablet and capsule lubricant	1.0-10.0
➢ Dusting powder	90.0-99.0
➢ Tablet and capsule diluent	5.0-30.0
➢ Anti-caking agent	---------

Description:

Talc is a very fine, white to grayish-white, odourless, impalpable, crystalline

powder. It adheres readily to the skin and is soft to the touch and free from grittiness.

Pharmacopeial specification:

Test	JP'01	PhEur'05	USP 28
Acid soluble substances	≤ 2.0%	--------	≤ 2.0%
pH	-----	7.0-9.0	------
Water soluble substances	------	≤ 0.2%	≤ 0.1%
Aluminium	------	≤ 2.0%	-----
Calcium	-----	≤ 0.9%	------
Iron	-----	≤ 0.25%	-----
Lead	-----	≤ 10 ppm	-----
Magnesium	-----	17.0-19.5	-----
Loss on ignition	≤ 5.0%	≤ 7.0%	≤ 6.5%
Arsenic	≤ 4 ppm	------	≤ 3 ppm
Heavy metals	------	------	≤ 0.004%

Typical properties:

Acidity/alkalinity : pH = 7-10 (In a 20% w/v aq.dispersion)

Moisture content : Talc absorbs insignificant amounts of water at 25°C/ RH90%.

Solubility : Practically insoluble in water, dilute acids, alkali's,

Stability and storage conditions:

Talc is a stable material and may be sterilized by heating at 160°C for not less

than 1 hour. It should be stored in a well-closed container in a cool, dry place.

Incompatibilities:

Talc is incompatible with quaternary ammonium compounds.

Safety:

Talc is not absorbed systematically following oral ingestion and is therefore regarded as an essentially non-toxic material.

Handling precautions:

Talc is irritant if inhaled and prolonged excessive exposure may cause pneumoconiosis.

Regulatory status:

Included in the FDA inactive ingredients guide (buccal tablets; oral capsules and tablets; rectal and topical preparations).

6. MATERIALS

Table No: 4 The chemicals used together with the company name

S.No	Name of chemicals	Manufacturing company
1.	Rizatriptan	Taj pharmaceuticals limited, India
2.	Crospovidone	Jiaozuo yuanhai fine chemicals, Japan.
3.	Croscamellose sodium	Amish drugs & chemicals, Ahmadabad.
4.	Low substituted hydroxy propyl cellulose	Shin-etsu chemicals co ltd. Japan.
5.	Mannitol	Merck, India.
6.	Aspartame	S.D. fine chemicals, Mumbai.
7.	Magnesium stearate	Harish chemicals Pvt Ltd., Ahamadabad
8.	Potassium dihydrogen ortho phosphate	Qualigens fine chemicals Pvt Ltd., Mumbai
9.	Sodium hydroxide pellets	Qualigens fine chemicals Pvt Ltd., Mumbai
10.	Hydrochloric acid	Qualigens fine chemicals Pvt Ltd., Mumbai
11.	KBr IR grade	Qualigens fine chemicals Pvt Ltd., Mumbai

Table No: 5 The equipments used together with the company name

S.No	Name of the equipment	Manufacturing company
1.	Electrical balance	SHIMADZU Scientific Instruments, Japan
2.	Single rotary tablet compression machine	Cadmach machinery Co.PVT.Ltd,India
3.	Hardness tester	Monosanto, St. Louis
4.	Friabilator	Roche friabilator
5.	Dissolution apparatus	Minicon equipments Pvt Ltd
6.	Micro syringe	Eonpipette(Bio Eras)
7.	Hot air oven	Minicon equipments Pvt Ltd
8.	KBr titer apparatus	Lasco equipment Pvt Ltd, Canada
9.	Bulk density test apparatus	Vergo instruments corporation, Mumbai
10.	UV	SHIMADZU Scientific instruments, Japan
11.	FTIR	SHIMADZU Scientific instruments, Japan

PREFORMULATION STUDIES

Preformulation can be defined as an investigation of physical and chemical properties of drug substance alone and when combined with excipients. The overall objective of preformulation testing is to generate information useful to the formulator in developing stable and bio-available dosage forms that can be mass produced. The following data must be considered.

Stability (Solid state) - Light, Temperature, Humidity

In vitro dissolution

For a tablet formulator's perspective, the most important preformulation information is the drug-excipient stability study. In the preformulation profile studies, physical mixtures are made of the drug and excipients materials in different ratios. The ratio is used even though is not the ratio anticipated for the final dosage form in order to maximize the probability of detecting a physical or chemical reaction should one occur. The analysis is made in visual cells or vials.

The sample vials were kept in different temperature and humidity conditions for a period of one month.

