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CHAPTER-1
INTRODUCTION

1.1 INTRODUCTION

Drug delivery through the oral mucosal membrane is considered as alternative to the oral route. The sublingual region of the oral cavity in the floor of the mouth is far more permeable than the buccal cavity (Leow et al., 1992). The permeability differences are usually based on the comparative thickness, supply of blood and keratinisation of the membranes. Difference in the permeability of the various mucous membranes, affects the amount of drug delivery from the physicochemical properties to be delivered. The sublingual root (Physiological pH 6.5) has the ability for providing a substitute to IV dosing for quick delivery of drugs to the systemic flow. It bypasses gastrointestinal and presystemic metabolism and is a suitable form for delivery of drugs relevant in patients with difficulties in swallowing (Kurosaki et al., 1991).

Tablets that are disintegrated/dissolved quickly in patient’s mouth are suitable for elderly, patients with swallowing difficulties and children (Fu et al., 2004), and in situations where portable liquids are not obtainable (Allen et al., 2003). The minute volume of saliva is generally enough for disintegration of tablet in the oral tract. The medication is absorbed either partially or entirely into circulation systemically from blood vessels surrounded by the sublingual mucosa or ingested as a solution to be immersed from the GIT. Sublingual
route generally provides a quicker onset of action compared to orally taken tablets and the fraction absorbed during the blood vessels of sublingual route bypass the hepatic system. The advantages of fast disintegrating tablets are increasing and being recognised in academics and in industries (Chang et al., 2000). The main approach in developing the fast dissolving tablets is by using super disintegrants like sodium starch glycolate (primogel, explotab), cross linked carboxy methyl cellulose (croscarmellose), crospovidone, polyvinylpyrrolidone (polyplasdone) etc and using highly water soluble excipients (Kucchekar et al., 2003).

These tablets exhibit a quick and impulsive disintegration in the mouth, when contacted with saliva, without alteration from the package; they can be extracted or handled (Schiermeier et al., 2002). The active ingredient can thus quickly dissolve in the saliva and can be absorbed through the membrane it passes, at the time of deglutition, if not sheltered from pre-gastric absorption. (Hisakadzu et al., 2002). To perform these needs, tablets must be extremely permeable, incorporating hydrophilic substances and should have the ability to quickly absorb water for a fast disaggregation of the matrix. Various techniques, like freeze drying, moulding or direct compression are at present engaged for the preparation of the formulations in the present pharmaceutical market. Honda et al (1998) published that a half of the patients experienced trouble in taking medication and felt that tablet was superior and easier compared to other formulations like capsules or powders.
1.1.1 Characteristics of fast disintegrating systems

1.1.1.1 Simplicity of administration

Fast disintegrating drug delivery systems are very easy to administer, handle and leads to betterment of patient compliance. Generally, aged people experience a lot of difficulty to swallow the dosage forms like solutions, suspensions, tablets and capsules due to dysphasia and tremors of extremities. This problem can be overcome by using fast dissolving delivery systems.

1.1.1.2 Medicament taste

Almost all drugs are unpalatable, fast disintegrating drug delivery systems frequently containing a medicament in a taste covered form. These drug delivery systems liquefy in the mouth of the patient and release the active ingredients as soon as they come in contact with the oral cavity. Taste masking of drugs was very important from patient point of view.

1.1.1.3 Hygroscopicity

Most of the dosage forms that dissolve fastly are very hygroscopic and does not maintain physical integrity at normal conditions such as humidity which requires special product packaging.

1.1.1.4 Friability

Fast disintegrating tablets should dissolve in mouth which are made up of soft-molded matrices (highly porous) and compressed into tablets using less compression force, making the tablets more friable.
It is not easy to handle and requires peel-off blister specialized packaging.

1.1.1.5 Mouth feel

Feel in the mouth is extremely important and the tablet should give pleasant feel to the patient. After disintegration of tablet, large particles that are not soluble or gradually soluble in saliva may give a disagreeable gritty feeling. It can be solved by keeping most of the particles under the lower size. In some instances, some flavors can enhance an improved perception of feeling in the mouth, ensuing that the product is less gritty, yet there is a change in the flavor. Effervescent can also be added to get better mouth feel and helps in disintegration and also reducing the dryness of a formulation.

1.1.2 Advantages of fast dissolving drug delivery through sublingual route

- Reduction in the dose there by minimizing the frequency of dosing (Heinemann et al, 1976).
- Convenient for patients who refuse to swallow the tablet, such as children, elderly people, mentally ill, disabled persons, bedridden patients, renal failure patients, stroke victims and uncooperative patients (Indurwade et al., 2002).
- Convenient way of management and precise dosing compared to liquids (Bredemberg et al., 2003).
- Water is not required to gulp down the dosage form, which is highly suitable for the patients who are travelling and having no access to water (Devarajan et al., 2000).
Good mouths feel of FDTs which helps to change the fundamental bitter view of medication particularly in children.

It provides advantages of liquid medication in solid dosage form.

Rapid dissolution of drug, which produces fast beginning of action, is absorbed through the oral cavity when the saliva passes downwards to the stomach. In these cases the availability of drugs to the body is enhanced.

Pre-gastric absorption results in increased bioavailability and as a result of reduction in doses, medical performance is improved by reducing the side effects. After administration, it leaves minimum or no residue in the mouth (Gole et al., 1993).

Conventional low cost packaging and processing equipments are available which are compatible with taste masking having pleasant mouth feel. They also show low sensitivity towards environmental situations such as temperature and humidity (Bhaskaran et al., 2002).

New opportunity for businesses like differentiation of product, product promotion, extension of patent and in the management of life cycle. Stability for longer time, since the medicine remains in solid form until it is consumed (Misra et al., 1999).

Enhances tablet disintegration, dissolution, drug absorption and onset of effect (Birudaraj et al., 2005).

Avoid gastric degradation of the drug in gastric and intestinal environment.
1.1.3 Approaches for fast disintegrating tablets

Conventional technologies for preparing fast dissolving tablets are as follows.

- Lyophilisation (freeze drying) technique.
- Tablet moulding technique
- Spray drying method
- Cotton candy method.
- Mass extrusion technique.
- Sublimation technique.
- Direct compression technique.

1.1.3.1 Lyophilization (freeze drying) technique

Formation of amorphous porous product in freeze-drying procedure dissolves the drug rapidly and is exploited in preparation of fast dissolving tablets. Lyophilization is a technique that involves removal of the solvent from the drug in frozen solution or in suspension using structure-forming additives (Renon et al., 2000). In this process drug solution along with polymer was poured in the preformed blister packs. These trays are then passed through tunnel of liquid nitrogen which freezes the drug solution or suspension. These blister packs are then charged into the refrigerator to continue for freeze drying. This method established improved absorption and increased bioavailability (Jaccard et al., 1985) and also gives glossy structure resulting in light weight and highly porous product (Azza et al., 2011). The major disadvantage is that this technique is very expensive (Habib et al., 2000), time consuming and fragility which
makes the formulation unsuitable for conventional packaging for those products which show poor stability under stress conditions (Corveleyn et al., 1997).

