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FORMULATION, DEVELOPMENT & EVALUATION OF ORODISPERSIBLE TABLET OF PROTEIN PUMP INHIBITOR

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INTRODUCTION

Medicine is an art that has been practiced since time immemorial whose exact start cannot be predicted as its history is routed right from the development of human civilization and is continued till now. The use of herbs and natural medicaments to relieve pain or to aid the sick in coping with their afflictions has been a part of all societies. In the Western world, medicine has developed since the time of the Greeks and Romans. The Hippocratic Oath reminds us of this nearly 2500-year history. Much prior to the modern day allopathic medicine, others systems like the oldest documented system of medicine- Ayurveda as well as Unani, and Siddha existed. However, the progress of medicine has been very different from that of many other arts within society. It has come of age after an incredibly long maturation period. As a function capable of offering a successful treatment for a human Ailment, medicine is very much a development of the last 100–150 years. Indeed, the major advances have come in the last 50–75 years.[1]

It is a triumph of modern pharmaceutics that most of the people do not give a thought to the difference between a white powder and a tablet, and think that ‒a drug is a drug is a drug. This huge presumption is doubtless, because we do not anymore make pharmaceutical formulation ourselves, and precious few of us have ever understood that complicated process. However, as suggested by A. Fox ‒A drug is not a drug is not a drug‖ because when administered to a human being, in the general case, it contains numerous things which we might have not even thought off.[1]

1.1 ORAL ROUTE

The oral route of drug administration is the most important and convenient method of administering drug. It is probable that at least 90% of all the drugs used to produce systemic effect are administered by the oral route. When a new drug is discovered the pharmaceutical company makes every effort to ensure that the drug can be so formulated that it is capable of being administered orally. If it cannot be administered by oral route, and should a more complex parentral route be the only alternative, then the drug is primarily relegated for administration in a hospital setting or physician‘s office. If self administration of drugs cannot be achieved, the sales of the drug may constitute only a small fraction what the market would be otherwise.[2]

Tablets and capsules have emerged as the most popular solid oral dosage forms used today. This includes conventional and controlled-release tablets as well as hard and soft gelatin capsules.[2] Tablet formulation and design may be described as the process whereby the formulator ensures that the correct amount of the active drug in the right form is delivered at or over the proper time at the proper rate and in the desired location, while having its chemical integrity protected to that point.[3]

By comparison, liquid oral dosage forms, such as syrups, suspensions, solutions, and elixirs are usually designed to contain one dose of medication in 5 to 30 ml. Such dosage measurements are typically contributing an error ranging from 20 to 50% when the drug is self-administered by the patient. However, tablets and capsules have the advantage of being unit dosage forms in which one usual dose of the drug has been accurately placed in it.[2]

However most elderly patients, children, and patients with dysphagia have difficulty in swallowing conventional tablets and hard gelatin capsules, and therefore do not take medication as prescribed by physicians. It is estimated that 35% of the general population, 30 to 40% of elderly nursing home patients, and 25 to 50% of patients hospitalized for acute neuromuscular disorders and head injuries have dysphagia. The main causes of dysphagia include esophageal disorder such as achalsia, Gastro Esophageal Reflux Disease GERD, cardiovascular conditions such as aneurysm.

Autoimmune diseases such as Sjondrome Sygren‘s, Auto Immune Deficiency syndrome, (AIDS). Thyroid surgery, radiation therapy to head and neck or oral cavity, and other neurological diseases such as cerebral palsy etc.[2]

1.1.1 Drawbacks of conventional tablets and capsules

Ghosh et al.[4] have described a survey conducted in patients having difficulty in swallowing tablets and identified the reasons for this difficulty. More than 26 percent of patients reported problems in swallowing tablets. Prominent complaints were size of the tablet, surface of the tablet, forms of tablets, taste of the tablets. Twice as many women as men experienced swallowing problems. Paediatric and geriatric patients in particular experienced the greatest difficulty in swallowing tablets as well as people who are ill and supine in bed and those patients who are busy travelling without having asses to water than younger patients in swallowing tablets.

1.2 Orodispersible Tablets

ODTs are becoming increasingly sophisticated as pharmaceutical scientists acquire a better understanding of the physicochemical and biochemical parameters pertinent to their performance. Recent advances in novel drug delivery (NDDS) aim to enhance safety and efficacy of drug molecule by formulation and to achieve better patient compliance. One such approach is orally disintegrating tablets (OrDTs) which has gained considerable attention as a preferred alternative to conventional tablets and capsules over the past three decades.

Products of ODT technologies entered the market in the 1980s and have grown steadily in demand, and their product pipelines are rapidly expanding. New ODT technologies address many pharmaceutical and patients needs, ranging from enhanced life-cycle management to convenient dosing for paediatric, geriatric, and psychiatric patients with dysphagia. The mouth dissolving tablets (MDT) or ODTs by overcoming the drawback associated with conventional tablets. These tablets disintegrate/dissolve/ disperse in saliva within few seconds.[5] USFDA has defined OrDTs tablet as –A solid dosage form containing medicinal substances, which disintegrate rapidly, usually within a matter of seconds, when placed upon the tongue.

Recently European Pharmacopoeia also adopted the term –ODT as a tablet that is intended to be placed in the mouth where it disperses rapidly before swallowing. These dosage forms dissolve or disintegrate in the patient‘s mouth within 15 seconds to 3 minutes without the need of water or chewing.[6]

Fast dissolve, quick dissolve, rapid melt, quick disintegrating, mouth dissolving, orally disintegrating, orodispersible, melt-in-mouth, tablets etc are some of the terms which are used

to refer to this unique form of drug delivery, which has many advantages over the conventional oral solid dosage forms.[7]

1.2.1 Salient Features of Orodispersible Tablets

The performance of ODTs depends on the technology used during their manufacture. The necessary property of such tablets is the ability to disintegrate rapidly and disperse or dissolve in saliva, thereby obviating the need for water. Various technologies have been developed that enable ODT to perform this unique function.

1.2.2 An ideal Orodispersible tablet should meet the following criteria

1) Ease of administration to the patient who cannot swallow, and patient who refuse to swallow such as paediatric, geriatric and psychiatric patients.
2) Ability to be swallowed without water which is highly convenient for patients who are travelling or when immediate access to water is difficult.
3) Rapid dissolution and absorption of the drug, which will produce quick onset of action.
4) Result in an increase in bioavailability compared to conventional drugs.
5) Have sufficient strength to withstand the rigors of the manufacturing process and post manufacturing handling.
6) Exhibit low sensitivity to environmental conditions such as humidity and temperature.
7) Be easily adaptable for manufacture using existing processing and packaging machinery.
8) Good mouths feel to change the perception of medication as bitter pill particularly in paediatric patients.

1.2.3 Advantages of Orodispersible tablets

1) Improved safety since the risk of choking or suffocation during oral administration seen with conventional formulations is overcome.
2) New business opportunity like product differentiation, product promotion, patent extensions and life cycle management.
3) Utility in cases such as motion sickness, sudden episodes of allergic attack or coughing, where an ultra rapid onset of action required.
4) Stability for longer duration of time, since the drug remains in solid dosage form till it is consumed.
5) Cost effective manufacturing.[8,9,6,7]

However it should be noted that high drug loading is possible in case of ODTs.

1.3 Tablet Disintegrants

For a drug to be readily absorbable by the body, it has first to be in solution. For most tablets, the first important step toward solution is breakdown of the tablet into smaller particles or granules, a process known as disintegration as specified in the USP/NF. Before a tablet dissolves, it has to disintegrate first, unless the tablet is designed for quick surface erosion. The materials used as disintegrants include starches, agar, amylose, cellulose and its derivatives, gum and its derivatives, gelatin, resins, and silicone compounds.

Research has established that one should not automatically expect a correlation between disintegration and dissolution. However, since the dissolution of a drug from the fragmented tablet appears to control partially or completely the appearance of the drug in the blood, disintegration is still used as a guide to the formulator in the preparation of an optimum tablet formula and as an in-process control test to ensure batch-to-batch uniformity.[2]

In the tablet disintegration process, several factors may affect the disintegration. They include the rate of water absorption, porosity of the tablet, processing parameters, and effect of active ingredients, surfactants, binders, and lubricants. Fast disintegration always requires fast absorption of water into the centre of the tablet. Thus, having open pore structures inside the tablets is very important for making fast dissolving tablets.[6]

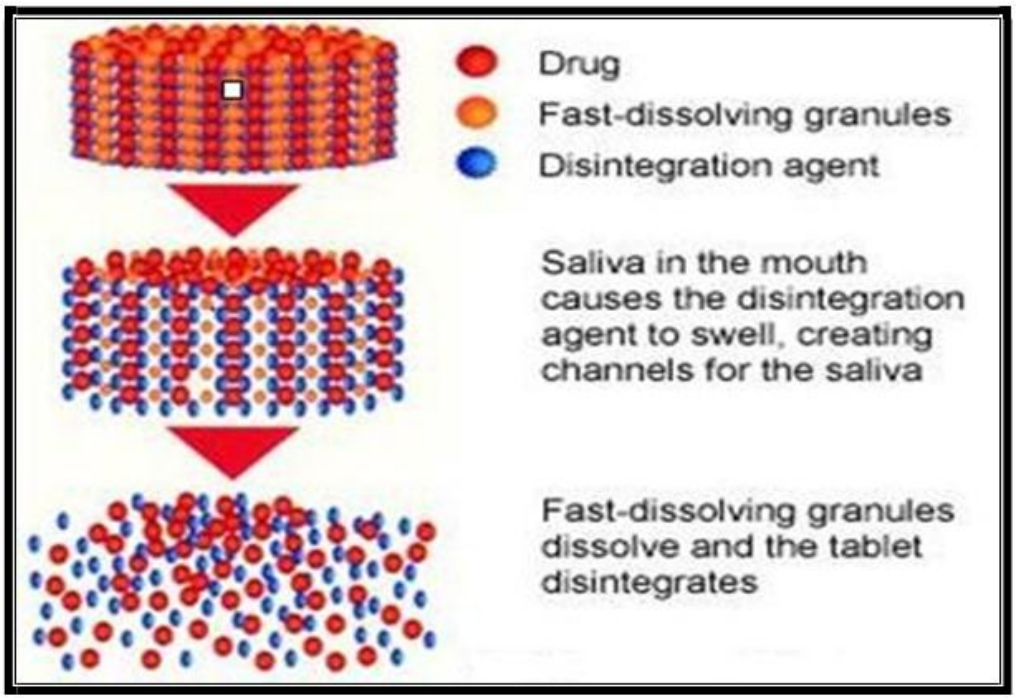


Fig. No. 1.4: Common steps in tablet disintegration.

1.3.1 Mechanism of tablet disintegration

The tablet breaks to primary particles by one or more of the mechanisms described below.

1.4.1.1 Disintegration by capillary Action.[10]

Disintegration by capillary action is always the first step. When tablets are placed in suitable aqueous medium, the medium penetrates into the tablet and replaces the air adsorbed on the particles, which weakens the intermolecular bond and breaks the tablet into fine particles. Water uptake by tablet depends upon hydrophilicity of the drug excipient and on tableting conditions. For disintegration by capillary action maintenance of porous structure and low interfacial tension towards aqueous fluid is necessary to help disintegration by creating a hydrophilic network around the drug particles.

1.4.1.2 Disintegration by heat of wetting (air expansion)[10]

When disintegrants with exothermic properties gets wetted, localized stress is generated due to capillary air expansion, which helps in disintegration of tablet. This explanation, however, is limited to only a few types of disintegrants and cannot describe the action of most modern disintegrating agents.