Fig No:8 FTIR spectrum of Rizatriptan

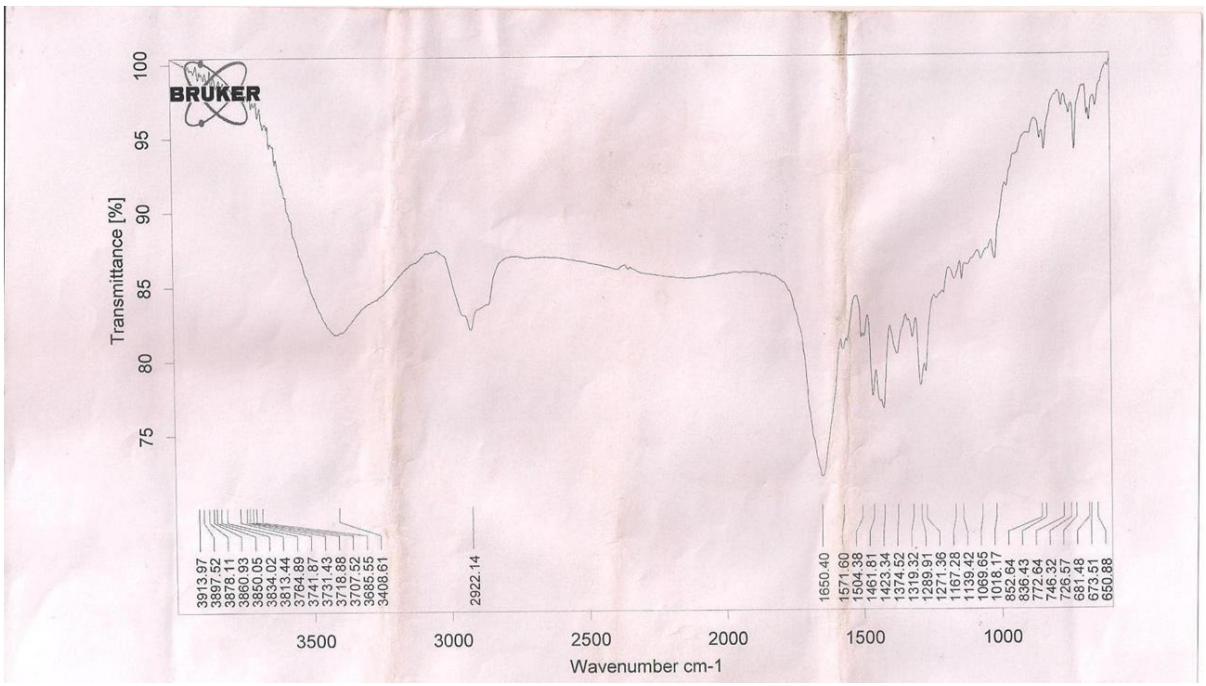


Fig No:9 FTIR spectrum of Rizatriptan+ Crospovidone

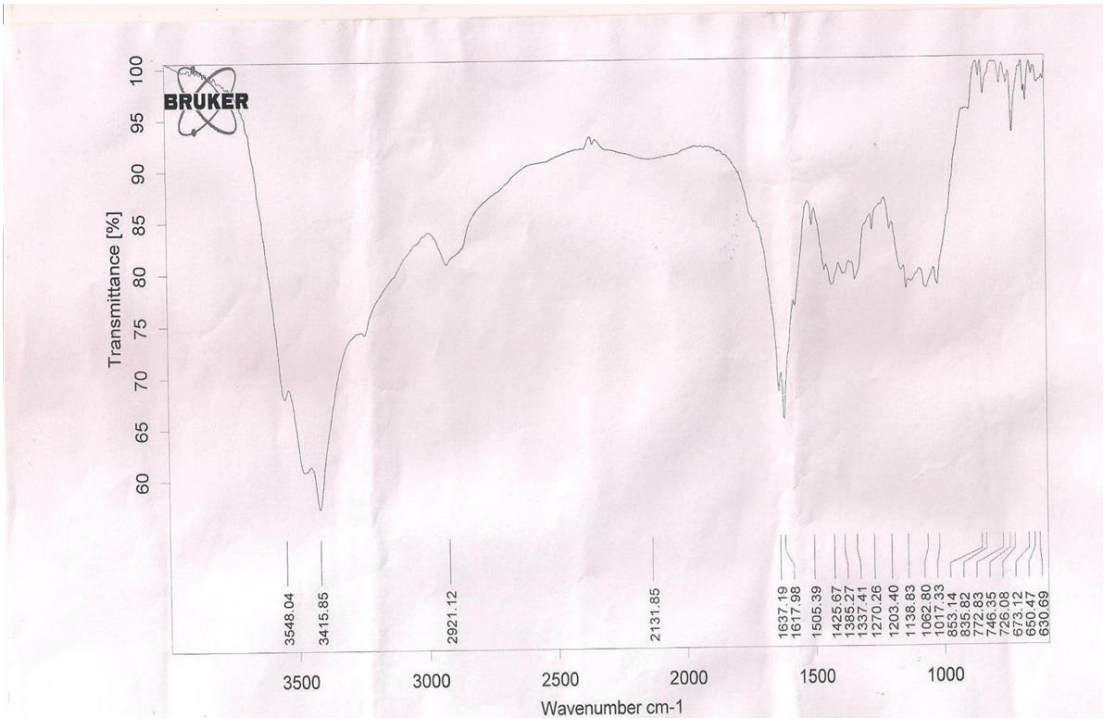


Fig No: 10 FTIR spectrum of Rizatriptan + Croscamellose sodium

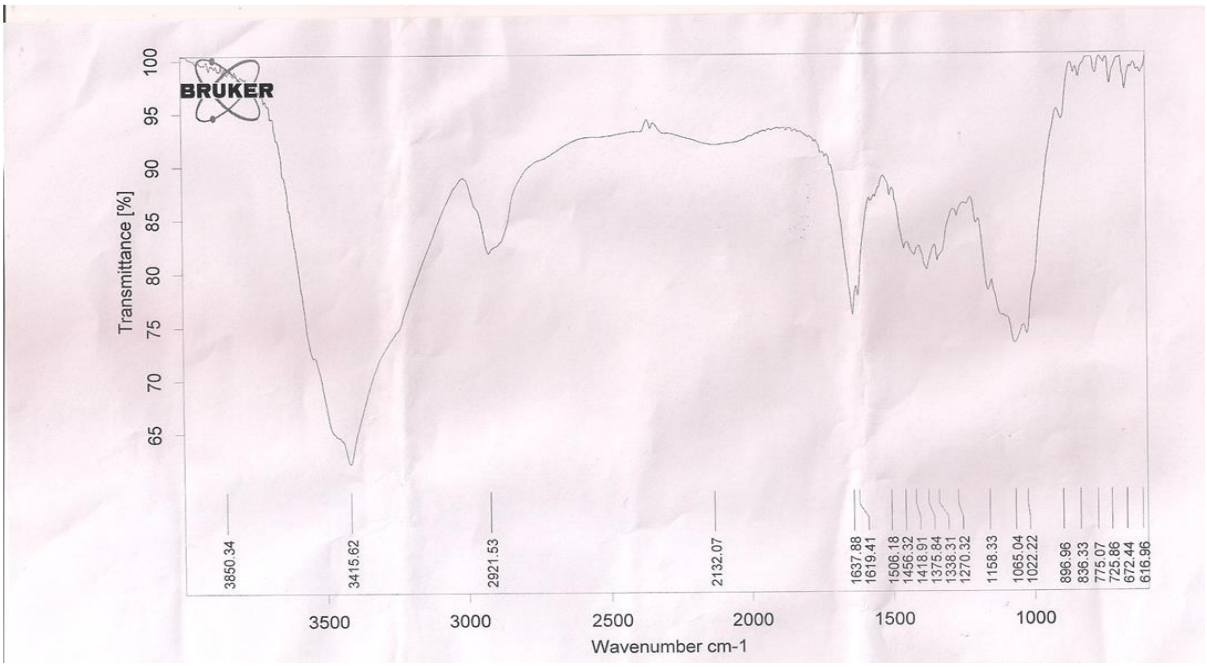
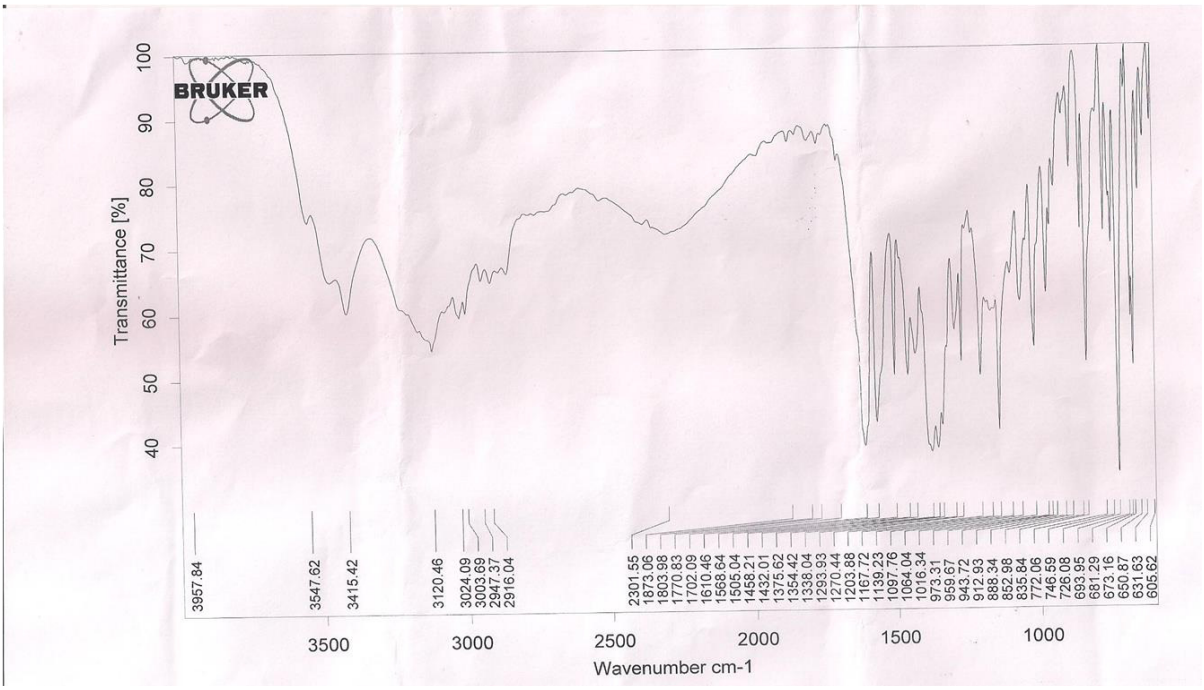


Fig No:11FTIR spectrum of Rizatriptan + L-HPC



FTIR for pure Rizatriptan and excipients were carried out, the peaks have appeared in pure Rizatriptan and excipients indicating no chemical interaction between pure Rizatriptan and excipients.

ANALYTICAL METHODS

Preparation of pH 6.8 buffer solution:

3.84gms of Potassium dihydrogen ortho phosphate was taken in 1000ml volumetric flask and the volume is made up with distilled water.

Preparation of stock solution:

100mg pure drug was taken in 100ml volumetric flask and the volume is made up with distilled water. From this 1ml is taken and diluted to 10ml in a 10ml volumetric flask. From this 1ml is taken and diluted to 10ml in an 10ml volumetric flask to get 10µg/ml concentration of solution.

Calibration curve of Rizatriptan in pH 6.8 buffer solution:

From the above stock solution take 1ml, 2ml, 3ml, 4ml, 5ml, 6ml and 7ml individually in 10ml volumetric flask and the volume is made up with distilled water and observe the absorbance at 226nm by UV method. The obtained peak areas against each dilution levels are shown in Table No:7 and the concentration Vs absorbance are plotted in a graph shown in Fig:8.

COMPATABILITY STUDIES

Infrared spectra matching approach was used for the detection of any possible chemical reaction between the drug and the excipients. A physical mixture (1:1) of drug and excipients was prepared and mixed with suitable quantity of potassium bromide. About 100mg of this mixture was compressed to form a transparent pellet using a hydraulic pressure at 10tons pressure. It was scanned from 4000-400cm^{-1} in a SHIMADZU FTIR Spectrophotometer. The IR spectrum of physical mixture was compared with those of pure drug and excipients and matching was done to detect any appearance or disappearance of peaks.

FORMULATION STEPS FOR SUBLINGUAL TABLETS (DIRECT COMPRESSION)

The fast disintegrating sublingual tablets of Rizatriptan (5mg) were prepared through direct compression method (without granules making step). According to the composition shown in Table No:8. Various steps (Sieving, Dry mixing, Lubrication & Compression) involved in the tablet production by direct compression method were orchestrated below:

- Sieving:
    - The active ingredient was passed through the sieve #40 followed by other ingredients were passed through the same sieve.
- Dry Mixing:
    - All the ingredients (Including the active ingredient) were taken in poly bag and mixed for 5mins to ensure uniform mixing of the ingredients with the drug.

- Lubrication:
    - The Magnesium stearate mixed with the powder mixture in a poly bag for 5mins to get a uniform blend.
- Compression:
    - Finally, the powder mixture was compressed into tablets using 7mm flat shaped punches in single rotary tablet compression machines at the weight of 100mg each.