1.1.3.2 Tablet molding technique

Tablet molding procedure is of two types. The first method (solvent method) consists of moistening of the powder bed with hydro-alcoholic solvent followed by compression at low pressure to appearance a wetted mass in molded plates i.e., compression molding. From this mass the solvent is separated by air drying. The prepared tablets by this method possess porous formation that hastens dissolution. The second method (heat molding method) involves preparation of suspension by mixing the drug with agar and sugar (manitol or lactose) then pouring them in blister packs, solidifying the agar at room temperature and drying at 30°C under vacuum. The presence of the binding agents increases the mechanical strength of the tablets (Masaki et al., 1995). In this taste masking of the tablets is an additional problem. These drug particles were formulated by spray congealing the lecithin molten mixture, polyethylene glycol and drug into lactose containing tablet triturate appearance. Similar to the freeze drying technique the tablets produced by this technique are easier to develop for industrial manufacturing.

1.1.3.3 Spray drying method

In this procedure gelatin is used as a matrix forming agent, mannitol as a diluent, crospovidone, croscarmellose sodium and sodium starch glycollate are used as superdisintegrants. The tablets
made using this method disintegrated within 20s in aqueous media (Allen et al., 1997). Highly porous product was obtained using this method (Allen et al., 2003).

1.1.3.4 Cotton candy method

This process is also called as candy floss and uses a spinning technique to produce floss-like arrangement, which looks like a cotton candy. The preparation, involves the formation of matrix using polysaccharides or saccharides by repeated action of flash melting followed by spinning (Meyers et al., 1995). The matrix which is produced is partly recrystallized to comprise enhanced flow properties (Pebley et al., 1994). This candy matrix is then subjected to milling process and then blended with drugs, additives and then compressed. This process can hold large drug doses and improve mechanical force. However it requires high temperature processing.

1.1.3.5 Mass extrusion technique

This type of expertise involves softening the blend of active ingredient using polyethylene glycol and methanol solvent mixture followed by subsequent removal of mass using the extruder or by using the syringe to get the product of cylinder into equal segments by using blade that is heated to shape into tablets. This cylinder is also used for the coating of granules having objectionable taste and thereby masking of bitterness can be done (Bhaskaran et al., 2002).
1.1.3.6 Sublimation technique

The key in quick disintegration of FDTs is to produce a porous formation in the tablet matrix. To make such a porous matrix in the tablets, volatile ingredients are involved in the process of sublimation. The ingredients such as ammonium carbonate, ammonium bicarbonate, camphor, urea, benzoic acid and naphthalene which are highly volatile can be compressed with other additives (Sharma et al., 2010). The volatile ingredients may be removed from the tablets by sublimation technique leaving behind a highly porous medium. Cyclohexane or benzene can be used for pore forming agents. The tablets prepared by this technique disintegrate in 10 to 20 seconds (Koizumi et al., 1997).

1.1.3.7 Direct compression technique

This technique is very simple and is generally a cost effective process which can be used for the preparation of FDT because of the improved availability of superdisintegrants and sugar based excipients (Kumar et al., 2010).

1.1.3.7.1 Superdisintegrants

Most of the FDT technologies are based on direct compression, using superdisintegrants which chiefly affects the rate of disintegration as well as dissolution. The existence of other water-soluble excipients and effervescents enhances the process of disintegration further.
1.1.3.7.2 Sugar based ingredients

This is one of the methods for preparing FDT by direct compression. They make use of bulking agents like mannitol, maltose, sorbitol etc. which exhibit more solubility and sweetness which impart taste masking property providing a satisfying mouth feel (Parul et al., 2006).

Takao et al (2005) classify sugar-based additives into 2 types based on the foundation of dissolution rate and moulding. Type-1 saccharides (mannitol and lactose) which reveal less mould ability but more dissolution rate. Type-2 saccharides (maltitol and maltose) disclose which provide more mould ability and less dissolution rate. In this method disintegration and solubilisation of tablet are due to the presence of superdisintegrants, water soluble ingredients and effervescent. The disintegration time is satisfactory though the efficiency is powerfully affected by the size and hardness of the tablet.

Conventional equipment, commonly available additives and fewer steps are involved in this technique. Elevated doses can be incorporated and the tablet’s final weight can simply exceed compared with other techniques. This method is widely used in developing FDTs because of the increased accessibility of excipients.

Addition of disintegrant in FDTs leads to fast breakdown of tablets and therefore, more dissolution. Sodium carboxymethyl starch (sodium starch glycollate), cross linked polyvinylpyrrolidone (crospovidone), modified cellulose (croscarmellose sodium), soy polysaccharides, gellan gum, xanthan gum, cross-linked alginic acid,
calcium silicate and ion exchange resins are used as superdisintegrants. FDTs can also be obtained by including effervescent disintegrants, which generates CO$_2$. The main disadvantage of effervescent disintegrants was its hygroscopic nature. Hence the manufacturers require humidity control conditions and needs to provide safety of the finished product. This reflects by and large the price of the finished product.

1.1.4 Patented technologies

1.1.4.1 Zydis technology

In this method the drug is made to dissolve (entrapped) in fast dissolving carrier (Seager et al., 1998). When these formulations are placed in the mouth, the structure (freeze dried) disintegrates immediately and water is required for swallowing (Chang et al., 2000). Gelatin, dextran (alginates) was included for the strength of the tablets. Saccharides such as mannital or sorbital were added for crystallinity, elegance and hardness. Water is added in manufacturing process to get porous tablet and various gums are used for the prevention of sedimentation of dispersed drug particles. Collapse protectant such as glycine is included to avoid reduction of tablet during freeze drying process.

1.1.4.2 Durasolv technology

CIMA labs contain the Durasolv patented technology. In this technology the tablets consist of drug, diluents and a flow promoter. The tablets were prepared by conventional tablet punching machine
and those tablets can be packed in blisters and this technology is useful for products having low amount of active ingredient.

**1.1.4.3 Orasolv technology**

This technique is invented by CIMA labs. The taste of active ingredient is masked and compressed at low compression forces to have lower dissolution time. The produced tablets are friable and soft.

**1.1.4.4 Flash dose technology**

This technology is originated by Fuisz. Nurofen meltlet which is a mouth tablet of ibuprofen uses flash dose technology and is the first product found by Biovail Corporation. These tablets contains matrix form self binding clip called as floss and are prepared by flash heating process.

**1.1.4.5 WOW tab technology**

Yamanouchi Pharmaceutical Company patented this technology. In this procedure, high and low moldable saccharides are used to get a strong tablet having fast melting. The active ingredient is mixed with lactose, mannitol, glucose and granulated with maltose, oligo saccharides and then compressed to get tablet.