1.4.1.3 Disintegration due to disintegrating particle-particle repulsive forces[10]

Another mechanism of disintegration attempts to explain the swelling of tablet made with _non-swellable‘ disintegrants. Guyot-Hermann has proposed a particle repulsion theory based on the observation that nonswelling particle also cause disintegration of tablets. The electric repulsive forces between particles are the mechanism of disintegration and water is required for it. Researchers found that repulsion is secondary to wicking.

1.4.1.4 *Disintegration by Swelling*[10]

Perhaps the most widely accepted general mechanism of action for tablet disintegration is swelling Tablets with high porosity show poor disintegration due to lack of adequate swelling force. On the other hand, sufficient swelling force is exerted in the tablet with low porosity. It is worthwhile to note that if the packing fraction is very high, fluid is unable to penetrate in the tablet and disintegration is again slows down.

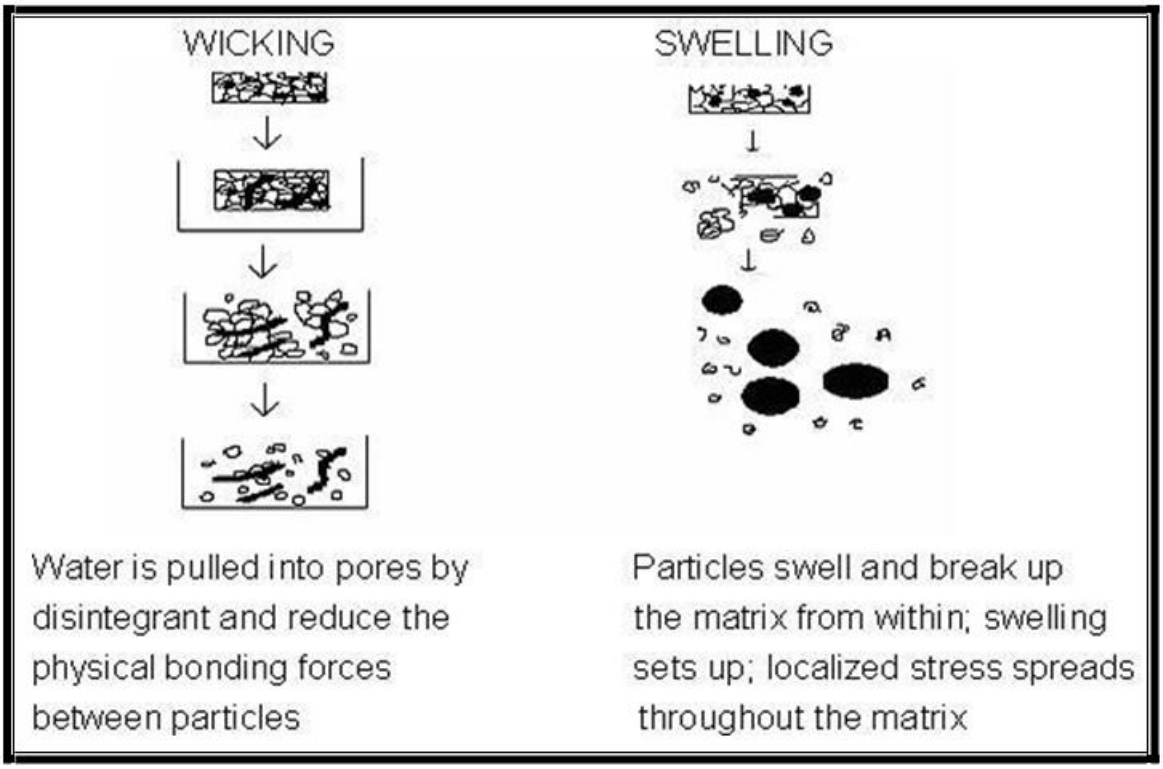


Fig. No 1.4.1.4: Disintegration of tablet by wicking and swelling

1.4.1.5 Disintegration due enzymatic reaction

Enzymes presents in the body could act as disintegrants. By destroying the binding action of binders some of the enzymes which act on the binders are listed in the Table1 shown below.

Table no. 1.4.1.5: List of enzymes and their use for the disintegration of tablets.

Enzymes	Binder
Amylase	Starch
Protease	Gelatin
Cellulose	Cellulose and its derivatives
Invertase	Sucrose

1.4.1.6 Disintegration due to deformation

Hess et al. had proved that during tablet compression, disintegrated particles get deformed and these deformed particles get into their normal structure when they come in contact with aqueous media or water. Occasionally, the swelling capacity of starch was improved when granules were extensively deformed during compression. This increase in size of the deformed particles produces a faster breakup of the tablet. This may be a mechanism of starch and has only recently begun to be studied.

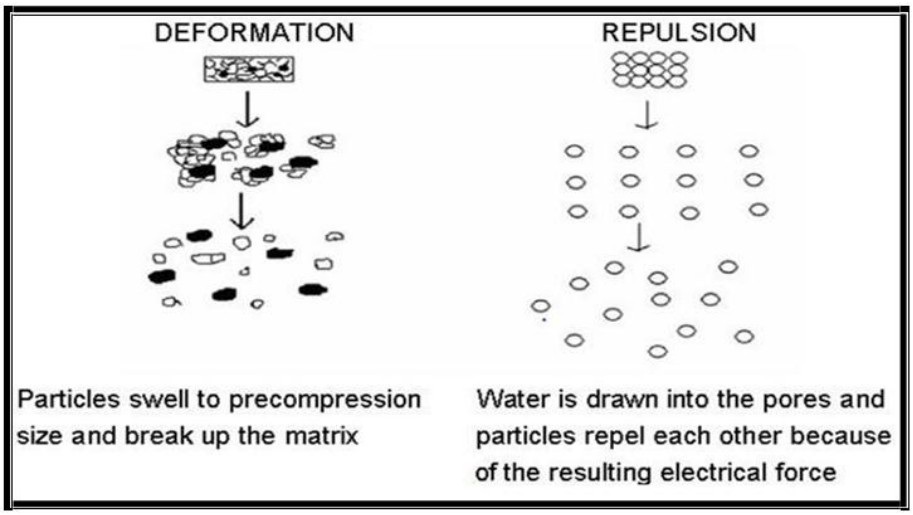


Fig. No. 1.4.1.6: Disintegration by deformation and repulsion.

1.4.1.7 *Disintegration due to release of gases*[10]

Carbon dioxide released within tablets on wetting due to interaction between bicarbonate or carbonate with citric acid or tartaric acid. The tablet disintegrates due to generation of pressure within the tablet. This effervescent mixture is used when it is desired to formulate very rapidly dissolving tablets or fast disintegrating tablet. As these disintegrants are highly sensitive to small changes in humidity level and temperature, strict control of environment is required during manufacturing of the tablets. The effervescent blend is either added immediately prior to compression or can be added in to two separate fraction of formulation.

Fig. No. 1.4.1.7: Release of gas during tablet disintegration.

1.5.Techniques For Preparing Orodispersible Tablets

Some of the techniques reported for the formulation of mouth ODTs are described below:

1.5.1. Freeze drying / lyophilisation.[11]

Freeze drying/ lyophilisation are the process in which water is sublimed from the product after it is frozen. This technique creates an amorphous porous structure that can dissolve rapidly. Briefly, the procedure involves dispersion of the active drug and aqueous solution of a carrier/polymer which is poured on the walls of preformed blister packs. The trays holding the blister packs are then passed through liquid nitrogen freezing tunnel to freeze the drug solution or dispersion. The frozen blister packs are next placed in refrigerated cabinets to continue the freeze-drying. After freeze-drying the aluminium foil backing is applied on a blister-sealing machine. Finally the blisters are packaged and shipped. The freeze-drying technique has demonstrated improved absorption and increase in bioavailability. The major disadvantages of lyophillization technique are that it is expensive and time consuming; fragility makes conventional packaging unsuitable for these products and poor stability under stressed conditions.

1.5.2 Tablet Moulding

Moulding process is of two kinds; solvent method and heat method. Solvent method involves moistening the powder blend with a hydro alcoholic solvent followed by compression at low pressures in moulded plates to form a wetted mass (compression moulding). The solvent is then removed by air-drying. The tablets manufactured in this manner are less compact than compressed tablets and posses a porous structure that hastens dissolution. The heat moulding process involves preparation of a suspension that contains a drug, agar and sugar (e.g. mannitol or lactose) and pouring the suspension in the blister packaging wells, solidifying the agar at the room temperature to form a jelly and drying at 30°C under vacuum. The mechanical strength of moulded tablets is a matter of great concern. Binding agents, which increase the mechanical strength of the tablets, need to be incorporated. Taste masking is an added problem to this technology.

The taste masked drug particles are prepared by spray congealing a molten mixture of hydrogenated cottonseed oil, sodium carbonate, lecithin, polyethylene glycol and an active ingredient into a lactose based tablet triturate form. Compared to the lyophillization technique, tablets produced by the moulding technique are easier to scale up for industrial manufacture.

1.5.3 Spray Drying[12]

In this technique, gelatin can be used as a supporting agent and as a matrix, mannitol as a bulking agent and sodium starch glycolate (SSG) or crosscarmellose sodium (CCS) or Crospovidone (CP) are used as superdisintegrants. Tablets manufactured from the spray-dried powder have been reported to disintegrate in less than 20 seconds in aqueous medium. The formulation contained bulking agent like mannitol and lactose, a superdisintegrant like SSG & CCS and acidic ingredient (citric acid) and/or alkaline ingredients (e.g. sodium bicarbonate). This spray-dried powder, which compressed into tablets showed rapid disintegration and enhanced dissolution.

1.5.4 Direct Compression

Direct compression represents the simplest and most cost effective tablet manufacturing technique. This technique can now be applied to preparation of ODT because of the availability of improved excipients especially superdisintegrants and sugar based excipients.

1.5.4.1 *Superdisintegrants*

Many orally disintegrating tablet technologies are based on direct compression, the addition of superdisintegrants principally affects the rate of disintegration and hence the dissolution. The presence of other formulation ingredients such as water-soluble excipients and effervescent agents further fastens the process of disintegration.

1.5.4.2 *Sugar Based Excipients*

This is another approach to manufacture ODT by direct compression. The use of sugar based excipients especially bulking agents like dextrose, fructose, isomalt, lactilol, maltilol, maltose, mannitol, sorbitol, starch hydrolysate, polydextrose and xylitol, which display high aqueous solubility and sweetness, and hence impart taste masking property and a pleasing mouth feel. Mizumito *et al.* have classified sugar-based excipients into two types on the basis of moulding and dissolution rate.

Type1 Saccharides (lactose & mannitol): low mouldability but high dissolution rate. Type2 Saccharides (maltose & maltilol): high mouldability and low dissolution rate.

1.5.5 Mass-Extrusion[13,14]

This technology involves softening the active blend using the solvent mixture of water-soluble polyethylene glycol and methanol and subsequent expulsion of softened mass through

the extruder or syringe to get a cylinder of the product into even segments using heated blade to form tablet. The dried cylinder can also be used to coat granules for bitter drugs and thereby achieve taste masking.

1.5.6 Cotton Candy Process

The flashdose is a mouth dissolving DDS (MDDDS) manufactured using Shearform technology in association with Ceform TI technology to eliminate the bitter taste of the medicament. The Shearform technology is employed in the preparation of a matrix known as _floss‘, made from a combination of excipients, either alone or with drugs. The floss is a fibrous material similar to cotton-candy fibers, commonly made of saccharides such as sucrose, dextrose, lactose and fructose at temperatures ranging between 180–266°F. However, other polysaccharides such as polymaltodextrins and polydextrose can be transformed into fibers at 30–40% lower temperature than sucrose.