EVALUATION OF POWDER MIXTURE

Formulated powder mixture were analysed for its bulk density, tapped density, flow Property, carr's index, and hausner's ratio.

Bulk density:

Weighed quantity of granules was transferred into a 50 ml measuring cylinder without tapping, during transfer the volume occupied by granules was measured. It is expressed in gm/ml. Bulk density was measured by using formula.

$$P = m/V_o$$

Where

P = Bulk density

V_o = Untapped volume

m = Mass of the blend

Tapped density:

Lab USP (II), the % Volume variation was calculated by following formula. Weighed quantity of granules was taken into graduated cylinder, volume occupied by granules was noted down. Then cylinder was subjected to 500 taps in tapped density tester .

$$P_t = m/V_i$$

Where,

P_t = Tapped density

V_i = Tapped volume

m = Mass of the blend

Angle of repose:

The prepared granules were assessed for its flow property by determining the angle of repose. The angle of repose was measured by allowing the granules to fall over a graph sheet placed on horizontal surface through a funnel kept at a certain convenient height (about 6 cm). The height of the heap was measured and then circumference of the base of heap was drawn on graph sheet with the help of a pencil. The radius of the circle obtained was measured. The angle of repose is given as,

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

where

θ = angle of repose

h = height of the heap

r = radius of the base of the heap

Carr's index:

After determining the poured bulk density the granules was then tapped mechanically for 100 times till a constant volume called tapped bulk density was obtained. Using poured bulk density and tapped bulk density the percentage compressibility of granules was determined, which is given as carr's compressibility index.

$$\text{Carr's compressibility index (\%)} = \frac{\text{Tapped bulk density} - \text{poured bulk density}}{\text{Tapped bulk density}}$$

$$\text{Poured bulk density} = \frac{\text{Mass of the granules}}{\text{Untapped volume of packing}}$$

$$\text{Tapped bulk density} = \frac{\text{Mass of the granules}}{\text{Tapped volume of packing}}$$

Hausner's ratio:

It was determined by the ratio of tapped density and bulk density.

$$\text{Hausner's ratio} = \frac{V_o}{V_i}$$

Where

V_o = Bulk density

V_i = Tapped density

Table No: 6 Limits for flow properties of powder

S.NO	Type of flow	Angle of repose	Carr's index	Hausner's ratio
1	Excellent	25-30	10	1-1.11
2	Good	31-35s	11-15	1.12-1.18
3	Fair	36-40(aid not needed)	16-20	1.19-1.25
4	Passable	41-45(may hang up)	21-25	1.26-1.34
5	Poor	46-55(must agitate)	26-31	1.35-1.45
6	Very poor	56-65	32-37	1.46-1.54
7	Very very poor	>66	>38	>1.60

EVALUATION OF SUBLINGUAL TABLETS

The formulated tablets were evaluated for the following parameters.

General appearance:

The formulated tablets were assessed for it's general appearance and observations were made for shape, colour, texture, and odour.

Thickness:

The thickness of the formulated Rizatriptan fast disintegrating sublingual tablets was measured by using digital vernier calipers. The mean thickness is reproduced in the Table No:10

Uniformity of weight:

20 tablets were selected and were weighed collectively and individually. From the collective weight, average weight was calculated. Each tablet weight was then compared with average weight to ascertain whether it was within permissible limits or not. Not more than two of the individual weights deviated from the average weight by more than 7.5% for 200mg tablets and none by more than double that percentage.

This results are reproduced in Table No: 10

Hardness test:

Hardness of the tablet was determined using the Pfizer hardness tester. The lower plunger was placed in contact with the tablet and a zero reading was taken. The plunger was then forced against a spring by turning a threaded bolt until the tablet fractured. As the spring was compressed a pointer rides along a gauge in the barrel to indicate the force. The results are reproduced in Table No: 10

Friability test:

20 previously weighed tablets were placed in the apparatus, which was given 100 revolutions and the tablets were reweighed. The percentage friability was calculated by using the following formula

Percentage friability = [(Initial weight-Average weight) / (Initial weight)] X 100

The results are reproduced in Table No: 10

Disintegration test:

Tablet disintegration study was performed in disintegration apparatus. One tablet in each of the six tubes in the basket were placed and the basket rack was positioned in a one litre beaker of water, at 37°C±2°C. The machine was operated until the tablets were completely disintegrated. Results were shown in Table No: 11

Drug content:

For the content uniformity test, 10 tablets were weighed and puverized to a fine powder, a quantity of powder equivalent to 5mg of Rizatriptan was transferred into a 10ml standard flask and the volume was made with mobile phase. Further 10ml of the above solution was diluted to 10ml with mobile phase.

Wetting time:

The tablets wetting time was measured by procedure that is the tablet was placed at the center of two layers of absorbent paper fitted into a dish. After the paper was thoroughly wetted with pH 6.8 phosphate buffer, excess buffer was completely drained out of the dish. The time required for the water to diffuse from the wetted absorbent paper throughout the entire tablet was then recorded using a stop watch. The results were shown in Table No: 11

Water absorption ratio:

A piece of tissue paper folded twice was placed in a small petri dish containing 6ml of buffer pH 6.8. A tablet was put on the tissue paper and allowed to completely wet. The wetted tablet was then weighed. Water absorption ratio, R was determined using following equation.

$$R = 100 \times W_a - W_b / W_a$$

Where , W_a = Weight of tablet after water absorption

W_b = Weight of tablet before water absorption

The results are presented in Table No: 11

In-vitro dissolution studies:

Dissolution apparatus : Type II USP (paddle type)

Dissolution medium : 6.8P^H Phosphate Buffer

Volume of receptor fluid : 900 ml

Temperature : 37°C±0.5°C

Rpm : 50 rpm

Total dissolution time : 10 min

Sampling time : 2,4,6,8 and10 minutes

Sampling volume : 5 ml

Analysis at : UV determinations at 226 nm.

Preparation of buffer: (pH 6.8):

3.84gms of Potassium di hydrogen ortho phosphate dissolved in 1000ml distilled water and the resultant solution was adjusted with Sodium hydroxide solution.

Stability studies of the tablet:

Stability of a formulation can be defined as the time from date on manufacture of the formulation until its chemical or biological activity is not less than a predetermined level of labeled potency and its physical characteristics have not changed appreciably or deleteriously.

Formulation and the development of a pharmaceutical product is not complete without proper stability analysis, carried out on it to assess their physical and chemical stability and the safety. The purpose of stability testing is to provide evidence on how the quality of a drug substance of drug product varies with time.

Under the influence of a variety of environmental factors such as temperature, humidity and light enabling recommended storage conditions, re-test periods and shelf- lives.

Generally, the observation of the rate at which the product degrades under normal room temperature requires a long time. To avoid the undesirable delay, the principles of the accelerated stability studies are adapted.

The international conference on harmonization (ICH) guidelines titled "Stability Testing of New Drug Substances and Product" (QIA) describes the stability test requirements for drug registrations application in the European Union, Japan and USA. ICH specifies the length of study and storage Conditions.

Long-term testing: 25±2°C/60%±5% RH for 12 months.

Accelerated testing: 40±2°C/75%±5% RH for 6 months.

Stability studies for the present work carried out at 25°C/60%RH and 40°C/75%RH for the selected formulation (F3) for 12 weeks.

Method:

The selective alu-alu packed formulations stored at 25°C/60%RH and 40°C/75%RH for 12 weeks and evaluated for their physical appearance and drug content at specified interval of time. The formulations were further scanned to observe any possible spectral changes. And also performed were in vitro dissolution studies. The results were tabulated in Table No:23, 24, 25.

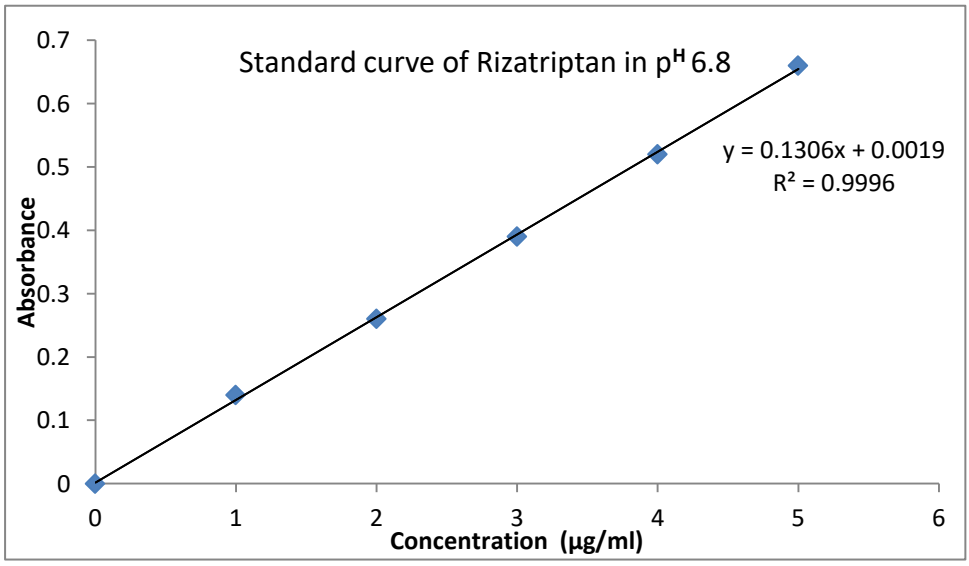
7. RESULTS AND DISCUSSION

Table presents the calibration curve of Rizatriptan in pH 6.8 phosphate buffer. The drug amount was analyzed by using UV method. The concentration Vs absorbance of the Rizatriptan standard solution having 0-7µg/ml concentration in medium yielded the straight line relationships as depicted in Fig No:8. The obtained coefficient for the straight line pH 6.8 Phosphate buffer is shown in Fig No: 8.