**1.1.5 Taste masking**

Many techniques exist for covering the drug’s bitter taste which includes taste masking with flavouring agents, sweetening agents and amino acids. Masking of taste is done by various methods such as polymer coating, conventional granulation.
1.1.5.1 Taste masking using sweetening agents, flavouring agents and amino acids

This method is used for masking of taste in chewable tablets and fluid preparations (paediatric) and is not useful for extremely harsh and water soluble drugs. Artificial flavouring and sweetening agents are usually worn with other taste-masking methods. The cooling effect of the taste masking agents helps in reducing the objectionable bitter taste. Menthol decreases the bitterness. Aspartame is a well-known sweetener in reducing the bitterness. A minute concentration i.e., 0.8% is useful in reducing the harsh taste of acetaminophen. Mannitol, starch, and lactose provided taste-masking of caffeine (Matsubara et al., 1990).

Artificial sweeteners like hesperidin dihydrochalcone 4'-β-D glycoside and neohesperidine dihydrochalcone have the capacity to cover bitter and salt tastes with lingering sweetness in them.

1.1.5.2 Taste masking using lipophilic vehicles

Poly-alcohols and lipids raise the mouth viscosity due to which the taste buds are coated and are called potential taste masking agents.

1. Guaifenesin melts granulation carnauba wax and veegum (magnesium aluminium silicate)

2. Cimetidine granulation GMS (glyceryl monostearate)

Lecithin and lecithin-like substances have power over objectionable taste in pharmaceuticals. Veegum along with soy lecithin is used to
cover the disagreeable talampicillin hydrochloride taste. The drug is either dissolved or dispersed into chloroform.

1.1.5.3 **Taste masking using hydrophilic vehicles**

In this method drug particles possess a barrier in the form of coating, thus the drug and taste buds’ interaction minimizes. Chewable tablets upon coating provide exceptional taste masking. Micro emulsion technique is used for masking the taste of the powders, chewable tablets and liquid formulations.

1.1.5.3.1 **Carbohydrates**

Orally given drugs can be taste masked by covering with carbohydrates. The bitter tasting drugs like pinaverium bromide, does not have objectionable taste when formulated by coating with cellulose or shellac mixture with polymer.

Masking the bitter taste of ibuprofen has been effectively done by air-suspension method to get microcapsules, which consist of core of crystalline ibuprofen along with eudragit coated chewable taste-masked character (Shen et al., 1996).

1.1.5.4 **Taste masking using inclusion complexation**

The drug molecule enters the opening of a complexing agent and forms stable complex. This agent is capable enough for covering the objectionable feel of drug by diminishing the oral solubility on swallowing, thus reducing the awareness of bitterness in taste. This technique is appropriate for lower doses of drugs. The Vander Waals forces are occupied in inclusion complexes (Nanda et al., 2002). β-
cyclodextrin is used as a complexing agent which is sweet in taste, non-toxic and cyclic oligosaccharide which is obtained from starch.

The bitterness of carbetapentane citrate (syrup) was condensed to 50% by making 1:1 complex (cyclodextrin). Pleasant ibuprofen solutions are formed at 1:10 to 1:15 ratio with ibuprofen and hydroxypropyl β-cyclodextrin. The complex covered the bitter factor but produced sore taste, which was covered by sweetening agents.

1.1.5.5 Taste masking using ion-exchange resins (IERs)

These are high Mol. Wt. polymers having both cationic and anionic functional groups. These resins are mainly used in formulations for stabilizing the sensitive components, delaying in release of drug, breaking up the tablets, and to cover the taste. Drug can be incorporated by exposing the resin to the drug repeatedly in a chromatographic column or increasing the contact of resin within drug solution.

There is an attachment of drugs to the resin substrate thus forming insoluble resonates by means of ionic bonding; there by separation of the drug-resin complex does not take place below the salivary pH environment. This properly masks disagreeable taste and odor of the drugs.

The release of drug from the resin is complex and dependent on the resin properties and the ionic surroundings within the GIT. The drug molecules that are in attachment with the resin are exchanged with ions that have charge are present in the GIT and diffused out of the resins.
1.1.5.6 Taste masking using miscellaneous approaches

1.1.5.6.1 Effervescent agent

Effervescent agents were useful and are beneficial for oral management of drugs. They are used for masking the taste for dosage forms that have no intention to dissolve in water earlier to administration. A composition of chewing gum with objectionable taste medicament was formulated in such a way that it provides the medicament to the oral track. It consists of a base of gum, an orally takable active ingredient, a taste masking agent (CO₂), a composition of optional desensitization (anaesthetics like benzocaine, etc.) and other inactive materials, such as organoleptic additives and bulking agents. Recently, fentanyl and prochlorperazine effervescent tablets were formulated to supply these drugs for absorption to the oral tract.

1.1.5.6.2 Salt preparation

Salt preparation is one of the classical approaches to cover the bitter drug taste by either decreasing solubility or by increasing hydrophobicity by reducing contact of bitter drugs with the taste buds. This approach differs from others to alter the chemical composition of the drug substance to make it less soluble in saliva and therefore less stimulating the taste buds. Addition of alkaline metal bicarbonate like NaHCO₃ covers the disagreeable taste of ibuprofen in watery medium. Objectionable taste of caffeine can be covered by forming as carbonated oral solid dispersion. Aspirin tablets are made bland by preparing aspirin in magnesium salts form.
1.1.5.6.3 Solid dispersion technique

In this technique, one (or) more drugs are spread in an immobile solid carrier. Solid dispersion of drug with the aid of polymers, sugar, or other appropriate agents is very practical for taste masking. The dimenhydrinate masking of bitterness can be done by formulating the solid dispersion of drug with polyvinyl acetate phthalate.

1.1.5.6.4 Group modification and pro-drug approach

The clarithromycin 2’ position’s alkylxyalkyl carbonates have covered bitterness and enhanced bioavailability when given orally.

Bland pro-drug of opioid drugs can be formulated for better buccal release. Bitter prodrugs of nalbuphine hydrochloride, naltrexone, naloxone, oxymorphone hydrochloride, butorphanonol, and levallorphan can be manufactured for buccal route of administration to get better bioavailability comparative to oral dosing devoid of objectionable taste.

1.1.5.6.5 Freeze drying method

This technology is used in developing fast-dissolving ODTS like Zydis and Lyoc technology. As the freeze drying process produced high porosity, Zydis in its tablet shaped dosage form disassociates in the mouth within seconds.

In Zydis process the drug has to be dissolved in a water soluble structure forming agent. The mixture is then placed into the blister pockets and then freeze dried. Gelatin and mannitol are most commonly used structural ingredients, starches and gums are the
other suitable excipients. This process is preferred in low solubility drugs which are easily freeze dried.

1.1.5.6.6 Wet spherical and continuous melt method

To cover the bitter taste of enoxacin, this method of microencapsulation process combined with this method was used.