This modification permits the safe incorporation of thermo labile drugs into the formulation. The tablets manufactured by this process are highly porous in nature and offer very pleasant mouth feel due to fast solubilization of sugars in presence of saliva.

1.5.7 Sublimation

To generate a porous matrix, volatile ingredients are incorporated in the formulation that is later subjected to a process of sublimation. Highly volatile ingredients like ammonium bicarbonate, ammonium carbonate, benzoic acid, camphor, naphthalene, urea, urethane and phthalic anhydride may be compressed along with other excipients into a tablet. This volatile material is then removed by sublimation leaving behind a highly porous matrix. Tablets manufactured by this technique have been reported to usually disintegrate in 10-20 sec. Even solvents like cyclohexane; benzene can be used as pore forming agents.

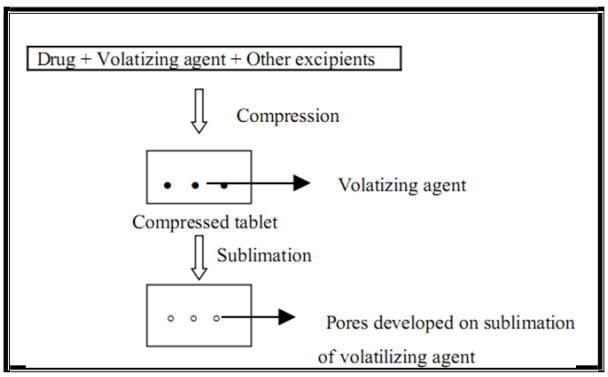


Fig. no. 1.5.6: Steps involved in manufacturing of ODTs by sublimation.

1.5.8 Nanonization

A recently developed Nanomelt technology involves reduction in the particle size of drug to nanosize by milling the drug using wet-milling technique. The nanocrystals of the drug are stabilized against agglomeration by surface adsorption on selected stabilizers, which are then incorporated into MDTs. This technique is especially advantageous for poorly water soluble drugs. Other advantages of this technology include fast disintegration/dissolution of nanoparticles leading to increased absorption and hence higher bioavailability and reduction in dose, cost effective manufacturing process, conventional packaging due to exceptional durability and wide range of doses (up to 200 mg of drug per unit).

1.5.9 Fast Dissolving Films

It is a new frontier in MDDDS that provides a very convenient means of taking medications and supplements. In this technique, a non-aqueous solution is prepared containing water soluble film forming polymer (pullulan, carboxy methylcellulose, hydroxypropyl methylcellulose, hydroxyl ethylcellulose, hydroxyl propylcellulose, polyvinyl pyrrolidone, polyvinyl alcohol or sodium alginate, etc.), drug and other taste masking ingredients, which is allowed to form a film after evaporation of solvent. In case of a bitter drug, resin adsorbate or coated microparticles of the drug can be incorporated into the film. This film, when placed in mouth, melts or dissolves rapidly, releasing the drug in solution or suspension form. The features of this system include paper thin films of size less than 2X2 inches, dissolution in 5 sec, instant drug delivery and flavoured after taste.[6]

1.6 Patented Technologies For Orodispersible Tablets

1.6.1 Zydis Technology.[15]

Zydis formulation is a unique freeze dried tablet in which drug is physically entrapped or dissolved within the matrix of fast dissolving carrier material. When zydis units are put into the mouth, the freeze-dried structure disintegrates instantaneously and does not require water to aid swallowing. The zydis matrix is composed of many material designed to achieve a number of objectives. To impart strength and resilience during handling, polymers such as gelatin, dextran or alginates are incorporated. These form a glossy amorphous structure, which imparts strength. To obtain crystallinity, elegance and hardness, saccharides such as mannitol or sorbitol are incorporated. Water is used in the manufacturing process to ensure production of porous units to achieve rapid disintegration while various gums are used to prevent sedimentation of dispersed drug particles in the manufacturing process. Collapse

protectants such as glycine prevent the shrinkage of zydis units during freeze-drying process or long-term storage. Zydis products are packed in blister packs to protect the formulation from moisture in the environment.

1.6.2 Durasolv Technology. [16,17]

Durasolv is the patented technology of Cima labs. The tablets made by this technology consist of drug, filler and a lubricant. Tablets are prepared by using conventional tabletting equipment and have good rigidity. These can be packaged into conventional packaging system like blisters. Durasolv is an appropriate technology for product requiring low amounts of active ingredients.

1.6.3 Orasolv Technology.[18]

CIMA labs have also developed Orasolv Technology. In this system active medicament is taste masked. It also contains effervescent disintegrating agent. Tablets are made by direct compression technique at low compression force in order to minimize oral dissolution time. Conventional blenders and tablet machine are used to produce the tablets. The tablets produced are soft and friable.

1.6.4 Flash Dose Technology.[19]

Flash dose technology has been patented by Fuisz Nurofen meltlet, a new form of ibuprofen as melt in mouth tablets (MIM) prepared using flash dose technology is the first commercial product launched by Biovail Corporation. Flash dose tablets consist of self-binding shear form matrix termed as –floss. Shear form matrices are prepared by flash heat processing.

1.6.5 Wow tab Technology.[20]

Wow tab technology is patented by Yamanouchi Pharmaceutical Co. WOW means—Without Water. In this Process, combination of low mouldability saccharides and high mouldability saccharides is used to obtain a rapidly melting strong tablet. The active ingredient is mixed with a low mouldability saccharide (eg lactose, glucose, and mannitol) and granulated with a high mouldability saccharide (eg Maltose, oligosaccharides) and compressed into tablets.[11]

1.6.6 Flash tab Technology.[19,20]

Prographarm laboratories have patented the Flash tab technology. Tablet prepared by this system consists of an active ingredient in the form of micro crystals. Drug micro granules may be prepared by using the conventional techniques like coacervation, micro encapsulation

and extrusion spheronisation. All the processing, utilized conventional tabletting technology.

Table 1.6: Marketed products along with the technology used, their inventors and the active ingredients present.

Patent Technology	Basis of Technology	Technology developed by Company	Active Ingredient (Brand Name)
Zydia	Lyophilization	R.P.Scherer. inc	Loratidine
Quicksolv	Lyophilization	Janssen Pharmaceutics	Risperidone
Lyoc	Lyophilization	Farmalyoc	Phloroglucinol Hydrate
Flashtab	Direct compression	Ethypharm	Ibuprofen
Orasolv	Direct compression	Cima Labs, Inc.	Paracetamol
Durasolv	Direct compression	Cima Labs, Inc	Zolmitriptan
Wowtab	Direct compression	Yamanouchi Pharma	Famotidine
Ziplets	DC Microcaps	Eurand International	Ibuprofen
Advatab	Diffuscap CR Tech.	Eurand International	Cetrizine
Flashdose	Cotton Candy	Fuisz Technology	Tramadol hydrochloride
Oraquick	Micromask taste masking	KV Pharm	Hyoscyamine Sulfate

1.7. Future Perspective

With continued innovations in pharmaceutical excipients, one can expect the emergence of more novel technologies for MDTs in the days to come. These innovations may involve modifying formulation composition and processing to achieve new performance end-points or the merger of new technological advances with traditional pharmaceutical processing techniques for the production of novel mouth dissolving dosage forms. It is reasonable to expect that future trends in innovations of drug delivery systems will continue to bring together different technological disciplines to create novel technologies.[5]

Proton Pump Inhibitors And Their Mechanism of Action

The term acid-peptic disorder encompasses a variety of relatively specific medical conditions in which injuries by gastric acid (and activated pepsin) is thought to play an important role. These disorders include gastroesophageal reflux disease (GERD), benign–pepticulcers of the stomach and duodenum, ulcers secondary to the use of conventional non-steroidal anti-inflammatory drugs (NSAIDs), and ulcers due to rare Zollinger-Ellison syndrome. It appears

that exposure of the involved tissue of acid is essential to the development of clinical symptoms in most instances of these diseases. Control of acidity is therefore a cornerstone of therapy in these disorders, even though this approach may not address the fundamental pathophysiological process.

Mankind has lived with peptic ulcers since ancient times. Perhaps the first description of this malady is the one inscribed on the pillars of the temple of Aesculapius of Epidaurus from around the fourth century B.C.: ―A man with an ulcer in his stomach. He incubated and saw a vision: the god seemed to order his followers to seize and hold him, that he might incise his stomach. So he fled, but they caught and tied him to the doorknocker. Then Asklepios opened his stomach, cut out the ulcer, sewed him again, and loosed his bonds.‖ Many prominent people have suffered from indigestion and ulcers, including the Roman emperor Marcus Aurtlius, whose death has been attributed by some to a perforated ulcer and whose physician was none other than Galen himself. Acid neutralization was recognised as effective treatment more than 12 centuries ago by Paulus Aeginata, who prescribed a mixture of Samian and Lemnian earths and milk, not unlike the milk- antacid regimens of the need twentieth century.

Since then, considerable advances in understanding the pathogenesis and treatment of acid-peptic conditions have occurred, culminating in the discovery of Helicobacter pylori (H. Pylori) and PPIs. We now know that eradication of H. Pylori effectively promotes healing of peptic ulcers and prevents their recurrence in most cases. PPIs have become the drugs of choice in prompting healing from erosive esophagitis and peptic ulcer because of their ability to nearly completely suppress acid production.[21]

In 1977 George Sachs & John Forte discovered the ―Proton pump‖ in the human body. After a lot of efforts in 1982 the first published clinical study was on omeprazole. PPIs were approved for prescription in 1989.[21]PPIs are widely used for treating acid- induced inflammation, ulcers of the stomach and duodenum, GERD, erosive esophagitis, heartburn, upper gastrointestinal bleeding in critically ill patients, and Zollinger-Ellison Syndrome. They are also used in combination with antibiotics for eradicating H. pylori infection of the stomach.[22]

PPIs are the most potent suppressors of gastric acid secretion are inhibitors of the gastric H^+,K^+-ATPase proton pump. In typical doses, these drugs diminish the daily production of acid (basal and stimulated) by 80% to 95%. Five PPIs are available for clinical use:

Omeprazole and its S-isomer, Esomeprazole, Lansoprazole, Rabeprazole and Pantoprazole. These drugs have different substitutions on their pyridine and/or benzimidazole groups but are remarkably similar in their pharmacological properties.

1.8.1 Chemistry

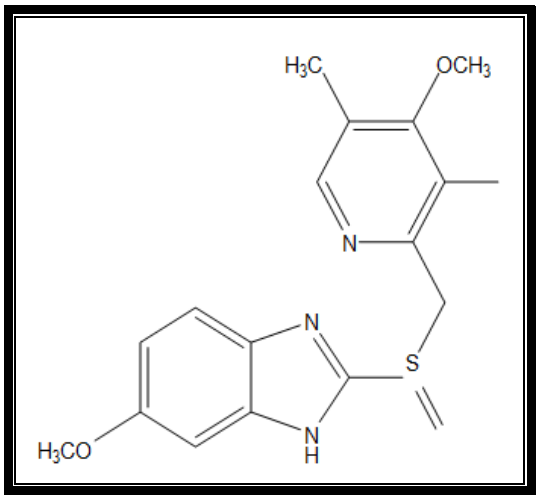


Fig No. 1.8.1.1: Structure of Omeprazole.