Table No: 7 Standard calibration curve of Rizatriptan in pH 6.8 phosphate buffer

S.No	Concentration (µg/ml)	Absorbance
1	0	0.00
2	1	0.14
3	2	0.26
4	3	0.39
5	4	0.52
6	5	0.66
7	6	0.77
8	7	0.90

Fig No: 12 Standard curve of Rizatriptan



Fast disintegrating sublingual tablets of Rizatriptan were prepared based on the composition shown in Table No: 8

- Formulation-1(F-1) consisted of 5mg Rizatriptan, 89mg mannitol, 3mg crospovidone, 2.5mg Aspartame and 0.5mg magnesium stearate.
- Fromulation-2(F-2) had 4mg crospovidone and 88mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-3(F-3) had 5mg crospovidone and 87mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-4(F-4) had 3mg croscamellose and 89mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-5(F-5) had 4mg croscamellose and 88mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-6(F-6) had 5mg croscamellose and 87mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-7(F-7) had 3mg L-HPC and 89mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-8(F-8) had 4mg L-HPC and 88mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-9(F-9) had 5mg L-HPC and 87mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.
- Fromulation-10(F-10) had 3mg crospovidone , 3mg croscamellose and 86mg of mannitol. Their remaining ingredients and their quantities are same that of formulation-1.

Since tablet formulation were prepared by direct compression method. Therefore all the ingredients in these tablet formulations were simply mixed in poly bag. So the mixtures were termed as “Powder mixtures”.

The powder mixtures were evaluated for flow characteristics (angle of repose), packing ability(bulk density, tapped density, carr’s index) and dry content prior to the preparation, of the tablets by direct compression method.

Table No: 8 Composition of Rizatriptan fast disintigratting sublingual tablets

Ingrdients	Quantity for tablet(mg)									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
Rztriptan	5	5	5	5	5	5	5	5	5	5
Crospovidone	3	4	5	-	-	-	-	-	-	3
Croscamellose sodium	-	-	-	3	4	5	-	-	-	3
L-HPC	-	-	-	-	-	-	3	4	5	-
Mannitol	89	88	87	89	88	87	89	88	87	86
Aspartame	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5	2.5
Magnesium stearate	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5	0.5

Preformulation studies:

Drug –Polymer compatibility studies by FTIR:

The FTIR spectra of Rizatriptan, crospovidone, L-HPC, croscamellose Sodium and the combination of drug and polymers were shows no significant interaction between drug and polymer. The FTIR spectra's of Rizatriptan, crospovidone, croscamellose sodium, L-HPC and mixture of drug along with polymers are shown in figure 22,23,24,&25

Flow properties:

The powder substances of drug and other excipients used for the formulation of Rizatriptan Fast disintegrating Sublingual tablets were evaluated for derived and flow properties include bulk density, tapped density, angle of repose, carr's index and hausner's ratio before carry out the formulations. The results were satisfactory and were shown in the Table No: 9

Table No: 9 Results of derived and flow properties

Formulation Code	Derived properties		Flow properties		
	Bulk density (mean±SD)	Tapped density (mean±SD)	Angle of repose (mean±SD)	Carr's index (mean±SD)	Hausner's ratio (mean±SD)
F1	0.27±0.01	0.25±0.015	32.3±0.2	10.45±1.97	1.14±0.02
F2	0.25±0.015	0.24±0.02	32.1±0.2	11.23±1.96	1.13±0.03
F3	0.26±0.015	0.26±0.01	31.5± 0.12	11.49±3.97	1.13±0.05
F4	0.25±0.015	0.29±0.015	30.43±0.14	12.02±1.81	1.15±0.02
F5	0.23±0.02	0.27±0.03	30.01±0.11	11.87±2.25	1.13±0.03
F6	0.24±0.01	0.27±0.006	30.05±0.13	11.38±3.16	1.13±0.04
F7	0.23±0.025	0.27±0.025	29.9 ±0.15	10.46±1.19	1.12±0.02
F8	0.22±0.01	0.26±0.017	30.98±0.11	10.59±3.61	1.12±0.05
F9	0.24±0.01	0.28±0.025	32.17±0.14	10.87±2.84	1.11±0.04
F10	0.22±0.015	0.26±0.032	31.78±0.12	14.21±1.11	1.15±0.01

Hardness test:

The hardness of tablets of each batch ranged between 2.4 to 3.1 kg/cm^2 (Table No.10). This ensures good handling characteristics for all batches.

Friability test:

The values of friability test were tabulated in Table No: 10. The percentage friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

Weight Variation test:

The percentage weight variations for all formulations were tabulated in Table No: 10. All the formulated (F1 to F10) tablets passed weight variation test as the % weight variation was within the standard pharmacopoeia limits of ±7.5% of the weight. The weights of all the tablets were found to be uniform with low standard deviation values

Table No: 10 Results of average weight,hardness, thickness, friability of all formulations

Formulation Code	Average weight (mg)	Hardness (kg/cm^2)	Thickness (mm)	Friability (%)
F1	101.4	2.8	2.8	0.25
F2	101.67	2.7	2.79	0.21
F3	100.13	2.8	2.84	0.26
F4	101.9	2.9	2.91	0.22
F5	101.7	2.7	2.84	0.24
F6	101.6	2.5	2.67	0.23
F7	101.63	3.1	2.79	0.21
F8	99.96	2.9	2.81	0.23
F9	101.56	2.9	2.77	0.24
F10	100.34	2.4	2.86	0.22

Drug content:

In order to estimate the amount of drug in each tablet for the therapeutic activity of Rizatriptan, the prepared tablets were evaluated for drug content as triplicate and the drug content was found to be in the range between 98.34 to 102.1%. The observed results indicate reproducible with minimum intra-batch variability and the results were shown in Table No: 11.

Wetting time:

The values of wetting time were tabulated in Table No: 11. The wetting time was lies between 7.2 to 15.1 sec.

Table No:11 Results of water absorption ratio, drug content, wetting time, disintegration of all formulations

Formulation code	Water absorption ratio(%)	Drug content(%)	Wetting time (Sec)	Disintegration time (Sec)
F1	27.18	99.91	12.3	15
F2	31.24	99.20	11.4	14
F3	34.17	99.54	9.3	12
F4	32.14	98.34	15.1	17
F5	29.38	101.11	12.5	14
F6	34.37	99.5	10.4	13
F7	40.24	102.1	14.5	18
F8	36.28	98.99	13.1	15
F9	38.34	99.32	11.4	14
F10	42.18	100.27	7.2	11

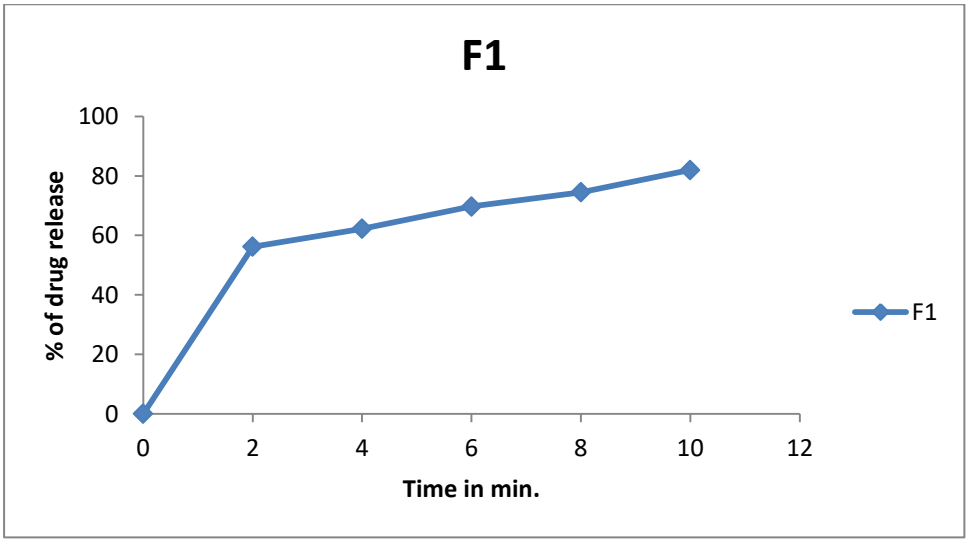
***In-vitro* drug release studies:**

All the formulations of prepared fast disintegrating sublingual tablets of Rizatriptan were subjected to in vitro release studies and these studies were carried out using dissolution media of Phosphate buffer 6.8 pH.