1.1.6 Mechanism of tablet disintegration and water absorption

When mouth dissolving tablets are placed in the mouth, upon contact with saliva the tablets disintegrate or dissolve instantaneously. There are four mechanisms involved in the tablet disintegration mechanisms

- Swelling
- Wicking
- Deformation
- Disintegrating particle/particle repulsive forces

1.1.6.1 Swelling

The most commonly established mechanism of tablet breakup is swelling. The tablets with elevated porosity confirm poor disintegration because of lack of sufficient swelling force and on the other hand in tablets with low porosity, the swelling force is sufficiently exerted. The fluid cannot be penetrated into the tablet when the packing fraction is more, thereby disintegration rate slows down.

1.1.6.2 Wicking

Capillary action mechanism is the first step in wicking. When the tablet is placed in the medium, it penetrates into the tablet and the air is replaced on particles, weakening intermolecular bond and
tablet breaks into finer particles. The water taken by the tablet depends up on the hydrophilicity of the drug or ingredient and on surroundings of tabletting. For this type of disintegrants, porous structure maintenance, less interfacial tension in the direction of aqueous fluids are compulsory which creates a hydrophilic network around drug particles and helps in disintegration.

1.1.6.3 Deformation

During compression of tablet, the disintegrated particles deform and these particles obtain normal structure when they are contacted with aqueous media. When granules are deformed expansively during compression, the swelling ability of starch is enhanced. The deformed particles increase in size and produce a breaking of the tablet. The starch may be followed by this deformation mechanism and has to be studied.

1.1.6.4 Disintegrating particle/particle repulsive forces.

Guyot-Hermann has projected repulsion theory of a particle that non-swelling particles also cause disintegration of tablets. The mechanism of disintegration is due to electric repulsive forces between particles and in order to have that repulsive forces water is required (Lachman et al., 1990). This mechanism of repulsion is secondary to wicking.
1.2 LITERATURE REVIEW

- **Azza et al., (2011)** developed fast disintegrating sublingual zolmitriptan tablets using freeze drying technique. They used gelatin as binder and manitol as matrix enhancing agent. The tablets disintegration and dissolution is enhanced with speeding the onset and drug absorption. This sublingual formulation gave faster and higher zolmitriptan plasma concentration in rabbits compared with oral marketed zolmitriptan formulation and constitutes an advance in migraine treatment.

- **Alessandro et al., (2010)** have written a review on migraine. They described strong epidemiologic evidence linking migraine and stroke in adults. In their review four major issues are summarized. 1. Migraine ischemic stroke relation 2. Migraine with increased cardiovascular risk factors 3. Migraine specific drugs 4. Migraine and ischemic vascular events.

- **Debjet et al., (2009)** wrote an overview on fast dissolving tablets. In that review they explained the tablets fast disintegration and dissolution in saliva without water within few seconds. They also explained the need of FDTs, their benefits, limitations, techniques for preparation of tablets, patented technologies, commercially available formulations, mechanisms of superdisintegrants, pre-formulation studies and the evaluation of those prepared tablets. They concluded that the problems experienced by the patients with conventional tablets can be overcome by fast dissolving tablets.
Mohanachandran et al., (2011) made an overview on superdisintegrants. They described about the use of right disintegrates in order to have optimal bioavailability and to improve the efficacy of solid dosage forms. Generally superdisintegrants were used at low concentrations typically 1-10 % compared with the total formulation weight. In their review they listed the various superdisintegrants being used in formulations which provide effective and safer delivery to the patient.

Shailesh Sharma et al., (2007) wrote a review on fast dissolving tablet: the future of compaction. They explained about the convenience of the fast dissolving formulations.


Jun et al., (2005) studied the pharmacokinetics of two oral formulations i.e. the capsule formulation as test and tablet formulation as reference. Both formulations contain 10 mg of rizatriptan. The plasma concentrations are analysed by using validated HPLC method. They estimated AUC, Cmax and Tmax, decided that the test and standard formulations were bioequivalent in context with rate and extent of drug absorption.

Chen et al., (2005) developed highly effective rizatriptan nasal spray to overcome the limitations of oral formulations. They investigated the pharmacokinetics and tolerability of nasal spray rizatriptan formulation. Each subject received either nasal spray or
oral tablet. The plasma concentrations were determined by HPLC. Rizatriptan was absorbed more rapidly in nasal spray within 5 minutes after dosing. There is no significant difference for AUC or Cmax.

- Sheeba et al., (2009) studied the effect of rising nifedipine load on fast disintegrating sublingual characteristics in emergency treatment of hypertension. This drug undergoes presystemic metabolism in the liver and gut wall. The bioavailability was found to be between 43%-77%. They prepared sublingual tablet as it bypasses the metabolism of the drug in liver so that the patient gets immediate relief from hypertension. In the preparation of sublingual tablets they used various superdisintegrants. Tablets were formulated using the direct compression technique. The evaluation tests of the prepared tablets were found to be satisfactory. The tablets have mixture of croscarmellose sodium and sodium starch glycolate, each 2mg showing fast dissolution and disintegration.

- Mutasem et al., (2006) determined the epinephrine drug concentration from fast disintegrating tablets. The plasma concentrations are same as dose obtained after 0.3mg IM injection. They compared 0, 10, 20 and 40mg of epinephrine in sublingual tablets compared with 0.3mg intramuscular epinephrine injection, they used rabbit model for the study. They concluded that the tablets containing 40mg of drug in sublingual formation shows same results as that of 0.3mg intramuscular injection. So this
shows that sublingual administration is one of the feasible alternatives to intramuscular injection.

- Elina et al., (2011) investigated improvement of absorption of less water soluble, first-pass metabolised perphenazine with sublingual formulation. In order to increase the absorption they have included cyclodextrin and made solid dispersion which increases the solubility of sublingual formulation. They proved that sublingual absorption is further enhanced by micronization of perphenazine.

- Toshihiro et al., (2003) developed lansoprazole fast disintegrating tablets which consist of enteric coated micro granules and inactive granules. They used manitol as the main excipient, HPC, microcrystalline cellulose and cross povidone as binders and disintegrants. They concluded that the tablets containing 47.4% of enteric coated micro granules gave sufficient strength and rapid disintegration in the mouth (<30s) and also did not show much effect in the acid or buffer stages of dissolution.

- Suzanne et al., (2006) compared the plasma concentrations of rizatriptan oral tablets and ODT with and without water in healthy human volunteers. All formulations contain 10mg of rizatriptan. The plasma samples were taken at different time intervals and T-max and AUC of all the formulations were compared. The T-max for ODT with water and ODT without water was found to be 0.67hrs and 1.33hrs respectively. Similarly the AUC $0-2hr$ for ODT with and without water were found to be 33.84hng/ml and 18.83hng/ml and AUC $0-1hr$ for ODT with water and without water
in rizatriptan tablets was found to be 17.07hng/ml and 13.32hng/ml respectively.