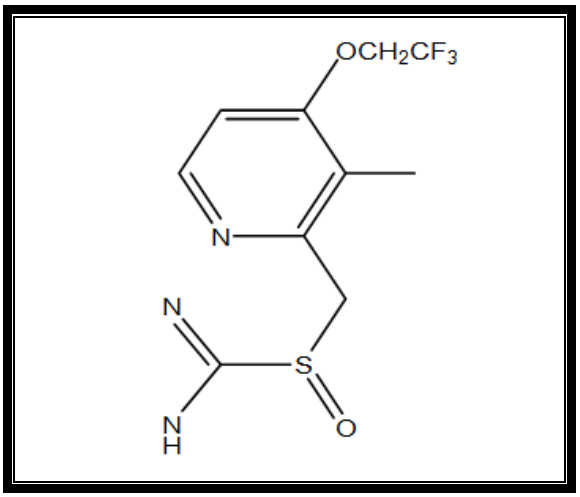


Fig. No. 1.8.1.2: Structure of Lansoprazole.

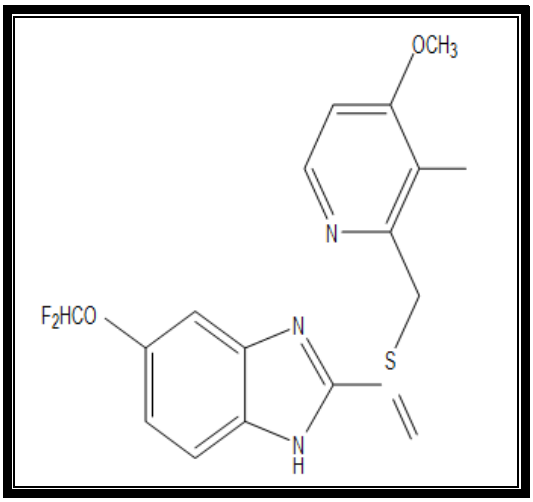


Fig. No.1.8.1.3 Structure of Pantoprazole.

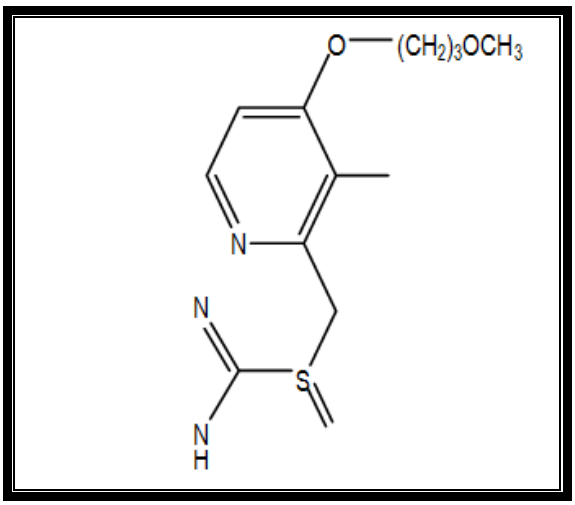


Fig. No. 1.8.1.3: Structure ofRabeprazole.

Omeprazole is a racemic mixture of R- and S-isomers; the S-isomer, esomeprazole (S-omeprazole), is eliminated less rapidly than R-omeprazole, which theoretically provides a therapeutic advantage because of the increased half-life. Despite claims to the contrary, all PPIs have equivalent efficacy at comparable doses.[22]

Pantoprazole 5-(difluromethoxy)-2-[[(3,4-dimethoxy-2-pyridinyl) methyl] sulfinyl] -1 *H*-benzimidazole, Omeprazole 5-methoxy-2-(((4-methoxy-3,5-dimethyl-2- pyridinyl) methyl) sulfinyl)-1*H*-benzimidazole) A molecule with benzimidazole.

Substitution exhibits potent and long-lasting inhibition of gastric acid secretion by selectively interacting with the gastric proton pump (K /H -ATPase) in the parietal cell secretory membrane.[23]

1.8.1 Stomach

The stomach is typically a J-shaped enlargement of the GIT directly inferior to the diaphragm in the epigastric, umbilical, and left hypochondriac regions of the abdomen. The stomach connects the esophagus to the duodenum, the first part of the small intestine.[24]

1.8.1.1 Anatomy of the Stomach

The stomach has four main regions: the cardia, fundus, body, and pylorus. The Cardia (CAR-dē-a) surrounds the superior opening of the stomach. The rounded portion superior to the left of the cardia is the fundus (FUN-dus) inferior to the fundus is the larger central portion of the stomach, called the body. The region of the stomach that connects to the duodenum is the pylorus (pī-LOR-us; *pyl-*= gate; *-orus*=guard); it has two parts, the pyloric antrum (AN-trum =cave), which is connects to the body of the stomach, and the pyloric canal, which leads into duodenum. When the stomach is empty, the mucosa lies in large folds, called rugae (ROO-gē = wrinkles), that can be seen with unaided eye. The pylorus communicates with the duodenum of the small intestine via a sphincter called pyloric sphinter. The concave medial border of the stomach is called the lesser curvature, and the convex lateral border is called the greater curvature.[24]

1.8.1.2 *Histology of the Stomach*

The stomach wall is composed of the same four basic layers as the rest of the GIT, with certain modifications. The surface of the mucosa is a layer of simple columnar epithelial cells called surface mucous cells. The mucosa contains a laminal propria (areolar connective tissue) and muscularis mucosae (smooth muscle). Epithelial cells extend down into the lamina propria. Where they form columns of secretory cells called gastric glands that line many narrow channels called gastric pits. Secretions from seeral gastric glands flow into each gastric pit and then into the lumen of the stomach.[24]

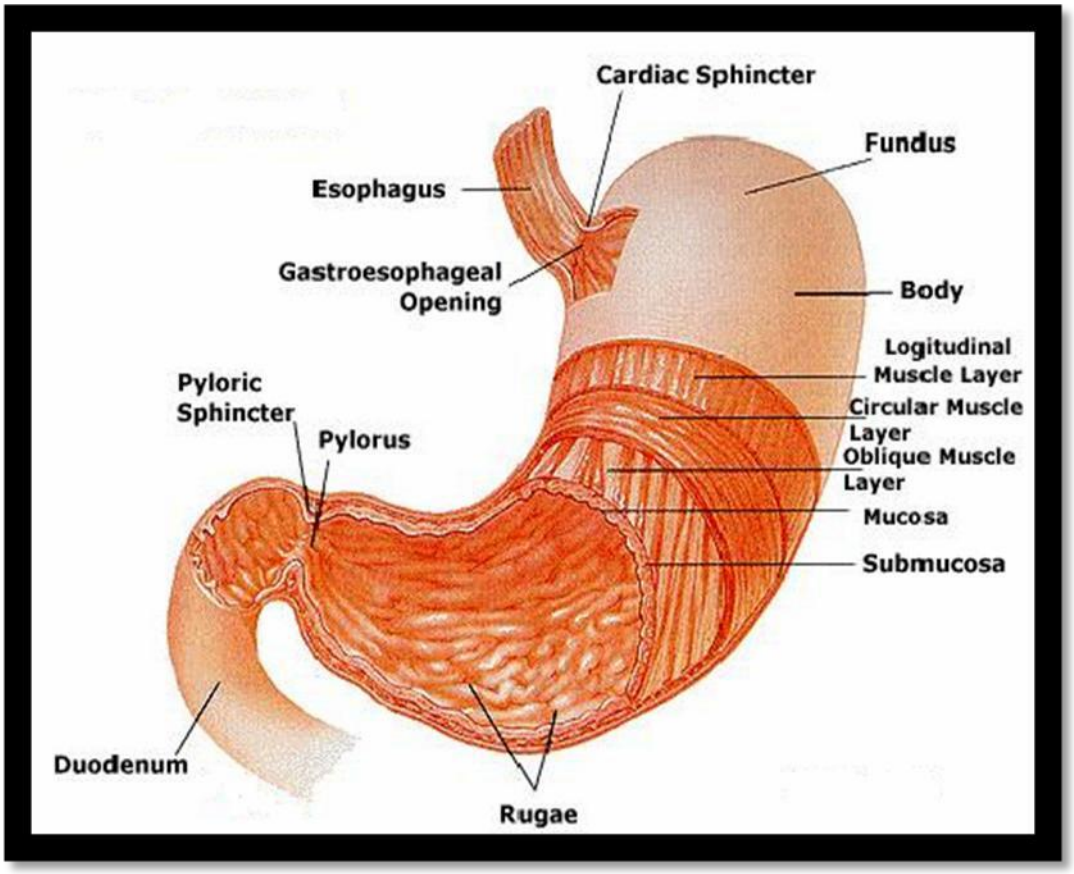


Fig. No. 1.8.2: Anatomy and physiology of stomach.

The gastric glands contain three types of *exocrine gland cells* that secrete their products into the stomach lume; mucous neck cells, cheif cells, and parietal cells, both surface mucous cells and mucous neck cells secrete mucus. Parietal cells produce intrinsic factor, which is needed for absorption of vitamin $B_{12,}$ and hydrochloric acid. The chief cells secrete pepsinogen and gastric lipase. The secretions of the mucous, parietal, and chief cells form gastric juice, which totals 2000-3000 ml/day. In addition, gastric glands include a type of enteroendocrine cells, the G cell, which is located mainly in the pyloric antrum and secretes the hormone gastrin into the bloodstream.[24]

1.8.1.3 *Mechanical and Chemical Digestion in the Stomach*

Parietal cells secrete hydrogen ions (H^+) and chloride ions (Cl^-) separately into the stomach lumen, the net effect are secretion of hydrochloric acid (HCl). Proton pumps powered by H^+/K^+ ATPases actively transport H^+ into the lumen while bringing potassium ions (K^+) into the cell. At the same time Cl^- and K^+ diffuse out through Cl^- and K^+ channels in the apical membrane. The enzyme *carbonic anhydrase,* which is especially plentiful in parietal cells, catalyzes the formation of carbonic acid (H_2CO_3) from water (H_2O) and carbon dioxide

(CO_2). As carbonic acid dissociates, it provides a ready source of H^+ for the proton pumps but also generates bicarbonate ions (HCO_3^-). As HCO_3^- builds up in the cytosol, it exits the parietal cell in exchange for Cl^- via Cl^-/HCO_3^- antiporters in the basolateral membrane. HCO_3^- diffuses into nearby blood capillaries. This –alkaline tide| of bicarbonate ions entering the bloodstream after a meal may be large enough to slightly elevate blood pH and make urine more alkaline.

The strongly acidic fluid of the stomach kills many microbes in food, and HCl partially denatures (unfolds) proteins in food and stimulates the secretion of hormones that promote the flow of bile and pancreatic juice. Enzymatic digestion of proteins also begins in the stomach. The only proteolytic (protein-digesting) enzyme in the stomach is pepsin, which is secreted by chief cells. Because pepsin breaks certain peptide bonds between the amino acids making up proteins, a protein chain of many amino acid are broken down into smaller peptide fragments. Pepsin is most effective in the very acidic environment of the stomach (pH 2); it becomes inactive at higher pH.[23]

1.8.1.4 Physiology of gastric secretion

Gastric acid secretion is a complex, continuous process in which multiple central and peripheral factors contribute to a common endpoint: the secretion of H^+ by parietal cells. Neuronal (acetylcholine, ACh), paracrine (histamine), and endocrine (gastrin) factors all regulate acid secretion. Their specific receptors (M_3, H_2, and CCK_2 receptors, respectively) are on the basolateral membrane of parietal cells in the body and fundus of the stomach. The H_2 receptor is a GPCR that activates the G_s-adenylylcyclase-cyclic AMP-PKA pathway. ACh and gastrin signal through GPCRs that couple to the G_q-PLC- IP_3-Ca^{2+} pathway in parietal cells. In parietal cells, the cyclic AMP and the Ca^{2+}- dependent pathways activate H^+,K^+-ATPase (the proton pump), which exchanges hydrogen and potassium ions across the parietal cell membrane. This pump generates the largest known ion gradient in vertebrates, with an intracellular pH of about 7.3 and an intracanalicular pH of about 0.8.