Table No*: 12 In vitro* release profile of Rizatriptan F-1 sublingual tablets

Time in mins	Cumulative percentage drug release of F-1
2	56.18
4	62.24
6	69.72
8	74.47
10	81.96

Fig 13: *In vitro* release profile of Rizatriptan F-1 sublingual tablets

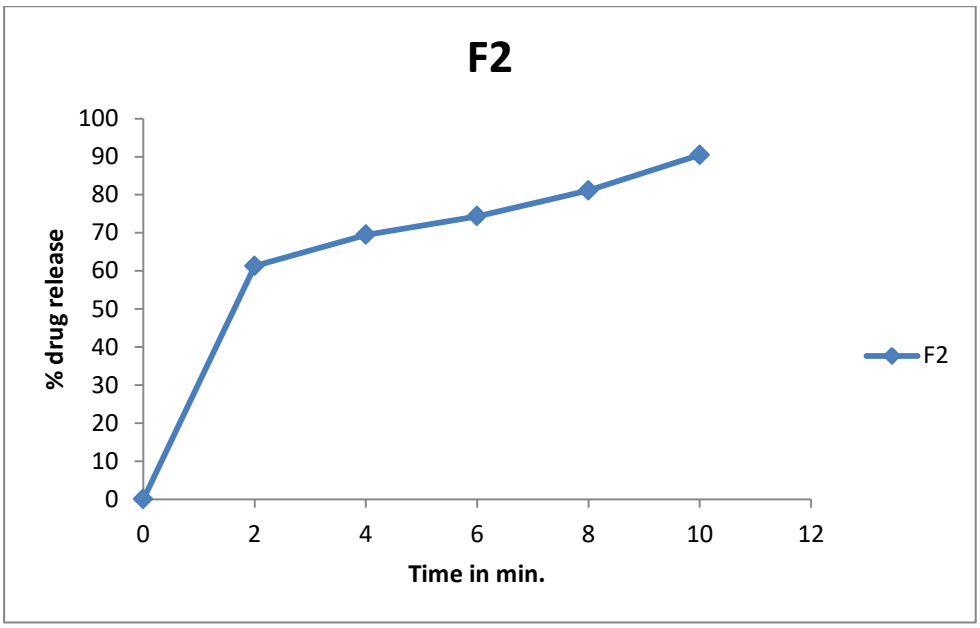


However the formulation was prepared by direct compression method with crospovidone 3mg and the drug release profile in pH 6.8 buffer up to 10mins dissolution time period were ranged between 56.18 to 81.96%. The % of super disintegrant in F1 is 3% and the % drug release at 2min is 56.18%.

***Table No: 13 In vitro* release profile of Rizatriptan F-2 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-2
2	61.27
4	69.46
6	74.34
8	81.12
10	90.46

Fig 14: *In vitro* release profile of Rizatriptan F-2 sublingual tablets

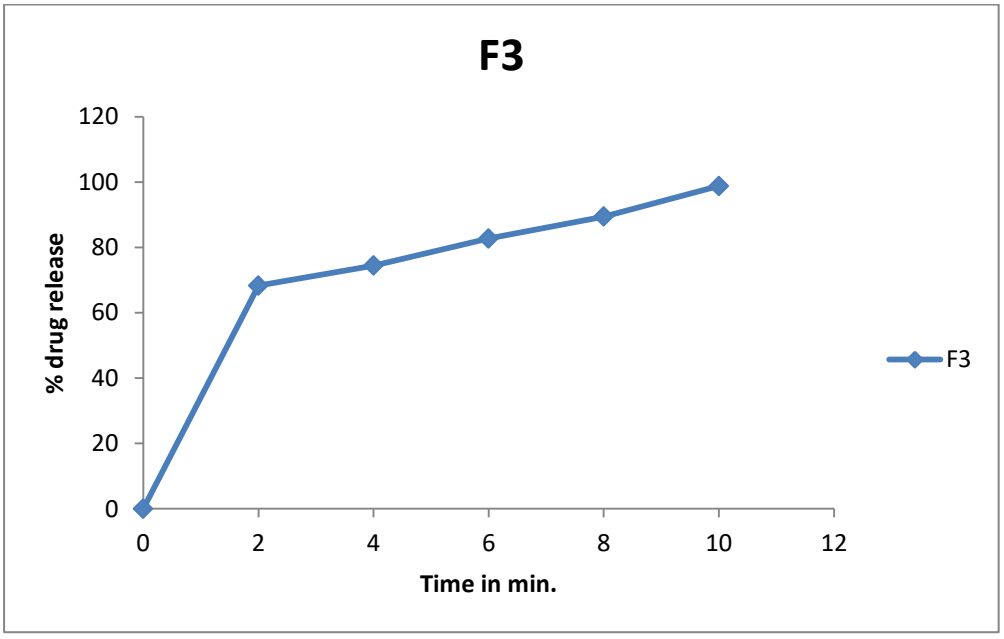


However the formulation was prepared by direct compression method with crospovidone 4mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 61.27-90.46%. The % of super disintegrant in F2 is 4% and the % drug release at 2min is 61.27%.

***Table No: 14 In vitro* release profile of Rizatriptan F-3 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-3
2	68.32
4	74.43
6	82.64
8	89.42
10	98.79

Fig 15: *In vitro* release profile of Rizatriptan F-3 sublingual tablets

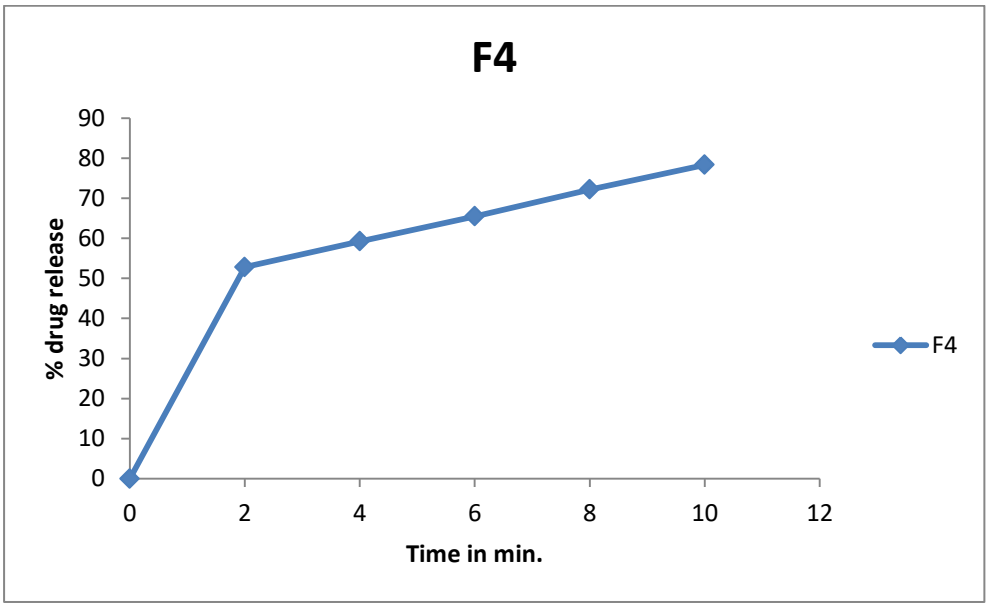


However the formulation was prepared by direct compression method with crospovidone 5mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 68.32-98.79%. The % of super disintegrant in F3 is 5% and the % drug release at 2min is 68.32%.

***Table No: 15 In vitro* release profile of Rizatriptan F-4 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-4
2	52.78
4	59.24
6	65.46
8	72.18
10	78.34

Fig 16: *In vitro* release profile of Rizatriptan F-4 sublingual tablets

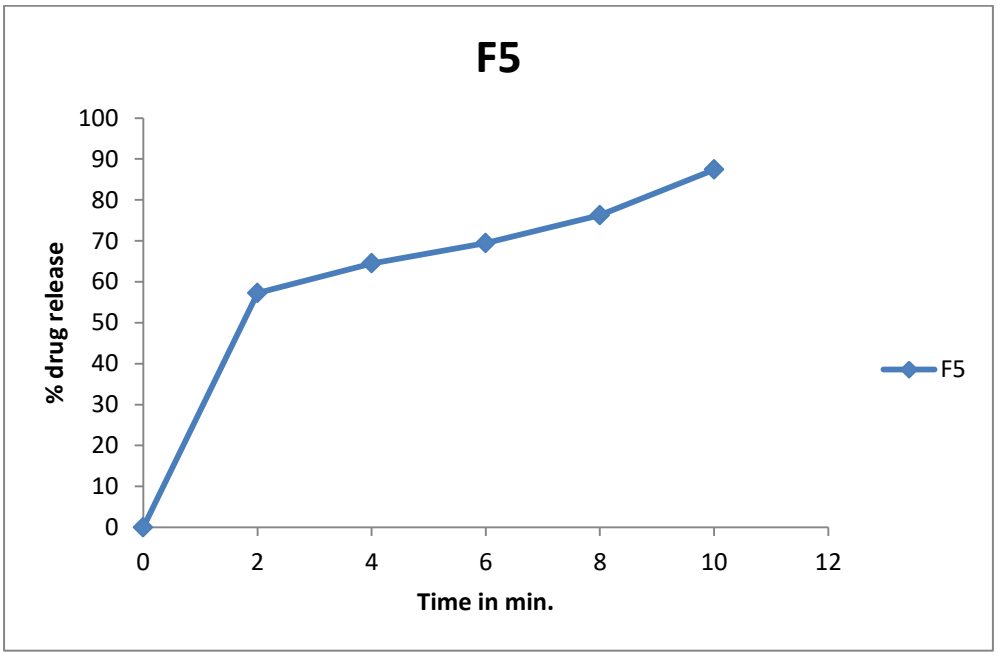


However the formulation was prepared by direct compression method with croscamellose 3mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 52.78-78.34%. The % of super disintegrant in F4 is 3% and the % drug release at 2min is 52.78%.