- Emma et al., (1998) conducted pharmacokinetic studies on 2.5mg and 5mg oral doses of zolmitripton in women and men. They compared pharmacokinetics in women and men. The absolute bioavailability was found to be 0.41 and 0.09 after 2.5mg and it was found to be 0.48 and 0.36 after 5mg in women and men respectively. The AUC after 2.5mg dose was found to be 18.4hng/ml and 23.1hng/ml correspondingly, in men and in women. The AUC after 5 mg dose was found to be 32.7hng/ml and 60.2hng/ml respectively. They concluded that these differences do not have clinical significance. The AUC and C-max depends on dose and as a mean it was fallen 13% and 16% respectively when the drug is administered after taking food. They concluded that the oral bioavailability was good at therapeutic doses in healthy humans and also proved that dose dependent pharmacokinetics does not affect the presence of food to clinical extent.

- Kamlesh et al., (1999) compared single IV 3mg, 30min infusion and single oral 10mg dose in six human healthy male volunteers. Total recovery of 94% radioactivity with unchanged rizatriptan was obtained. The metabolites excreted in the urine (89% IV dose, 82% oral dose). From this study the absorption of rizatriptan was affected by a moderate first pass metabolism due to which the bioavailability was found to be 47%.
Keny et al., (2010) prepared mouth disintegrating rizatriptan benzoate tablets using superdisintegrants like crospovidone, carboxymethyl cellulose, indion 414 and indion 234 by direct compression methods. The physical tests of formulated tablets were evaluated. The \textit{in vitro} release and assay was done by using HPLC. \textit{In vitro} and \textit{in vivo} DT was creating to be 4 to 7s and 6 to 19 s respectively. 90\% of drug was released within 20 min. They concluded that the formulation containing indion and crospovidone exhibited higher release rates.

Sunita et al., (2010) developed rizatriptan fast disintegrating tablets for migraine treatment. The superdisintegrants like CP, CCS and SCG were used with the diluents such as lactose, MCC and manitol. They concluded that the tablets prepared using crospovidone and MCC exhibited less disintegration time. Further the disintegration time was reduced with the addition of spray dried lactose.

Acharjya et al., (2010) developed three simple, accurate, precise and inexpensive UV methods. The drug exhibited maximum absorption at 0.5-20 µg/ml concentration at 227 nm and at the concentration of 0.5 to 8.0 µg/ml at 281 nm respectively. They derivatized spectrum into 1\textsuperscript{st} and 2\textsuperscript{nd} order. The trough at 233 nm for D1 and crest at 238 nm for D2 were measured. From these two methods the drug showed linearity from 0.5-20 µg/ml. They concluded that this method shows good results in the concerning
concentration range, accuracy, precision, robustness and ruggedness.

- Khedkar et al., (2009) developed fast, effective, simple, sensitive, rapid and reproducible UV-Spectrophotometric method for view of rizatriptan in tablet and bulk form that shows absorbance at 225 nm in concentration range of 1-10 µg/ml. They validated this method with respect to precision, linearity, LOD, LOQ, specificity and sensitivity.

- Sameer et al., (2009) studied presence of calcium silicate and lubricants on β-cyclodextrin based FDTs. They also evaluated the effects of moisture at 75, 85 and 95% RHs. They used factorial design to optimise the concentrations of calcium silicate as disintegration enhancing agent and magnesium stearate as lubricant. In the results they have concluded that the concentration of calcium silicate does not have any effect but though the presence of lubricant was very significant for degeneration and rigidity of the tablet. They found 1.5 percent of magnesium stearate gave 23.4 seconds DT and hardness as 1.2 kg. They also concluded that at 75% moisture the hardness does not have any effect where as at 85% and 95% treatment with moisture, the hardness of the tablet was increased. However the disintegration time was not effected.

- Lee et al., (1999) studied the pharmacokinetics and dose proportionality of 2.5-15 mg rizatriptan oral single dose as solution administered to healthy human volunteers. The plasma and urine
samples were collected and the rizatriptan concentrations were determined for drug content up to 12 and 24 hours respectively. The pharmacokinetics of the drug was linear for doses of 2.5 to 10 mg in men and 2.5 to 5 mg in women. From this study they concluded that the plasma concentrations of rizatriptan were little superior in females compared to males. Non-renal clearance of the drug was detected.

- Anupama et al., (2009) developed mouth dissolving tablets of oxcarbazepine to get desired and intended benefits. They used direct compression technology and solid dispersion method. In the first method they have used crospovidone and aspartame. In solid dispersion they used polyvinyl pyrrolidone K-30; PEG 6000 in various weight ratios. They concluded that solid dispersion technology was the better substitute to the direct compression technology for the development of mouth dissolving tablets especially for the drugs that are less soluble in water.

- Arjun et al., (2010) prepared rosiglitazone mouth dissolving tablets in diabetes mellitus for long therapy. Sodium starch glycollate, crospovidone and croscarmellose sodium were used as super disintegrants. The mouth dissolving tablets having 1:1 ratio of croscarmellose sodium and crospovidone showing maximum release of the drug. They also conducted stability studies at 40°C/75% relative humidity. The formulations were stable.

- Honey et al., (2008) optimised and formulated fast disintegrating tablets of ondansetron HCl or domperidone using aminoacetic acid,
carmellose and sodium alginate to prevent nausea and vomiting. They revealed that domperidone optimised FDTs better than domperidone FDTs containing cross carmellose or crospovidone. They concluded that this novel mixture of excipients can be used for deliverance of water insoluble drugs instead of superdisintegrants.

- Shapero et al., (2006) studied clinically an international open-label study. It includes new, substantial variables applicable to PCPs and recruits patient’s present prime care who diagnosed migraine. They treated migraine attack/month with zolmitriptan ODT 2.5mg. 595 patients are treated with 7171 migraine attacks with ODT tablet. Out of those 504 of them finished six months questionnaire, 380 patients still wish to continue ODT tablet. From this study they indicated that patient-oriented end-points are significant and encouragable to the physicians than conventional end point, making them to decide on their own managing the migraine.

- Rahul et al., (2009) studied and optimised fast disintegrating tablets in three stages and in each stage hardness, friability and disintegration time was studied and they revealed that in stage-I hardness and disintegration time improved with increased gelatine concentration. In stage-II saccharides like sorbitol, mannitol and sucrose in different ratios were added (10 percent and 80 percent), good results were obtained with mannitol containing formulations which was carried for the next stage and in that stage (stage III) they have added polymers to enhance mouth feel and pre-gastric
withholding (carbopol 974P-NF). Pluronic F127 (6%) showed increased disintegration time and viscosity without any change in mechanical properties.