The most important structures for CNS stimulation of gastric acid secretion are the dorsal motor nucleus of the vagal nerve, the hypothalamus, and the solitary tract nucleus. Efferent fibers originating in the dorsal motor nuclei descend to the stomach *via* the vagus nerve and synapse with ganglion cells of the enteric nervous system. ACh released from postganglionic vagal fibers directly stimulates gastric acid secretion through muscarinic M_3 receptors on the basolateral membrane of parietal cells. The CNS predominantly modulates the activity of the

enteric nervous system *via* ACh, stimulating gastric acid secretion in response to the sight, smell, taste, or anticipation of food (the "cephalic" phase of acid secretion). ACh also indirectly affects parietal cells by increasing the release of histamine from the enterochromaffin-like (ECL) cells in the fundus of the stomach and of gastrin from G cells in the gastric antrum.

ECL cells, the source of gastric histamine secretion, usually are in close proximity to parietal cells. Histamine acts as a paracrine mediator, diffusing from its site of release to nearby parietal cells, where it activates H_2 receptors. The critical role of histamine in gastric acid secretion is dramatically demonstrated by the efficacy of H_2-receptor antagonists in decreasing gastric acid secretion.[21]

Gastrin, which is produced by antral G cells, is the most potent inducer of acid secretion. Multiple pathways stimulate gastrin release, including CNS activation, local distention, and chemical components of the gastric contents. Gastrin stimulates acid secretion indirectly by inducing the release of histamine by ECL cells; a direct effect on parietal cells also plays a lesser role.[21]

Somatostatin (SST), which is produced by antral D cells, inhibits gastric acid secretion. Acidification of the gastric luminal pH to <3 stimulates SST release, which in turn suppresses gastrin release in a negative feedback loop. SST-producing cells are decreased in patients with *H. pylori* infection, and the consequent reduction of SST's inhibitory effect may contribute to excess gastrin production.[21]

1.9 Mode of Action

PPIs are prodrugs that require activation in an acid environment. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and accumulates in the acidic secretory canaliculi. Here, it is activated by proton- catalyzed formation of a tetracyclic sulfenamide trapping the drug so that it cannot diffuse back across the canalicular membrane.[21]

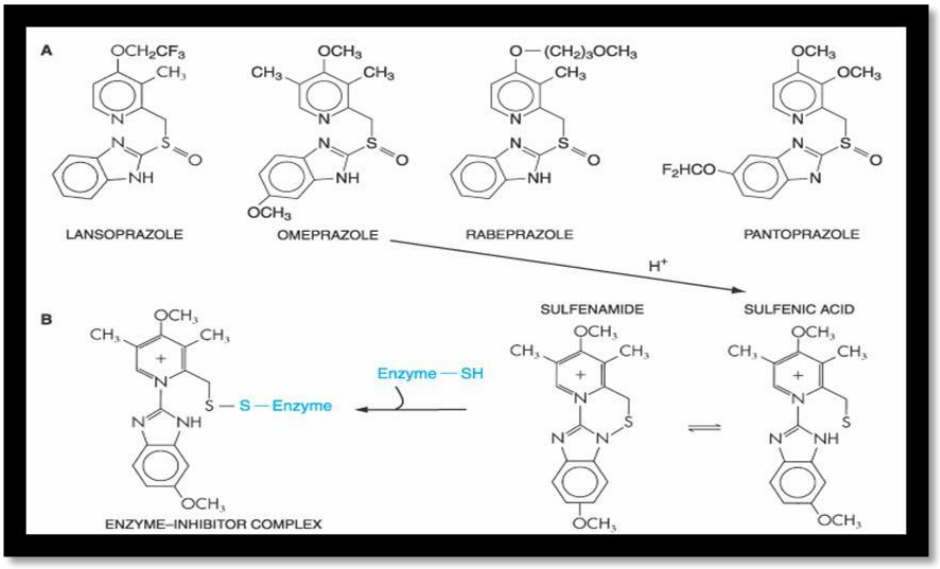


Fig no. 1.9a: A Inhibition of Gastric H^+/K^+-ATPase proton pump.

B- Conversion of Omeprazole to a sulfenamide in the acidic secretory canaliculi of the Parietal cell.

The activated form then binds covalently with sulfhydryl groups of cysteines in the H^+/K^+-ATPase, irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24- to 48-hour) suppression of acid secretion, despite the much shorter plasma half-lives (0.5 to 2 hours) of the parent compounds. Because they block the final step in acid production, the PPIs are effective in acid suppression regardless of other stimulating factors.[21]

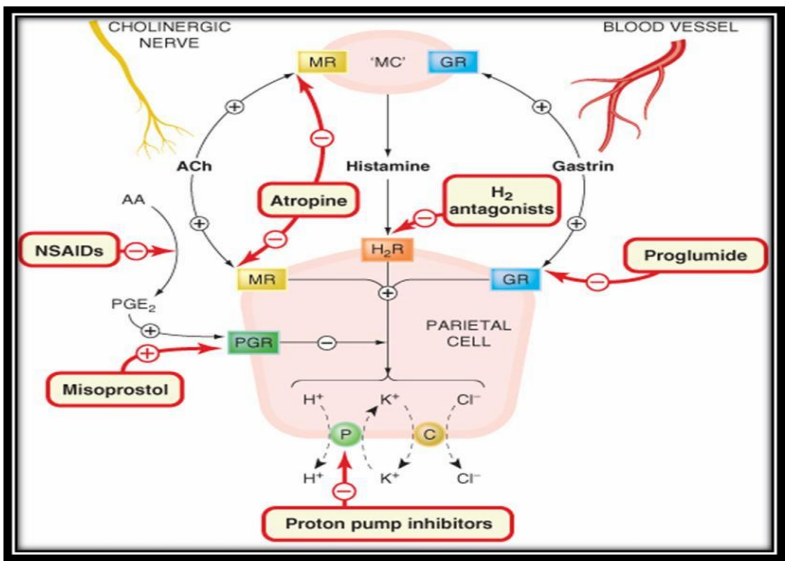


Fig. no. 1.9b: Mode of action of Proton Pump Inhibitors.

1.10 The Rapeutic Uses

1.10.1 Duodenal Ulcer.[25]

The recommended adult dose Of PPIs for the oral treatment of duodenal ulcer is 40 mg as PPIs are given once daily in the morning. Healing usually occurs within 2 weeks. For patients not healed after this initial course of therapy, an additional course of 2 weeks is recommended.

1.10.2 Gastric Ulcer

The recommended adult oral dose of PPIs for the oral treatment of gastric ulcer is 40 mg given once daily in the morning. Healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional course of 4 weeks is recommended.

1.10.3 Helicobacter Pylori Associated Duodenal Ulcer [25]

PPIs/Clarithromycin/Metronidazole Triple Combination Therapy: The recommended dose for H. pylori eradication is treatment for seven days with PPIs 40 mg together with clarithromycin 500 mg and metronidazole 500 mg, all twice daily.

PPIs/Clarithromycin/Amoxicillin Triple Combination Therapy: The recommended dose for H. pylori eradication is treatment for seven days with PPIs 40 mg together with clarithromycin 500 mg and amoxicillin 1000 mg, all twice daily.

1.10.4 Symptomatic Gastroesophegal reflux Disease[25]

The recommended adult oral dose for the treatment of symptoms of GERD, including heartburn and regurgitation, is 40 mg once daily for up to 4 weeks. If significant symptom relief is not obtained in 4 weeks, further investigation is required.

1.10.5 Reflux Esophagitis.[25]

The recommended adult oral dose of PPIs is 40 mg, given once daily in the morning. In most patients, healing usually occurs within 4 weeks. For patients not healed after this initial course of therapy, an additional 4 weeks of treatment is recommended.

For the prevention of relapse in patients with reflux esophagitis, the recommended adult oral dose is 20 mg PPIs are given once daily in the morning and the dose is increased to 40 mg once daily in the morning in the case of recurrence.

1.10.6 Pharmacokinetics of Proton pump inhibitor.[21]

Since an acidic pH in the parietal cell acid canaliculi is required for drug activation, and since food stimulates acid production, these drugs ideally should be given about 30 mins before meals. Concurrent administration of food may reduce somewhat the rate of absorption of PPIs, but this effect is not thought to be clinically significant. Concomitant use of other drugs that inhibit acid secretion, such as H_2-receptor antagonists, might be predicted to lessen the effectiveness of the PPIs, but the clinical relevance of this potential interaction is unknown.

1.10.7 Absorption and Distribution

PPIs are absorbed rapidly in both rat and dog. Peak plasma levels are attained within 15 to 20 mins in the rat and after about 1 hour in the dog. Oral bioavailability is 33% in the rat and 49 % in the dog. Following absorption, autoradiography and quantitative tissue distribution experiments have shown that PPIs get rapidly distributed to extra vascular sites. Following administration of PPIs, distribution of radioactivity in the blood and most organs is found to be uniform initially. After 16 hours, radiolabelled PPIs are predominantly detected in the stomach wall. After 48 hours, the entire administered radioactivity is found to have been excreted. Penetration of the blood-brain barrier by radiolabelled PPIs is very low. Protein binding in the rat and dog is 95% and 86%, respectively.[26]

1.10.8 Metabolism

PPIs get readily bound to serum proteins (98%) and almost completely metabolized in the liver. Renal elimination represents the major route of excretion (about 82%) for the metabolites of PPIs. If we consider pantoprazole for e.g. the main metabolite of pantoprazole sodium in both the serum and urine is desmethylpantoprazole as a sulphate conjugate. The half-life of the main metabolite (about 1.5 hours) is not much longer than that of pantoprazole sodium (approximately 1 hour).Once in the small bowel, PPIs are rapidly absorbed, highly protein bound, and extensively metabolized by hepatic CYPs, particularly CYP2C19 and CYP3A4. Several variants of CYP2C19 have been identified. Asians are more likely than Caucasians or African-Americans to have the CYP2C19 genotype that correlates with slow metabolism of Pantoprazole (23% *vs.* 3%, respectively), which has been suggested to contribute to heightened efficacy and/or toxicity in this ethnic group. Although the CYP2C19 genotype is correlated with the magnitude of gastric acid suppression by Pantoprazole in patients with gastroesophageal reflux disease, there is no evidence that the CYP2C19 genotype predicts clinical efficacy of these.[26]

Because not all pumps or all parietal cells are active simultaneously, maximal suppression of acid secretion requires several doses of the PPIs. For example, it may take 2 to 5 days of therapy with once-daily dosing to achieve the 70% inhibition of proton pumps that is seen at steady state. More frequent initial dosing (*e.g.*, twice daily) will reduce the time to achieve full inhibition but is not proven to improve patient outcome. Since the proton pump inhibition is irreversible, acid secretion will be suppressed for 24 to 48 hours, or more, until new proton pumps are synthesized and incorporated into the luminal membrane of parietal cells.[21]

Pantoprazole sodium alone is absorbed rapidly following administration of a 40 mg enteric coated tablet. Its oral bioavailability compared to the i.v. dosage form is 77% and does not change upon multiple dosing. Following an oral dose of 40 mg, C_{max} is approximately 2.5mg/mL with a t_{max} of 2 to 3 h. The AUC is approximately 5 mgh/L. Pantoprazole sodium shows linear pharmacokinetics after both i.v. and oral administration. Therefore, elimination half-life, clearance and volume of distribution are independent of the dose. Concomitant intake of food has no influence on the bioavailability of pantoprazole sodium. Chronic renal failure does not lead to drug accumulation with once-a-day dosing of the PPIs. Hepatic disease substantially reduces the clearance of esomeprazole and lansoprazole. Thus, in patients with severe hepatic disease, dose reduction is recommended for esomeprazole and should be considered for lansoprazole.[25]

1.11 Need For The Development of Orodispersible Tablets

To prevent degradation of PPIs by acid in the gastric lumen, oral dosage forms are mostly supplied in different formulations: (1) enteric-coated drugs contained inside gelatin capsules (omeprazole, esomeprazole, and lansoprazole); (2) enteric-coated granules supplied as a powder for suspension (lansoprazole); (3) enteric-coated tablets (pantoprazole, rabeprazole, and omeprazole. The delayed-release and enteric-coated tablets dissolve only at alkaline pH substantially improve the oral bioavailability of these acid-labile drugs.