***Table No: 16 In vitro* release profile of Rizatriptan F-5 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-5
2	57.26
4	62.47
6	69.43
8	76.27
10	87.38

Fig 17: *In vitro* release profile of Rizatriptan F-5 sublingual tablets

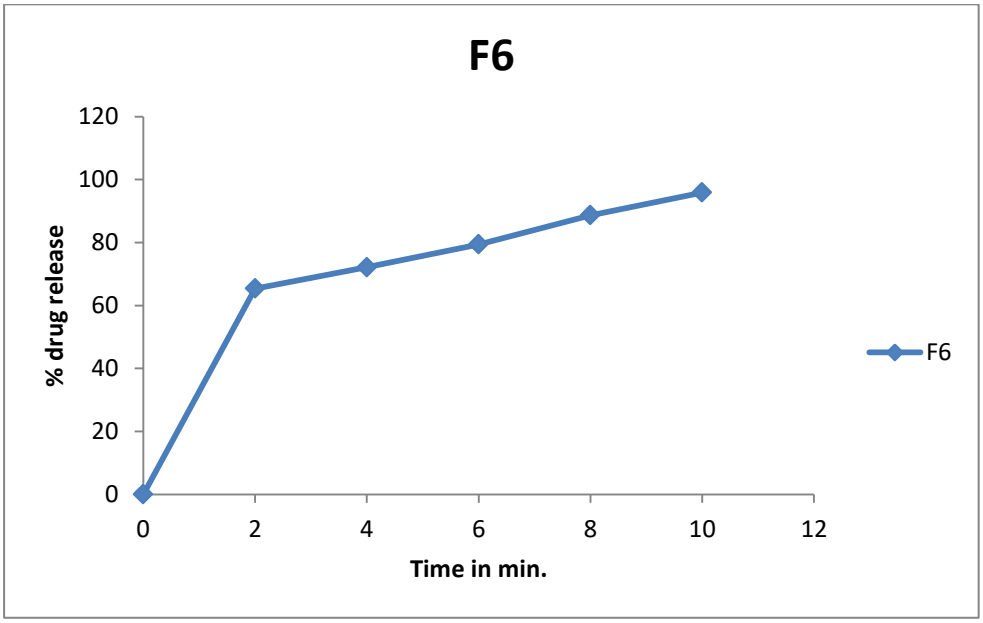


However the formulation was prepared by direct compression method with croscamellose 4mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 57.26-87.38%. The % of super disintegrant in F5 is 4% and the % drug release at 2min is 57.26%.

***Table No:17 In vitro* release profile of Rizatriptan F-6 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-6
2	65.37
4	72.14
6	79.42
8	88.65
10	95.90

Fig 18: *In vitro* release profile of Rizatriptan F-6 sublingual tablets

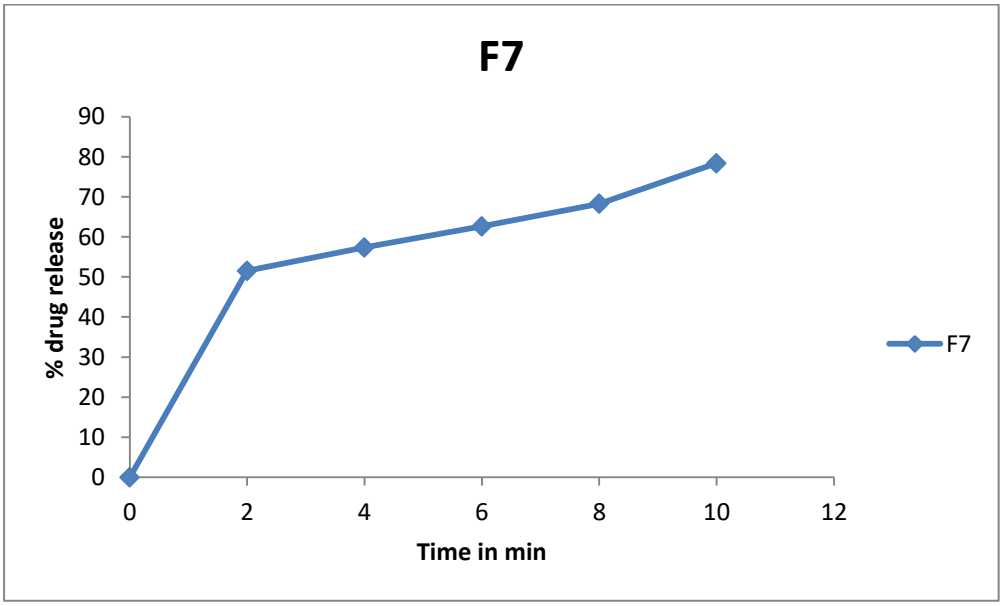


However the formulation was prepared by direct compression method with croscamellose 5mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 65.37-95.9%. The % of super disintegrant in F6 is 5% and the % drug release at 2min is 65.37%.

Table No:18 In vitro **release profile of Rizatriptan F-7 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-7
2	51.51
4	57.34
6	62.64
8	68.27
10	77.38

Fig 19: *In vitro* release profile of Rizatriptan F-7 sublingual tablets

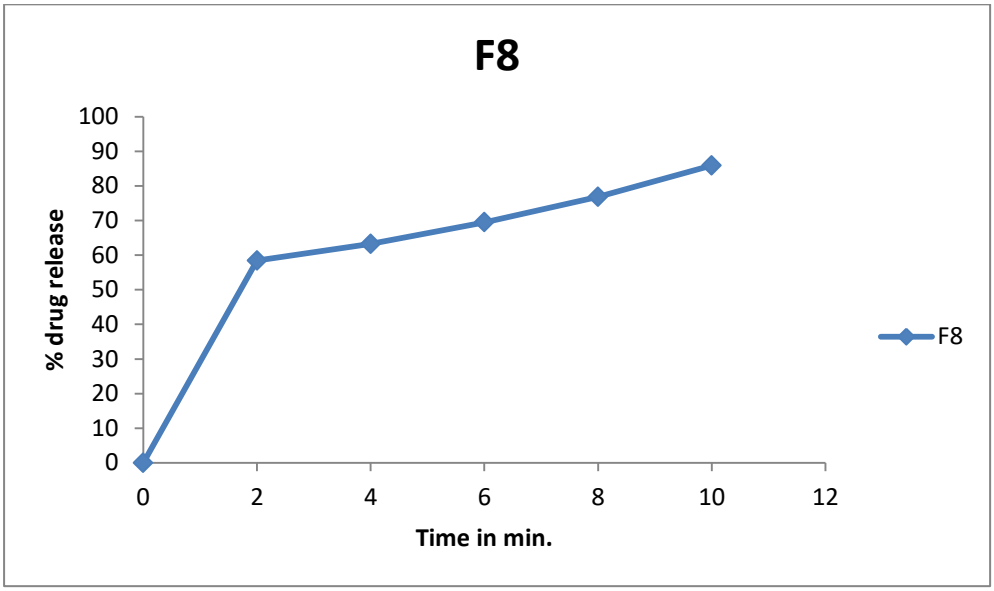


However the formulation was prepared by direct compression method with L-HPC 3mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 51.51-77.38%. The % of super disintegrant in F7 is 3% and the % drug release at 2min is 51.51%

***Table No:19 In vitro* release profile of Rizatriptan F-8 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-8
2	58.42
4	63.21
6	69.78
8	76.82
10	85.87