- Takao et al., (2005) studied on the improvement of compressibility of low compressible saccharides; modification of the particle was done by coating and granulating the low compressible saccharide with a high one. They also discovered that high compressible saccharides can also be used as a binder solution in the amorphous state after the completion of granulation stage. They concluded that the prepared tablets have sufficient hardness, fast disintegration time, manufactured by simple commonly available equipment and used for wide range of drug dosages.

- Mutasem et al., (2006) have developed sublingual tablets of fast disintegrating epinephrine tablets. They have prepared four formulations with 0 percent, 6 percent, 12 percent and 24 percent of epinephrine bitartrate. The excipients used were MCC (PH-301), low-substituted HPC (LH11) and magnesium stearate and tablets were obtained by direct compression method. These tablets had been evaluated for physical parameters. In all the formulations hardness, disintegration time and wetting time was found to be suitable for sublingual administration.

- Takuma et al., (2008) made an effort to produce fast disintegrating furosemide tablet using direct compression method. They used MCC, croscarmellose sodium, xylitol and sucrose stearic acid ester. The tablets produced using sodium starch glycollate by
solvent (organic) evaporation technique and showed hardness >30 N and disintegration time was < 20s which was concluded by them to be suitable for preparing fast disintegrating tablets.

- Yara et al., (2009) evaluated bioequivalence of two commercial ondansetron 8mg tablets. They have used simple, sensitive, rapid, LC-MS method of ondansetron for determination in human samples. Bioequivalence between both was determined by 90% confidence interval for the Cmax ratios of AUC for the test and the reference products. They concluded that the test as well as reference formulations are bioequivalent.

- Kilic et al., (2007) developed a specific and sensitive LC-MS method for zolmitriptan and their metabolites determination in human samples. The internal standard and analytes (paroxetine) were extracted with ethyl acetate: dichloromethane (4:1) and were separated using isocratic mobile phase in XTerra RP18 column. This validated method was used in pharmacokinetic studies. The mobile phase consists of acetonitrile, 5mM ammonium acetate and formic acid (50:50:0.053, vole/vole/vole).

- Vijayakumar et al., (2010) developed a sensitive, specific, linear, stability indicating Hp-LC method for the analysis of zolmitriptan related substances. They concluded that this method is used for detecting, quantifying impurities (known and unknown) and degradation products during routine analysis of zolmitriptan and stability studies.
Asad et al., (2007) developed simple, rapid, gainful and extraction gratis Spectrophotometric method for zolmitriptan determination in formulations. In this method they made a reaction of zolmitriptan in acetonitrile with 0.2% 2, 3-dichloro-5, 6-dicyano-1, 4-benzoquinone to form a colour product and showed absorbance at 555 nm. They concluded that this method can be used for determination of zolmitriptan in formulations.

Sharma et al., (2010) prepared MDTs of domperidone using camphor and crospovidone with the help of direct compression method. By exposure to vacuum the camphor was sublimed. These tablets were subjected for friability and disintegration time. They found that the tablets with optimum concentrations of camphor and higher percentage of crospovidone results in rapid disintegration.

Kumar et al., (2010) developed mouth dissolving tablets of sildenafil citrate using CCS, CRP, MCC and starch by direct compression method. They concluded that tablet containing crospovidone and croscarmellose sodium between 2-8% was disintegrated quickly (30s).

Prashant et al., (2010) developed and evaluated mouth dissolving meloxicam tablets. The tablets were manufactured by wet granulation. The ingredients used were crospovidone, colloidal silica dioxide, camphor, lactose and PVP solution in ethyl alcohol. The prepared tablets were subjected for physical tests. They found that the formulation containing camphor and crospovidone effects
the parameters like wetting time, disintegration time and percentage friability and also concluded an effective vacuum drying technique which is an important alternative approach in place of more expensive adjuvant.

➢ Takao et al., (2008) developed taste masked fast disintegrating famotidine tablets using spray dry method. The excipients used were aqua coat ECD30 and Eudragit NE30D or triacetin. They established that the spray dried process produced flavour masked particles for FDTs.

1.3 NEED FOR INVESTIGATION

The require for patient compliance dosage forms were increased since last decade. This has lead to the development of new techniques. The development of new drug formulations is time consuming and expensive these days. So increased efforts is a challenge for researchers in producing cost effective dosage forms for the development of new dosage forms using existing drugs. Currently tablets and capsule dosage forms are available as drug delivery systems. However, patient groups like geriatric, paediatric, mentally retarded and uncooperative will not prefer to take conventional dosage forms (Prajapati et al., 2009). To fulfil these needs the researchers have invented novel oral dosage forms known as fast disintegrating tablets that disintegrate quickly in the saliva within few seconds without using water. Sublingual route of administration produces quicker commencement of action than conventional tablets and part
absorption from the blood vessels of sublingual route bypasses the first pass effect (Birduraj et al., 2005).

Various methods are used to devise fast disintegrating tablets (Allen et al., 2003). One of the easiest and cost effective tablet techniques which require incorporation of superdisintegrants and highly water soluble excipients to get fast disintegration and dissolution. Water or heat is not required in this technique during preparation and it is most ideal for drugs which are moisture and heat sensitive.

Migraine affects 6% in males and 18% in females with 34 attacks per year for men and 37 attacks per year for women (Lipton et al., 1993; Hu et al., 1999). It is characterised by unilateral, pulsating moderate to severe headache (Fenuik et al., 1985; Stovner et al., 2006), commonly accompanied by nausea, vomiting, phonophobia and photophobia (Zimma et al., 2011). The attack lasts for 4-72 hrs in adults (Launer et al., 1999). Two types of migraine are identified i.e., migraine with aura and migraine without aura. Major issues considered in migraine are cervical artery dysfunction (Hedlund et al., 2009), increased prevalence of cardiovascular risk factor caused due to migraine specific drugs (Lipton et al., 2004), analgesic over doses, refractory migraine, migraine in elderly, during pregnancy and menstrually triggered migraine. It is believed to be due to the release of serotonin chemical or 5HT to the blood stream from its storage site resulting in changes in neurotransmitter and blood vessels in the
brain. This causes pain in neurons and the blood vessels wall become irritated.

Zolmitriptan and rizatriptan are class-III drugs, serotonin 5-HT receptor agonists and are widely used in the treatment of migraine. The symptoms of migraine include pain, nausea and photophobia or phonophobia (Marcelo et al., 2003). Both the drugs are completely absorbed followed by oral administrations. The therapeutic activity of the drugs are due to agonist effect at the 5-HT IB/ID receptors on intra cranial blood vessels, trigeminal system sensory nerves which causes constriction of cranial vessel and the inhibition of release of pro-inflammatory neuropeptide. Some triptans are available by means of various routes of administration apart from oral tablets like ODTs, rectal suppositories and intranasal administration, etc. Current methods of administering anti-migraine drugs suffer from major efficacy limitation due to degradation in the GIT and low absorption of the drug. Oral formulations of anti-migraine drugs have large doses (20-30mg) leading to nausea, vomiting and other adverse effects. Most of the anti-migraine drugs are subjected to first pass metabolism. Low bioavailability and slow onset causes both the drugs to be completely absorbed following oral administration of action and large inter-subject variability. Injectable forms need lower dose as related to other non-injectable methods of administration which causes inconvenience of an injection and problems with the self administration are self evident.
1.3.1 Advantages of sublingual route.