Until recently, the requirement for enteric coating posed a challenge to the administration of PPIs in patients for whom the oral route of administration is not available. These patients and those requiring immediate acid suppression now can be treated powdered drug combined with sodium bicarbonate (pantoprazole) which has less patient compliance then tablet formulation or parenterally with pantoprazole or lansoprazole, both of which are approved for intravenous administration in the United States. An intravenous formulation of esomeprazole is available in Europe but not in the United States. Thus an orodispersible tablet is a need to

be developed which increases the patient compliance by many folds.

1. OBJECTIVE

The purpose of this research is to prepare ODTs consisting of superdisintegrnts and PPIs by direct compression method and to evaluate their quick disintegration and immediate release properties. The effect of various formulations and process variables on the particle morphology, micromeritics properties, *in- vitro* release behaviour, etc. Pantoprazole will be used as a representative drug for the PPI in this research project. Methods used for Pantoprazole will be equally applicable to other PPIs.

2.1 Objectives of The Present Research Work

1. Fabrication of Pantoprazole loaded ODTs as immediate releasing DDS employing superdisintegrating agents and bicarbonates.
2. Increase in stability which is achieved by incorporation of the bicarbonates for increasing the stability of the drug.
3. To make available most of the drug at the site of action thus higher suppression of acid secretion.
4. To increase patient convenience and compliance.
5. To compare the various formulations using different excipients and choosing the best formulation as per ICH guidelines.
6. Characterized of the incompatibilities by FTIR.
7. Estimated the drug concentration in the prepared formulations.
8. Calculate the disintegration time of various formulations.
9. Evaluated the ODTs by *in vitro* dissolution and the mechanism of release/dissolved.
10. Stability studies were conducted for the optimized formulations.

2.2 Why Only Ppis

- PPIs are the most potent suppressors of gastric acid secretion thus inhibiting the gastric H^+/K^+-ATPase (PP). In typical doses, these drugs diminish the daily production of acid (basal and stimulated) by 80% to 95%.
- They are the drugs of choice for the treatment of various gastro intestinal disorders.
- Administration of conventional tablets of PPIs has been reported to exhibit longer lag time as they are enteric coated and fluctuations in the plasma drug levels, resulting either in reduction in drug conc. in the blood.
- Administration of conventional tablets of PPIs does not let the accumulation of the drug

at the site of action thus instant relief is not achieved; fast dissolution and absorption of the drug which will result quick onset of action and accumulation of PPI at the site of action.

- Dose of PPIs is less so it is a potent candidate for ODTs.
- Most elderly patients, children, and patients with dysphagia have difficulty in swallowing conventional tablets and hard gelatin capsules, and therefore do not take medication as prescribed by physicians. It is estimated that 35% of the general population, 30 to 40% of elderly nursing home patients, and 25 to 50% of patients hospitalized for acute neuromuscular disorders and head injuries have dysphagia will be benefited by this invention.

2. Review of Literature

Jungnickle PW. reviews the pharmacology, clinical efficacy, and tolerability of pantoprazole in comparison with those of other available PPIs. Like other PPIs, pantoprazole exerts its pharmacodynamic actions by binding to the proton pump (H^+/K^+-adenosine triphosphatase) in the parietal cells but, compared with other PPIs, its binding may be more specific for the proton pump. Pantoprazole is well absorbed when administered as an enteric-coated, delayed-release tablets, it was hepatically metabolized via cytochrome P2C19 to hydroxyl pantoprazole, an inactive metabolite that subsequently undergoes sulfate conjugation. The elimination half-life ranges from 0.9 to 1.9 hours was found to be independent of dose. Pantoprazole has similar efficacy to other PPIs in the healing of gastric and duodenal ulcers, as well as erosive esophagitis, and as part of triple-drug regimens for the eradication of Helicobacter pylori from the gastric mucosa. It is well tolerated, with the most common adverse effects being headache, diarrhea, flatulence, and abdominal pain. In clinical studies, it has been shown to have no interactions with various other agents, including carbamazepine, cisapride, cyclosporine, digoxin, phenytoin, theophylline, and warfarin.[27]

Bell W, Staar U. *et al* studied the action of the H^+/K^+ -ATPase inhibitors such as pantoprazole and omeprazole by comparing then in different *in vitro* test systems. In a gastric membrane vesicle under conditions it shows acidification of the vesicle interior, pantoprazole and omeprazole inhibited H^+/K^+-ATPase activity. Their study showed that both drugs inhibited, with similar potency, papain activity at pH 3.0 inactivated the enzyme in a similar time-dependent manner; at pH 5.0 omeprazole was more potent than pantoprazole and enzyme inhibition was faster than with pantoprazole. The results indicate that pantoprazole is

a potent inhibitor of H^+/K^+-ATPase under highly acidic conditions and that it is more stable than omeprazole at a slightly acidic pH such as pH 5.0.[28]

Li XQ. *et al.* compared the potency and specificity of the currently used PPIs, omeprazole, esomeprazole, lansoprazole, pantoprazole, and rabeprazole, as inhibitors of four cytochrome P450 enzymes (CYP2C9, 2C19, 2D6, and 3A4), they performed *in vitro* studies using human liver microsomal preparations and recombinant CYP2C19. They did the sample analysis using selected reaction monitoring liquid chromatography/tandem mass spectometry. With several systems for CYP2C19 activity (two marker reactions, S- mephenytoin 4-hydroxylation and R-omeprazole 5-hydroxylation, tested in either human liver microsomes or recombinant CYP2C19), the five PPIs showed competitive inhibition of CYP2C19 activity for lansoprazole, omeprazole, esomeprazole, pantoprazole, and rabeprazole. Their data suggest that, although the inhibitory profiles of the five studied PPIs were similar, lansoprazole and pantoprazole are the most potent *in vitro* inhibitors of CYP2C19 and CYP2C9, respectively. Esomeprazole showed less inhibitory potency compared with omeprazole and it‘s R-enantiomer. The inhibitory potency of rabeprazole was relatively lower than the other PPIs, but its thioether analog showed potent inhibition on the P450 enzymes investigated, which may be clinically significant.[29]

Tutuian R. *et al.* evaluated the effect of once-daily doses of pantoprazole, 10, 20 and 40 mg, on gastric acidity in healthy volunteers. They selected thirty-six subjects which received pantoprazole in a three-way crossover design study. Ambulatory 24-h intragastric pH and distal oesophageal pH were monitored at baseline and on the last day of each treatment period. The measured endpoints were the median intragastric and oesophageal pH, the percentage of time the intragastric pH < 4 and oesophageal pH < 4 and the area under the curve for gastric acidity over 24 h. Safety was evaluated by incidence and severity of adverse events. In conclusion, pantoprazole demonstrates a dose-related effect in the range 10–40 mg once daily. The once-daily dose of 40 mg provides the highest and most consistent control of gastric pH, especially at night.[30]

Raghunath AS. *et al.* reviewed the available preclinical and clinical studies comparing esomeprazole with lansoprazole in the healing and maintenance of erosive esophagitis, and to compare the budgeting impact of the 2 strategies. Comparative tolerability was also reviewed. The search terms used were gastroesophageal reflux disease, reflux esophagitis, and proton pump inhibitor; all comparisons of esomeprazole and lansoprazole at any dose were

considered. The comparative studies that were identified fell into 4 categories: (1) Intragastric acid suppression studies; (2) Randomized controlled trials in the healing of erosive esophagitis; (3) Randomized controlled trials in the maintenance of erosive esophagitis; and (4) Health economic analyses. Based on these studies, when healing doses (esomeprazole 40 mg once daily, lansoprazole 30 mg once daily) and low doses (20 and 15 mg once daily, respectively) were compared, it was seen that the data for esomeprazole and lansoprazole indicate clinical and cost- effectiveness advantages for esomeprazole in the healing and maintenance of erosive esophagitis compared with lansoprazole.[31]

Numans ME. *et al.* estimated the diagnostic test characteristics of successful PPI treatment with objective measures of GERD by performing a meta-analysis based on the published literature. They reviled that for a successful short-term treatment with a PPI in patients suspected of having GERD does not confidently establish the diagnosis when GERD is defined by currently accepted reference standards.[32]

Ren S. *et al.* evaluated the chemical stability of a PPIs, rabeprazole sodium, in simulated intestinal fluid (pH 6.8) containing various generally recognized as safe listed excipients, including Brij 58, Poloxamer 188, Cremophor RH40, Gelucire 44/14 and PEG 6000. After incubation at 37 and 60°C, the amounts of rabeprazole and its degradation product, thioether rabeprazole, were quantitated by HPLC analysis. The main degradation product was separated and characterized by LC/MS. The degradation of rabeprazole followed first-order kinetics. In the absence of any excipients, the rate constants (k) obtained at 37 and 60°C were 0.75 and 2.78 h−1, respectively. In contrast, the addition of excipients improved its stability. Among several excipients tested in this study, Brij 58 displayed the greatest stabilizing effect. The stabilizing mechanisms of these hydrophilic polymeric excipients with optimal HLB values could be partially explained in terms of their solubilizing efficiency and micellar formation for thioether-rabeprazole. In conclusion, rabeprazole formulations that contain suitable excipients would improve its stability in the intestinal tract, thereby maximizing bioavailability.[33]

Armstrong D. *et al.* compared acid suppression (time with pH > 3.0, 4.0, 5.0 and 6.0) produced by standard doses of oral esomeprazole and IV pantoprazole in healthy subjects. They concluded, in healthy subjects, esomeprazole, 40 mg oral dose dispersed in water, produces greater acid suppression than pantoprazole 40 mg IV oral dose after 1 and 5 days of medication.[34]

Wahbi AAM. *et al.* showed that the compensation method and other chemometric methods (derivative, orthogonal function and difference spectrophotometry) have been applied to the direct determination of omeprazole, lansoprazole and pantoprazole in their pharmaceutical preparations. Colourimetric methods are time consuming and need special reagents. The A_{max} method has been proved to be inaccurate due to matrix interference. They reported that the other methods are not stability indicating, while the present methods using difference spectrophotometry eliminate acid induced degradation products proved to be stability indicating. The spectrophotometric methods are more versatile and easy to apply than the polarographic and voltammetric methods. The chromatographic methods need special equipment that may not be available in certain Q. C. laboratories. The disadvantage of the proposed methods was that they cannot be applied to biological fluids containing these compounds and their conjugated forms. They validated these methods; the limits of detection where carried out. These proposed methods have been applied to the determination of the three drugs in their grastro-resistant formulations. The difference spectrophotometric method is unaffected by the presence of acid induced degradation products; hence can be used as a stability indicating assay.[35]