Fig 20: *In vitro* release profile of Rizatriptan F-8 sublingual tablets

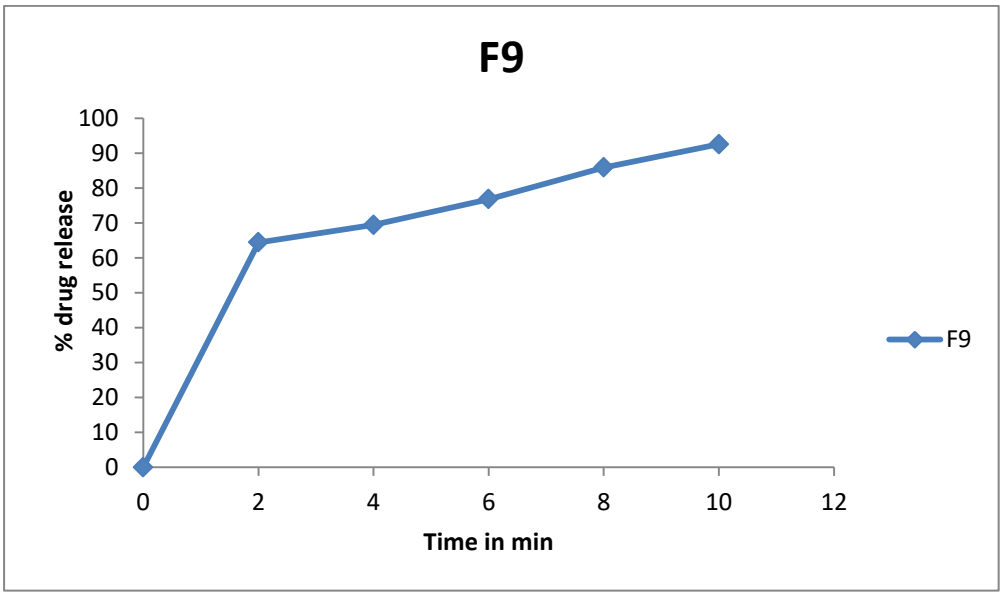


However the formulation was prepared by direct compression method with L-HPC 4mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 58.42-85.87%. The % of super disintegrant in F8 is 4% and the % drug release at 2min is 58.42%.

***Table No: 20 In vitro* release profile of Rizatriptan F-9 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-9
2	64.39
4	69.43
6	76.79
8	85.87
10	92.54

Fig 21: *In vitro* release profile of Rizatriptan F-9 sublingual tablets

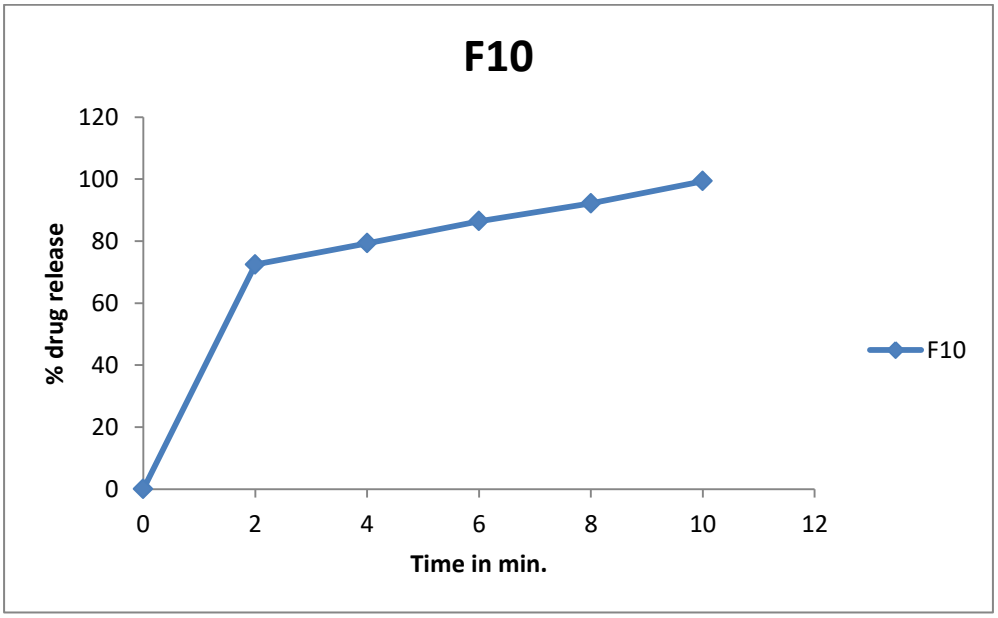


However the formulation was prepared by direct compression method with L-HPC 5mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 64.39-92.54%. The % of super disintegrant in F9 is 5% and the % drug release at 2min 64.39%.

***Table No: 21 In vitro* release profile of Rizatriptan F-10 sublingual tablets**

Time in mins	Cumulative percentage drug release of F-10
2	72.46
4	79.31
6	86.44
8	92.18
10	99.34

Fig 22: *In vitro* release profile of Rizatriptan F-10 sublingual tablets

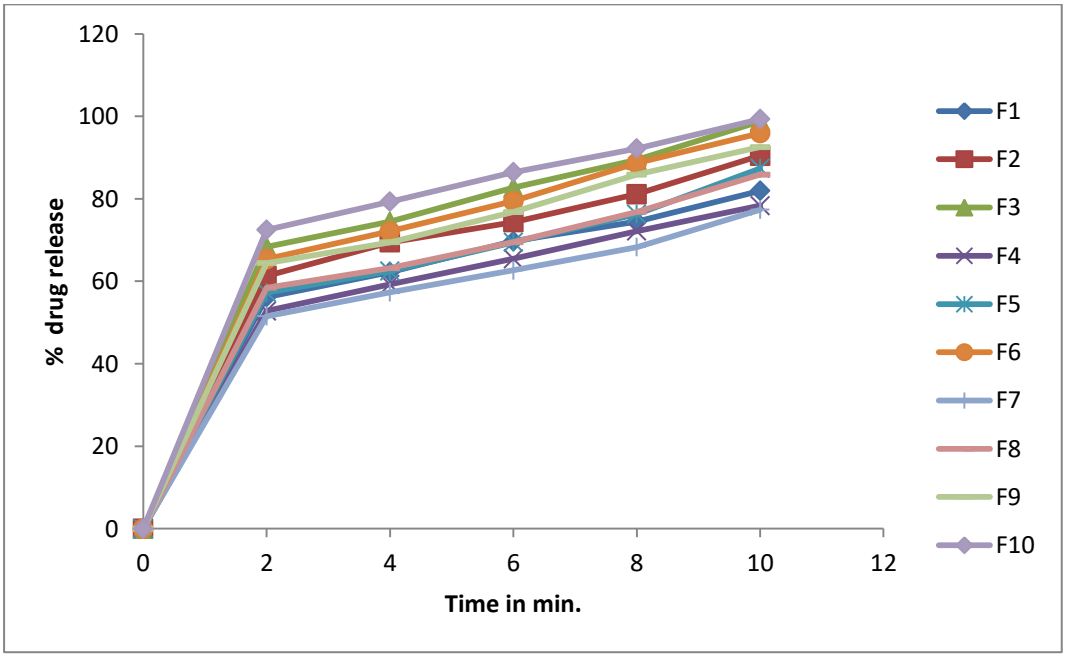


However the formulation was prepared by direct compression method with crospovidone 3mg and croscamellose 3mg and the drug release profile in pH 6.8 buffer upto 10mins dissolution time period were ranged between 72.46-99.36%. The % of super disintegrant in F10 is 6% and the % drug release at 2min is 72.46%.

Table No: 22 Drug release profile of all formulations

Time in mins	% Drug Release									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
2	56.18	61.27	68.32	52.78	57.26	65.37	51.51	58.42	64.39	72.46
4	62.24	69.46	74.43	59.24	62.47	72.14	57.34	63.21	69.43	79.31
6	69.72	74.34	82.69	65.46	69.43	79.42	62.64	69.48	76.79	86.44
8	74.47	81.12	89.42	77.18	76.27	88.65	68.27	76.82	85.87	92.18
10	81.96	90.46	98.79	78.34	87.38	95.9	77.38	85.87	92.54	99.34

Fig 23: Drug release profile of all formulations



All the formulations were prepared by direct compression method with different superdisintegrants at different concentrations. The drug release profile for all the formulations were performed for 10 min in pH 6.8 phosphate buffer. The formulation F1 shows 81.96% at the end of 10th min. The formulation F2 shows

90.46% at the end of 10^{th} min. The formulation F3 shows 98.79% at the end of 10^{th} min. The formulation F4 shows 78.34% at the end of 10^{th} min. The formulation F5 shows 87.38% at the end of 10^{th} min. The formulation F6 shows 95.9% at the end of 10^{th} min. The formulation F7 shows 77.38% at the end of 10^{th} min. The formulation F8 shows 85.87% at the end of 10^{th} min. The formulation F9 shows 92.54% at the end of 10^{th} min. The formulation F10 shows 99.34% at the end of 10^{th} min.

STABILITY STUDIES

Stability studies are to be carried out as per ICH guidelines for F3 batch of this product for three months.