- Enhances tablet disintegration and dissolution
- Speeding drug absorption and onset of effect
- Avoid first pass hepatic metabolism
- Avoid gastric irritation, nausea and vomiting
- Reduction in the dose thereby minimizing the frequency of dosing
- Convenient for administering to children and elderly people
1.4 DRUG PROFILE

1.4.1 Zolmitriptan

Zolmitriptan belongs to selective 5-hydroxytryptamine 1B/1D receptor agonist.

**Structure:**

![Zolmitriptan Structure](image)

IUPAC name: (S)-4-[[3-[2-(dimethylamino) ethyl]-1H-indol-5-yl]methyl]-2-oxazolidinone.

CAS NO: 139264-17-8.

Mol. For.: C\textsubscript{16}H\textsubscript{21}N\textsubscript{3}O\textsubscript{2}.

Mol. Wt.: 287.36 gm/mol.

Phy. State: White or almost white powder.

M.P: 136 to 141\textdegree C.

Category: Anti-migraine

Solubility: Slightly soluble in water and freely soluble in 0.1M HCL.

Dose: 2.5mg, 5mg up to 10mg (maximum).

Half life: 2 to 3 hours.

Bioavailability: Approximately 40% absolute bioavailability.

Absorption: Well absorbed through GIT.
Metabolism: It is converted into N-desmethyl metabolite which is active such that the concentration of metabolite is about 2/3rd of zolmitriptan as the strength of metabolite is 2-6 times that of parent and contributes a major part on the whole effect after zolmitriptan administration (Dowson et al., 2005).

Adverse effect: Tightness in the chest, bluish tongue to the skin, cold arms and legs, dizziness, drowsiness, rashes on skin, swelling of the eye lids or face, smallness of breath.

Stability: Stored at room temperature, protected from heat, moisture and sunlight.

1.4.2 Rizatriptan Benzoate

Rizatriptan benzoate was a selective 5-hydroxytryptamine 1B/1D receptor agonist.

**Structure:**

![Structure of Rizatriptan Benzoate]

IUPAC name: N, N-dimethyl-5-(1H-1,2,4-triazol-1-ylmethyl)-1H-indole-3-ethanamine monobenzoate.

CAS NO: 145202-66-0.

Mol. For.: C_{22}H_{25}N_{5}O_{2}.

Mol. wt: 391.47 g/mol.

Phy. state: White or almost white crystalline solid.
M.P: 178 to 180°C.
Category: Anti-migraine drug.
Solubility: 42mg/ml at 25°C in water.
Dose: 5mg, 10mg (7.27mg-14.53mg of the benzoate salt) up to 30mg (maximum).
Half life: 2-3 hours.
Bioavailability: 45% oral bioavailability.
Absorption: Food does not have any effect on absorption.
Metabolism: The metabolism is through oxidation by means of monoamine oxidase A to metabolite i.e., indole acetic acid that is inactive at the receptor. A metabolite N-monodesmethyl-rizatriptan with comparable pharmacological activity as parent compound and is identified in small concentration (14%) in plasma.
Adverse effects: Pain in the chest, tightness, chest pressure, pulsation heart beat, heaviness, feeling of blurring warmth, heat and lack of sensation.
Stability: Store at room temperature in closed container protected from direct sunlight, heat and moisture, preferably below 15 to 30°C.
1.5 POLYMER PROFILE

1.5.1 Sodium starch glycollate

Pregelatinized starch occurs as moderately coarse to find powder, white to off-white in colour, odourless with slight characteristic taste.

Mol. for: \((C_6H_{10}O_5)n\).

Non-proprietary names:

BP: Pregelatinized starch

PhEur: Amylum pregelificatum

USPNF: Pregelatinized starch.

Synonym: Compressible starch, lycatab C, Instastarch, lycatab PGS, merigel.

CAS No.: 9005-25-8

Che. name: Sodium carboxymethyl starch

Structure:

![Structure of Sodium Starch Glycollate](image)

Category: Tablet and capsule diluent, disintegrant and binder.

Applications in pharmaceutical technology: Widely used as binding agent, diluent and disintegrating agent in tablet and capsule formulations (Jarosz et al., 1982), it is used as a binder in tablets.
(Suzuki et al., 1976). In those formulations, this pregelatinized starch is self lubricating. When it is used with other excipients there is a need of adding lubricant (Pilpel et al., 1971). Pregelatinized starch can also be used in wet granulation process.

Storage:

Tablets prepared with this have good storage properties (Gordon et al., 1990) and are stable. It is stored in properly closed container and protected from moisture and temperature. The physical nature of sodium starch glycollate remains unchanged for 3-5 years at moderate temperatures and humidity.

Incompatibilities: Incompatible with ascorbic acid (Botha et al., 1987).

Safety: SSG is extensively used in oral formulations and is considered as non-hazardous and non-irritant material.

1.5.2 Croscarmellose sodium

Croscarmellose sodium is a cross linked sodium carboxymethyl cellulose polymer.

Nonproprietary names:

- Croscarmellose sodium- BP
- Carmellosum natricum conexum- PhEur
- Croscarmellose sodium- USPNF

Synonym:

Ac-Di-Sol; cross linked carboxymethylcellulose sodium; Explocel; cellulose gum modified; Nymcel ZSX; Pharmacel XL; Primellose;

Che. name: Cellulose, carboxymethyl ether, sodium salt, cross linked

CAS No.: 74811-65-7
Molecular weight: 90,000 to 70,000

**Structure:**

![Chemical Structure Diagram]

Category: Tablet and capsule disintegrant.

Applications:

It is used as disintegrates in granules, tablets and capsules (Dahl et al., 1991; Ferrero et al., 1997). In tablet formulations, it may be used in dry and wet methods. In wet granulation process, the croscarmellose sodium can be included in both stages, so that the wicking, swelling ability of the croscarmellose sodium is utilized (Gordon et al., 1993). Up to 5% w/w concentrations can be used as disintegrant, but normally 2% w/w was used in the tablets which are prepared by direct processes of manufacturing and concentration 3% w/w can be used for wet-granulation method.

Physical Description:

White or greyish-white odourless powder.

Storage conditions:

Though it is a hygroscopic material but is stable. It must be stored in a cool, dry place in a well closed container.
Safety:
Mainly used as a disintegrant in oral formulations and is nontoxic and non-irritant material.

1.5.3 Crospovidone

Synthetic homopolymer of N-vinyl-2-pyrrolidinone.