Moustafa AAM. *et al.* introduced spectrophotometric procedures for determination of two irreversible PPIs, lansoprazole and pantoprazole sodium sesquihydrate Two methods were based on charge transfer complexation reaction of these drugs, where they act as n-donors, with either p acceptor 2,3-dichloro-5,6-dicyano-1,4- benzoquinone and with s acceptor as iodine. A third method was also investigated depending on ternary complex formation with eosin and copper. The coloured products were quantified spectrophotometrically using absorption bands. The suggested methods have the advantages of being simple, accurate, sensitive and suitable for routine analysis in control laboratories. 2,3-dichloro-5,6-dicyano-1,4-benzoquinone and iodine methods utilize a single step reaction and single solvent. The iodine acceptor method was more sensitive in the case of lansoprazole than pantoprazole. The ternary complex method did not require prior extraction procedure and have the advantages of sensitivity, simplicity and reproducibility. All these methods can be used as general methods for the spectrophotometric determination of lansoprazole and pantoprazole sodium sesquihydrate in bulk and in pharmaceutical formulations. They are convenient for Q.C. and routine determination of these drugs.[36]

Ramakrishna NVS. *et al.* developed a very sensitive and selective HPLC method with UV detection and validated for quantitation of pantoprazole in human plasma. Following a single-step liquid–liquid extraction with methyl tertbutyl ether/diethyl ether (70/30, v/v), the analyte and internal standard (zonisamide) were separated using an isocratic mobile phase of 10milli moles of phosphate buffer (pH 6.0)/acetonitrile (61/39, v/v) on reverse phase Waters symmetry C18 column. A linear range of 20–5000 µg/mL was established. This HPLC method was validated with between-batch and within-batch respectively. This validated method is sensitive and repeatable enough to be used in pharmacokinetic studies.[37]

Rajic KK. *et al.* developed first-order UV-derivative spectrophotometry, applying zero-crossing method was developed for the determination of omeprazole, omeprazole sulphone, pantoprazole sodium salt, and N-methylpantoprazole in methanol/ammonia 4.0% v/v, where the sufficient spectra resolutions of drug and corresponding impurity were obtained, using the amplitudes. Method showed good linearity, accuracy and precision (repeatability and reproducibility). They experimentally determined values of LOD ($\mu g/ml^{-1}$). Zero-crossing method in the first-order derivative spectrophotometry showed the impurity/drug intermolecular interactions, due to the possible intermolecular hydrogen bonds, confirmed by divergences of experimentally obtained amplitudes for impurities OMS and NPA in comparison to expected values according to regression equations of calibration graphs.[38]

Farinha A. *et al.* demonstrated that the increasing number of omeprazole containing products available in the market raises questions of therapeutic equivalence and/or generic substitution. The bioequivalence evaluation between two or more formulations provides information about *in vivo* performance. The products are considered to have a similar therapeutic efficacy when used under the same therapeutic conditions. They reported the design, results and some important aspects involved in a bioequivalence study between two solid oral formulations from different manufacturers. Some important findings were the high intra-subject variability observed for C_{max} and the variability observed between subject profiles, probably caused by the multi unit type of formulations studied.[39]

Choi HG, Jung JH. *et al.* developed omeprazole buccal adhesive tablets, and also studied the release and bioavailability of omeprazole delivered by buccal adhesive tablets composed of sodium alginate, hydroxypropylmethylcellulose, magnesium oxide and CCS. They concluded that CCS enhanced the release of omeprazole from the tablets. The analysis of the release mechanism showed that CCS changed the release profile of omeprazole from first to

zero-order release kinetics by forming porous channels in the tablet matrix. However, it decreased the bioadhesive forces and stability of omeprazole tablets in human saliva. The tablet where composed of omeprazole: sodium alginate: hydroxypropylmethylcellulose: magnesium oxide: CCS in the ratio of 20:24:6:50:10 mg which may be attached to the human cheek without collapse and also enhanced the stability of omeprazole in human saliva for at least 4 hrs, giving a fast release of omeprazole. The plasma conc. of omeprazole in hamsters increased to maximum at 45 min after buccal administration and remained at the high level for 6 hrs. The buccal bioavailability of omeprazole in hamsters was 13.763.2%. These results demonstrate that the omeprazole buccal adhesive tablet would be useful to deliver omeprazole which degrades very rapidly in acidic aqueous medium and undergoes hepatic first-pass metabolism after oral administration.[40]

3. METHODOLOGY

4.1 Plan of Work

1 Design of ODTs formulations: By direct compression

2 Evaluation for the precompression parameters:

- Bulk density
- Tapped density
- Angle of repose
- Carr‘s Inndex
- Hausner‘s ratio

1. Evaluation of ODTs formulations

- Colour.
- Shape.
- Hardness.
- Friability.
- Tablet thickness.
- Weight variation.
- Drug content uniformity.
- *In vitro* dispersion time.
- *In vitro* dissolution rate.

2. Drug-excipient interaction studies: Done by FTIR.
3. Short-term accelerated stability studies for the selected formulations.

2.2 MATERIALS USED

Table No. 4.2: Materials used with their grade and their manufacturers or suppliers.

Sr. No.	Materials	Grade	Manufacturer/Supplier
1.	Pantoprazole sodium	A.G	Vasudha pharma chem ltd.
2.	Omeprazole sodium	A.G	Vasudha pharma chem ltd.
3.	CP	A.G	K. P. Pharmaceuticals.
4.	CCS	A.G	K. P. Pharmaceuticals.
5.	SSG	A.G	Vara Pharma chem. ltd
6.	L-HPC	A.G	Vara Pharma chem. ltd
7.	Pregelatinized starch	A.G	Rosswell industries
8.	Sodium Bicarbonate	A.G	Qualigen fine chem
9.	Potassium Bicarbonate	A.G	Qualigen fine chem
10.	Agar gum Tag powder	A.G	SD fine chem.
11.	Gaur gum	A.G	SD fine chem.
12.	Camphor	A.G	Hindustan crystals
13.	Menthol	A.G	Hindustan crystals
14.	Thymol	A.G	Hindustan crystals
15.	Mannitol DC	A.G	Hebei Huaxi Pharmaceutical. China
16.	Aspartame	A.G	Sinosweet co ltd.
17.	Sodium Stearyl Fumarate	A.G	Rosswell industries
18.	Talc	A.G	Fine chem. Ltd. Mumbai
19.	HCl	L.G	Ranbaxy fine chem. Ltd
20.	Ethanol	L.G	Ranbaxy fine chem. Ltd

Here A.G indicates Analytical grade and L.G indicates Laboratory grade

4.2.1 Proton Pump Inhibitors

For this research work **Pantoprazole Sodium** was used as a representative for the class of PPIs.

Category: Antiulcer.

Chemical designation: Pantporazole sodium is chemically designated as 5-(difluromethoxy)-2-[[(3,4-dimethoxy-pyridin-2-yl) methyl] sulphinyl]benzimidazol-1- ide, sesquihydrate.

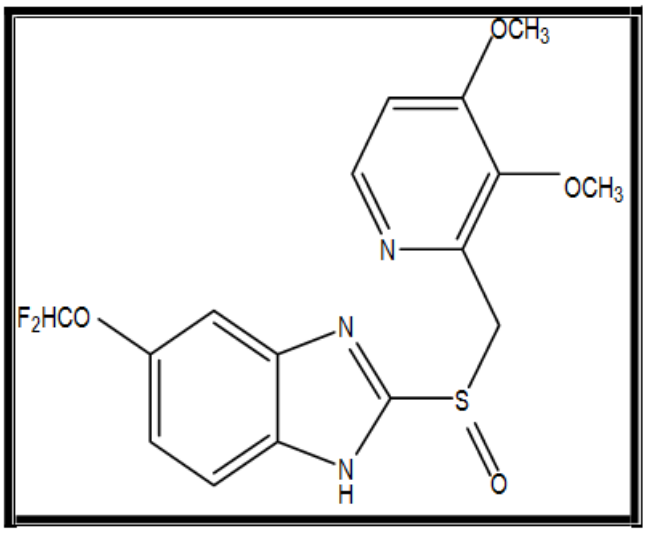


Fig. No. 4.2.1: Chemical Structure of Pantoprazole Sodium.

Empirical Formula: $C_{16}H_{14}F_2N_3\frac{1}{2}H_2O$

Molecular weight: 432.4.

Melting Point: Because of gradual degradation of pantoprazole sodium during heating, the melting point cannot be determined.

Description: Pantoprazole sodium is a white to off- white power which contains not less than 98.0 percent and not more than 102.0 percent of $C_{16}H_{14}F_2N_3\frac{1}{2}H_2O$ calculated on the anhydrous basis.

Solubility: Pantoprazole sodium is freely soluble in ethanol, soluble in water, and slightly soluble in hexane.

PKa: 3.92 pyridine; 8.19 benzimidazole

PH: 1% aqueous solution has a pH of 10.05 and 10% aqueous solution has a pH of 10.85.

Storage: Store protected from light and moisture, between 2°C to 8°C.

Usual strength: 20 to 40mg.[58]

Clinical pharmacology

Pantoprazole is a prodrug that requires activation in an acid environment. After absorption into the systemic circulation, the prodrug diffuses into the parietal cells of the stomach and

accumulates in the acidic secretory canaliculi. Here, it is activated by proton-catalyzed formation of a tetracyclic sulfenamide, trapping the drug so that it cannot diffuse back across the canalicular membrane. The activated form then binds covalently with sulfhydryl groups of cysteines in the H^+/K^+-ATPase, irreversibly inactivating the pump molecule. Acid secretion resumes only after new pump molecules are synthesized and inserted into the luminal membrane, providing a prolonged (up to 24- to 48-hour) suppression of acid secretion, despite the much shorter plasma half-lives (0.5 to 2 hours) of the parent compounds. Because they block the final step in acid production, the PPIs are effective in acid suppression regardless of other stimulating factors.

Therapeutic Uses

It is used principally to promote healing of gastric and duodenal ulcers and to treat GERD, including erosive esophagitis, which is either complicated or unresponsive to treatment with H_2-receptor antagonists. It is also mainstay in the treatment of pathological hypersecretory conditions, including the Zollinger-Ellison syndrome. Pantoprazole Sodium is FDA approved for treatment and prevention of recurrence of nonsteroidal antiinflammatory drug (NSAID)-associated gastric ulcers in patients who continue NSAID use. In addition, it is FDA approved for reducing the risk of duodenal ulcer recurrence associated with H. pylori infections.

Adverse effects

Pantoprazole sodium generally causes remarkably few adverse effects. The most common side effects are nausea, abdominal pain, constipation, flatulence, and diarrhea. Subacute myopathy, arthralgias, headaches, and skin rashes also have been reported. As noted above, all PPIs are metabolized by hepatic CYPs and therefore may interfere with the elimination of other drugs cleared by this route.

Contraindication

Pantoprazole sodium is contraindicated in patients with a history of hypersensitivity to pantoprazole Sodium or to any constituents of the medication.

Warnings

When gastric ulcer is suspected, the possibility of malignancy should be excluded before therapy with pantoprazole sodium is instituted since treatment with pantoprazole sodium may alleviate symptoms and delay diagnosis.

***Use in* Pregnancy:** There are no adequate or well-controlled studies in pregnant women. It should not be administered to pregnant women unless the expected benefits outweigh the potential risks to the foetus.

Use in Nursing Mothers: It is not known whether pantoprazole sodium is secreted in human milk. It should not be given to nursing mothers unless its use is believed to outweigh the potential risks to the infant.

Use in Children: The safety and effectiveness of pantoprazole sodium in children has not yet been established.

Precautions

Carcinogenicity: Effects of long-term treatment relate to hypergastrinemia, possible enterochromaffin-like (ECL) cell hyperplasia and carcinoid formation in the stomach, adenomas and carcinomas in the liver and neoplastic changes in the thyroid.