Table No23: Stability studies:

S.No	Parameters	Stability conditions at	
		25°C 60%RH	40°C 75% RH
1	Physical appearance	No change	No change
2	Friability	0.26%	0.263%
3	Hardness	2.8 kg/cm^2	2.9 Kg /cm^2
4	Assay	99.54%	99.55%

Evaluation parameter values at different temperature conditions

Drug release profile for Formulation F3

Table No:24 Dissolution profile of optimized batch F3 at 25°C±2ºC/60% ± 5% RH

Time in min	Percentage of drug release at 25°C±2ºC/60% ± 5%RH
	% of drug release for F3
0	0
1	68.34
2	74.47
3	82.68
4	89.47
5	98.82

Fig 24: **Dissolution profile of optimized batch F3 at 25°C±2ºC/60% ± 5% RH**

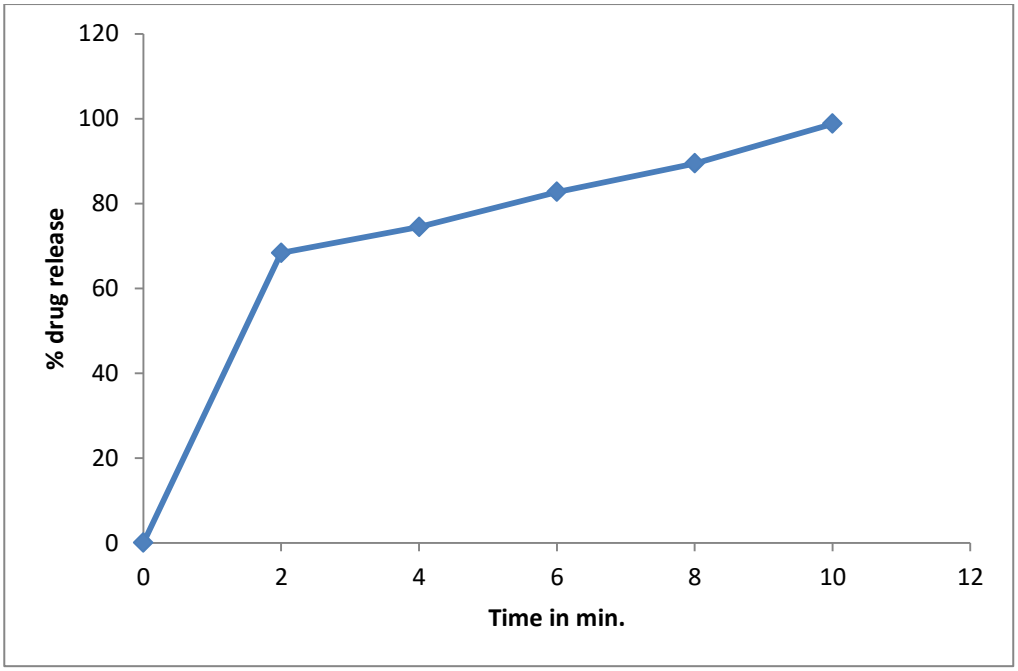
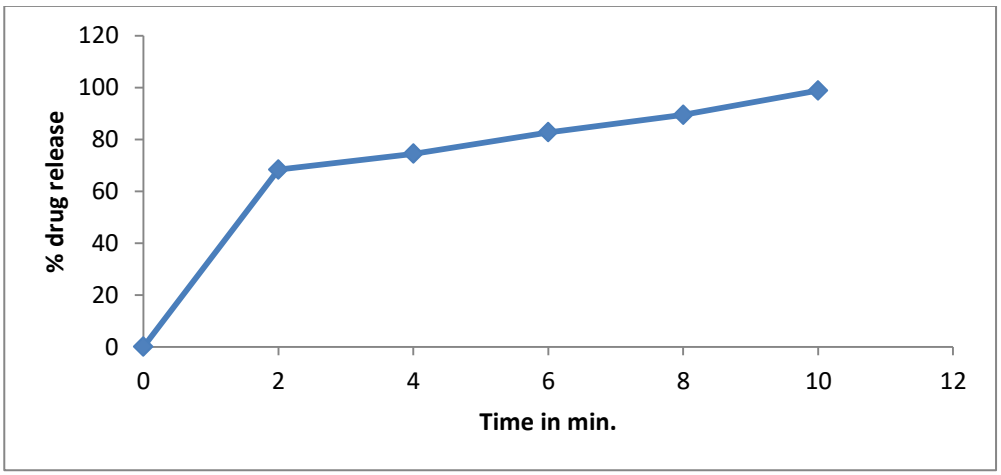


Table No:25 Dissolution profile of optimized batch F3 at 40°C±2ºC/75% ± 5% RH

Time in min	Percentage of drug release at 40°C±2ºC/75% ± 5%RH
	% of drug release for F3
0	0
1	68.35
2	74.47
3	82.68
4	89.45
5	98.81

Fig 25: Dissolution profile of optimized batch F3 at 40°C±2ºC/75% ± 5% RH



Stability studies were performed for formulation F-3, optimized formulation.

There is no change in physical appearance and there is slight increase in friability, hardness and assay.

The dissolution profile of the optimized batch at 25°C±2ºC/60% ± 5% RH and 40°C±2ºC/75% ± 5% RH was calculated and observed that there is slight decrease in the percentage of drug released.

8. SUMMARY & CONCLUSION

SUMMARY

In the present study, Rizatriptan sublingual tablets 100mg were prepared by using super disintegrants crospovidone, croscamellose sodium and L-HPC at different concentrations.

The values of blend parameters evaluated within the prescribed limits and shows good free flow property.

Angle of repose of the powder mixture prepared for tablet preparation ranged from $29^0.9^1$-$32^0.3^1$ and was within the pharmacopeial limits.

The bulk density and tapped density of the powder mixture were within the limits and the values are 0.22-0.27 g/cm^3 and 0.24-0.29 g/cm^3 respectively.

The compressibility index was calculated for the powder mixture and was within the range of 10.45-14.21%.

The hausner's ratio was calculated and the range of the ratio is 1.11-1.15. If the ratio value is closer to one then the powder mixture has good flow property.

The tablets were prepared by direct compression method using single rotary tablet punching machine with 7mm punch.

Drug content in the tablet was determined by dissolving it in the buffer and the drug content is determined by serial dilution. The percentage drug content of all formulations were found to be between the range of 98.34-100.27%.

The hardness of the tablet was calculated by using Monte's hardness apparatus and the values were within the range of 2.4-3.1 kg/cm^2.

The thickness of the tablet was calculated by using vernier calipers and the thickness of the tablet was found to be 2.67-2.94 mm.

In all the formulations the friability values are less than 1% and it is within the limits.

Wetting time of the tablets lies between 7-16secs. Among all the formulations, F-10 showed less wetting time of 7.2secs as it in mixed with the super disintegrants crospovidone (3mg) and croscamellose sodium (3mg).

Water absorption ratio of the tablets was found to be in the range of 27.18-42.18%.

Disintegration time of the sublingual tablets was found to be between 11-18secs which should be as low as possible to show quick onset of action. Increasing the amount of super disintegrants caused the decrease in the disintegration time.

The formulation F3 was kept for stability studies in stability chamber for 25°C/60%RH and 40°C/75%RH for 3 months. No significant changes were seen in the formulation. There was a slight increase in hardness, disintegration time and slight decrease in percentage drug release.

The results of the in-vitro drug release for different batches of fast disintegrating sublingual tablets of Rizatriptan were given in Table No:22.

After subjecting the tablets to in vitro dissolution studies for 10mins in pH 6.8 phosphate buffer in USP model I apparatus at 50rpm, formulations F1 showed 81.96%, F2 showed 90.46%, F3 showed 98.79%, F4 showed 78.34%, F5 showed 87.38%, F6 showed 95.9%, F7 showed 77.38%, F8 showed 85.87%, F9 showed 92.54% and F10 showed 99.34% drug release.

From the above percentage of drug release values, F1, F4 & F7 were less than 85% after 10mins. F2, F5, F8 & F9 batches showed drug release ranging from 85 to 95%.Whereas F3, F6 & F10 showed excellent drug release of more than 95%. Among these three the optimum formulation is F10 but F3 was selected as a best formulation because of its best mouth feel.

The mixing of super disnintegrants with the drug alters the dissolution rate and plays important role in the drug release. Higher the concentration of superdisintegrants increase the amount of drug release.

CONCLUSION

The active pharmaceutical ingredient Rizatriptan was subjected to preformulation studies, which encompasses the drug excipients compatibility study and the results obtained with selected excipients showed compatability with Rizatriptan drug.

In the present study, fast disintegrating sublingual tablets of Rizatriptan 100mg were prepared by using croscamellose sodium, crospovidone and L-HPC as super disintegrants at the concentration of 3%, 4% and 5% of each and compared the effect of each at different concentrations, and finished the optimum formulation. A total number of 10 formulations were prepared by using different super disintegrants at different concentrations. Among this, formulation F-10 showed maximum effect but formulation F-3 was selected as best formulation because of its wonderful mouth feel which contains drug (5mg), crospovidone 5mg, mannitol (87mg), aspartame(2.5mg) and magnesium stearate(0.5mg). Stability studies were also done for the formulation F-3.

Various physico-chemical parameters are tested for this formulation showed good results. From the release study and mathematical models it was concluded that the novel formulation can bypass the first pass metabolism and produced the quicker onset of action.

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