Nonproprietary name:
- BP: Crospovidone
- PhEur: Crospovidonum
- USPNF: Crospovidone

Synonym:
Cross linked povidone; E1202; Kollidon CL-MPolyplasdone XL- 10; Kollidon CL; polyvinylpolypyrrolidone; PVPP; Polyplasdone XL; 1-vinyl-2-pyrrolidinone homopolymer.

Che. Name:
1-Ethenyl-2-pyrrolidinone homopolymer

CAS No.: 9003-39-8

Mol. Formula: \((\text{C}_6\text{H}_9\text{NO})_n\)

Mol. weight: > 1 000 000
**Structure:**

![Structure Diagram]

Category: Tablet disintegrant.

Applications:

As tablet disintegrant, dissolution agent (2–5%) in tablets which are prepared by direct, wet and dry processes (Hipasawa et al., 2004). It quickly shows high capillary action and pronounces hydration capacity, with small tendency in gel formation. The big particles exhibit a quicker disintegration than smaller ones. It can also be used for enhancing solubility.

Physical description:

White or Off-white free-flowing tasteless, odourless hygroscopic material.

Storage conditions:

Hygroscopic, stored in closed airtight container in a dry and cool place.

Incompatibilities:

Compatible with most organic and inorganic excipients, when it is contacted with water, crospovidone form molecular adducts with other materials.

Safety:

Used in oral products and is considered as a nontoxic, non-irritant.
1.5.4 Microcrystalline cellulose (Avicel pH102)

Purified partially polymerized cellulose

Nonproprietary name:

- Microcrystalline cellulose- BP
- Microcrystalline cellulose- JP
- Cellulosum microcristallinum- PhEur
- Microcrystalline cellulose- USPNF

Synonym:

Avicel PH; cellulose gel; Celphere; Celex; Ceolus KG; E460; Emcocel; Ethispheres; Fibrocel; Pharmacel; crystalline cellulose; Tabulose; Vivapur.

Chemical Name: Cellulose

CAS NUMBER: 9004-34-6

Molecular Formula: (C₆H₁₀O₅)n where n=200.

Molecular Weight: 36,000.
**Structure:**

![Chemical structure of microcrystalline cellulose]

**Category:**
Adsorbent; suspending agent; diluent for tablets, capsules and as a disintegrant for tablets.

**Applications:**

Widely used as binder, diluent in formulations of tablet and capsule. In tablets it is used in both compression techniques (Wallace et al., 1983). In addition to this it also used as lubricant and disintegrant (Omray et al., 1986) in tablet manufacturing. Microcrystalline cellulose is also used in cosmetic formulations and in food products.

**Physical description:**

White, odourless, tasteless, crystalline powder having porous particles.

**Storage conditions:**

Though it is hygroscopic material but it is stable. This should be stored in a cool and dry place preferably in air tight container.

**Safety:**

It is commonly used in oral, food products and is considered as nontoxic and non-irritant. Consumption of huge quantities may have
laxative effect, although it is not having problem when included in pharmaceutical formulations as an excipient (Cooper et al., 1983).

**1.5.5 Mannitol (D-mannitol)**

It is a hexahydrate alcohol associated with mannose and is isomeric with sorbitol.

Mol. formula: C$_6$H$_{14}$O$_6$.

Mol. weight: 182.17

Category: Sweetening agent, diluent for tablets and capsule, tonicity agent, vehicle for lyophilized formulations.

Description:

White, odourless, crystalline or free flowing granules. It is having sweet taste and the sweetening powder is similar to glucose and half sweet as sucrose and also gives cooling sensation in the mouth. Mannitol shows polymorphism phenomenon.

Application:

In pharmaceutical preparation it is chiefly used as a tablet diluting agent (10-90%).

**1.5.6 Aspartame**

Nonproprietary names:

- BP: Aspartame
- PhEur: Aspartamum
- USPNF: Aspartame

Che. Name:

N-α-l-Aspartyl-l-phenylalanine 1-methyl ester
Structure:

Category: Sweetening agent.

Applications:

It is intensely used as a sweetening agent in beverage products, food products, in pharmaceutical preparations including tablet formulations (Joachim et al., 1987), powders and in vitamin preparations. It improves flavour and it can be used to cover some of the disagreeable taste characteristics. This has 180-200 times sweetening power compared to sucrose.

Storage conditions:

It is stable in dry conditions. Hydrolysis occurs due to the presence of moisture and forms l-Aspartyl-l-phenylalanine, 3-benzyl-6-carboxymethyl-2, 5-diketopiperazine and β-l-Aspartyl-l-phenylalanine methyl ester.

Safety:

Aspartame is most widely used in oral pharmaceutical dosage formulations, in beverages, and in food preparations as a powerful sweetener and is considered as nontoxic material. The WHO has set suitable daily dose ingestion for aspartame at 40 mg/kg body-weight (FAO/WHO 1981).
1.5.7 Magnesium stearate

It consists of mixture of solid organic acids containing variable portions of stearate and palmate of magnesium.

Nonproprietary name:

- Magnesium stearate- BP
- Magnesium stearate-JP
- Magnesii stearas-PhEur

Synonym:

Magnesium octadecanoate, magnesium salt, octadecanoic acid, stearic acid and magnesium salt.

Chemical name: Octadecanoic acid magnesium salt.

CAS No.: 557-04-0

Stru. Formula: \([\text{CH}_3 (\text{CH}_2)_{16}\text{COO}]_2 \text{Mg}\).

Mol. Weight: 591.34

Category: Lubricant for tablet, capsule.

Applications:

Magnesium stearate was commonly used in cosmetics, pharmaceuticals and in food industry. It is chiefly used as flow promoting agent in capsule, tablet manufacturing at 0.25% w/w and 5.0% w/w concentrations. It is also found as an excipient in barrier cream.

Storage conditions:

Stable and stored in an air tight container preferably in cool, dry place.
Safety: Used as pharmaceutical ingredient and is considered as nontoxic for oral formulations.

1.6 OBJECTIVES
In the present study the main objectives were

- To develop fast disintegrating sublingual tablet formulations using zolmitriptan and rizatriptan (5-HT_{1B/1D} receptor agonist) anti-migraine drugs.
- To evaluate the powder formulations for Micromeritic properties.
- To determine prepared tablets for physical parameters, *in vitro* release studies and characterization of optimized formulation.
- To establish the stability of optimized formulation.
- To compare *in vivo* release studies using rabbit as the animal model.

1.7 RESEARCH WORK PLAN

- Literature review
- Selection of excipients
- Selection of superdisintegrants
- Preparation of fast disintegrating sublingual tablets
- Evaluation of sublingual tablets
- Micromeritic properties of prepared powder formulations
- Determination of physical properties of tablets
- *In vitro* release studies
- Characterization
- Stability studies
- *In vivo* release studies
- Documentation of the results
- Summary
- Conclusion