Pediatric and Geriatric studies: Short-term and long-term treatment with pantoprazole sodium in a limited number of patients up to 6 years have not resulted in any significant pathological changes in gastric oxyntic exocrine cells. A slight increase in AUC (12%) and C_{max} (7%) for pantoprazole sodium occurs in elderly volunteers when compared to younger volunteers. The daily dose used in elderly patients, as a rule, should not exceed the recommended dosage regimens.

***Hepatic insufficiency*:** The half-life increased to 7 - 9 h, the AUC increased by a factor of 5 to 7, and the C_{max} increased by a factor of 1.5 in patients with liver cirrhosis compared with healthy subjects following administration of 40 mg pantoprazole. Similarly, following administration of a 20 mg dose, the AUC increased by a factor of 5.5 and the C_{max} increased by a factor of 1.3 in patients with severe liver cirrhosis compared with healthy subjects.[59]

Renal insufficiency: No dose reduction is required when pantoprazole sodium is administered to patients with impaired kidney function as the difference in AUCs between patients who are dialyzed and those who are not is 4%.

***Drug drug interactions*:** Pantoprazole sodium is metabolized in the liver via the CYP 450 system. Pharmacokinetic drug interaction studies in man did not demonstrate the inhibition of the oxidative metabolism of the drug. Pantoprazole sodium does not interact with

carbamazepine, caffeine, diclofenac, ethanol, glibenclamide, metoprolol, antipyrine, diazepam, phenytoin, nifedipine, theophylline, warfarin, digoxin, or oral contraceptives. Concomitant use of antacids or consumption of food does not affect the pharmacokinetics of pantoprazole sodium. Changes in absorption should be taken into account when drugs whose absorption is pH dependent, e.g., ketoconazole, are taken concomitantly.

Clinical studies have shown that there is no pharmacokinetic interaction between pantoprazole and the following antibiotic combinations: metronidazole plus clarithromycin, metronidazole plus amoxicillin, amoxicillin plus clarithromycin.

In a preclinical study, pantoprazole in combination therapy with various antibiotics (including tetracycline, clarithromycin, and amoxicillin) was shown to have a potentiating effect on the elimination rate of H. pylori infection.

Others: Generally, daily treatment with any acid blocking medicines over a long time (e.g. longer than 3 years) may lead to malabsorption of cyanocobalamin caused by hypo- or achlorhydria. Rare cases of cyanocobalamin deficiency under acid-blocking therapy have been reported in the literature and should be considered if respective clinical symptoms are observed.[58]

Symptoms and treatment of overdosage

Some reports of overdosage with pantoprazole have been received. No consistent symptom profile was observed after ingestion of high doses of pantoprazole. Doses of up to 240 mg i.v. were administered and were well tolerated.

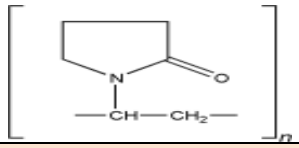
Treatment should be supportive and symptomatic. Pantoprazole is not removed by hemodialysis.[60,61]

4.2.2 Excipient Profiles

4.2.2.1 Crospovidone

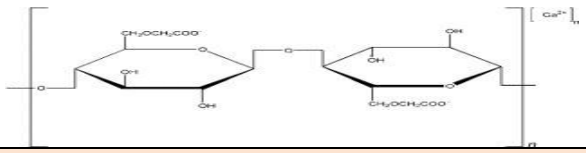
Table No. 4.2.2.1: Crospovidone.

Synonyms:	Crosslinked povidone; E1202; Kollidon CL; Kollidon CL M;Polyplasdone XL; Polyplasdone XL-10 polyvinylpolypyrroli-done; PVPP; 1-vinyl-2-pyrrolidinone homopolymer
Nonpropietary Names:	BP-CP, PhEur- Crospovidonum, USPNF- CP
Chemical Name and	1-Ethenyl-2-pyrrolidinone homopolymer [9003-39-8]

CAS Registry No.:	
Description:	White to creamy-white, finely divided, free flowing, practically tasteless, odourless or nearly odourless, hygroscopic powder.
Structural Formula:	
Empirical Formula &Molecular Weight:	(C6H9NO)n >10,00,000.
Solubility and storage conditions:	Since CP is hygroscopic, it should be stored in an airtight container in a cool, dry place.
Functional categories:	Tablet disintegrant.
Applications:	Used as disintegrant and dissolution agent at a conc of 2-5%.
Incompatibilities:	CP when exposed to a high water level, may form molecular adduct with some materials.

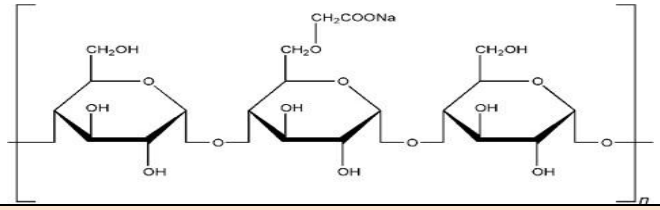
4.2.2.2 Croscarmelose sodium

Table No. 4.2.2.2: Croscarmelose Sodium.

Synonyms:	Ac-Di-Sol; crosslinked carboxymethylcellulose sodium; Explocel; modified cellulose gum; Nymcel ZSX; Pharmacel XL; Primellose; Solutab; Vivasol
Nonpropietary Names:	BP-Croscramellose sodium, PhEur- Carmellosum natricum conexum, USPNF- Croscarmellose sodium.
Chemical Name and CAS Registry No.:	Cellulose, carboxymethyl ether, sodium salt, cross linked [74811-65-7].
Description:	CCS occurs as an odourless, white or greyish white powder.
Structural Formula:	
Empirical Formula and Molecular Weight:	The USPNF 23 describes carboxymethylcellulose calcium as the calcium salt of a polycarboxymethyl ether of cellulose.
Solubility:	Insoluble in water. Practically insoluble in acetone, ethanol.
Functional categories:	Tablet and capsule disintegrant.
Use:	Disintegrant in capsules 10–25 & in tablets 0.5–5.0
Applications:	It is used in oral pharmaceutical formulations as a disintegrant for capsules, tablets, and granules.
Stability and Storage Conditions:	It is a stable though hygroscopic material. It should be stored in a well closed container in a cool, dry place.
Incompatibilities:	The efficacy of disintegrants may be slightly reduced when formulations are prepared by wet-granulation process.

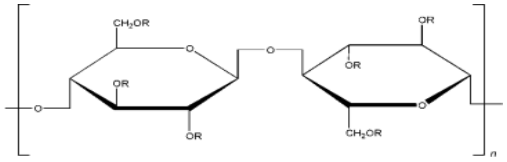
4.2.2.3 Sodium Starch Glycolate

Table No. 4.2.2.3: Sodium Starch Glycolate.

Synonyms:	Carboxymethyl starch, sodium salt; Explosol; Explotab; Glycolys; Primojel; starch carboxymethyl ether, sodium salt; Tablo; Vivastar P.
Nonpropietary Names:	BP: Sodium starch glycollate, PhEur:Carboxymethylamylum natricum, USPNF: SSG.
Chemical Name and CAS Registry No.:	Sodium carboxymethyl starch [9063-38-1]
Description:	SSG is a white to off-white, odourless, tasteless, free-flowing powder.
Structural Formula:	
Melting point:	Does not melt, but chars at approximately 200°C.
Functional categories:	Tablet and capsule disintegrant.
Applications:	It is commonly used in tablets prepared by either direct compression or wet-granulation processes. The usual conc. employed in a formulation is between 2% and 8%, with the optimum conc. about 4%, although in many cases 2% is sufficient.
Stability and storage properties:	SSG is stable and should be stored in a well-closed container.
Incompatibilities:	SSG is incompatible with ascorbic acid.

4.2.2.4 Hydroxypropyl Cellulose, Low-Substituted

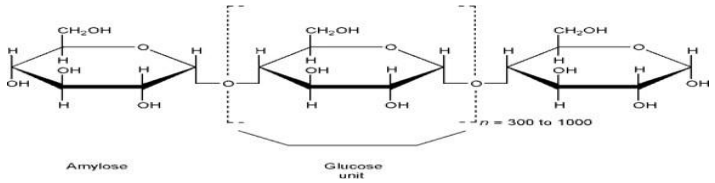
Table No. 4.2.2.4: Hydroxypropyl Cellulose, Low-Substituted.

Synonyms	Hyprolose, low-substituted; L-HPC
Nonpropietary Names	JP: Low-substituted hydroxypropylcellulose, USPNF: Low substituted hydroxypropyl cellulose
Chemical Name and CAS Registry No.:	Cellulose, 2-hydroxypropyl ether (low substituted) [78214-412].
Description	L-HPC occurs as a white to yellowish white powder or granules. It is odourless and it is tasteless.
Structural Formula:	 **Fig: Where is R is H or $[CH_2CH(CH_3)O]_mH$**
Empirical Formula:	(—OCH2CHOHCH3).
Grade:	LH-11, LH-21, LH-31, LH-22, LH-32, LH-20, LH-30
Solubility and storage conditions:	L-HPC is a stable, though hygroscopic, material. The powder should be stored in a well- closed container.

Melting point:	Its decomposition is at 275°C.
Functional categories:	Tablet and capsule disintegrant; tablet binder.
Applications:	It is primarily used in tableting as a disintegrant, and as a binder in wet granulation.
Stability and Storage Conditions:	L-HPC is a stable, though hygroscopic, material. The powder should be stored in a well- closed container.
Incompatibilities:	It may react with as alkaline substance.

4.2.2.5 Starch Pregelatinized

Table No. 4.2.2.5: Starch Pregelatinized.

Synonyms:	Compressible starch; Instastarch; Lycatab C; Lycatab PGS; Merigel; National 78-1551; Pharma-Gel; Prejel; Sepistab ST 200; Spress B820; Starch 1500 G; Tablitz; Unipure LD; Unipure WG220.
Nonpropietary Names:	Pregelatinised starch, PhEur: Amylum pregelificatum, USPNF: Pregelatinized starch.
Chemical Name and CAS Registry No.:	Pregelatinized starch [9005-25-8].
Description:	Pregelatinized starch occurs as a moderately coarse to fine, white to off-white coloured powder. It is odourless and has a slight characteristic taste.
Structural Formula:	 **Fig: Where is R is H or $[CH_2CH(CH_3)O]_mH$**
Empirical Formula:	$(C_6H_{10}O_5)$ n where n = 300–1000
Solubility and storage conditions:	It is practically insoluble in organic solvents. Slightly soluble to soluble in cold water.
Moisture content:	pregelatinized maize starch is hygroscopic.
Functional categories:	Tablet and capsule diluent, disintegrant and tablet binder.
Applications:	Pregelatinized starch is a modified starch used in oral capsule and tablet formulations as a binder, diluent, and disintegrant. In comparison to starch.

4.2.2.6 Sodium Bicarbonate

Table No. 4.2.2.6: Sodium Bicarbonate.

Synonyms:	Baking soda; E500; Effer-Soda; monosodium carbonate; sodium acid carbonate; sodium hydrogen carbonate.
Nonpropietary Names:	Sodium bicarbonate, JP: Sodium bicarbonate, PhEur: Natrii hydrogenocarbonas, USP: Sodium bicarbonate.
Chemical Name and CAS Registry No.:	Carbonic acid monosodium salt [144-55-8]
Description:	Sodium bicarbonate occurs as an odourless, white, crystalline powder with a saline, slightly alkaline taste. The crystal structure is monoclinic prisms

Empirical Formula:	$NaHCO_3$
Molecular Weight:	84.01
Solubility:	It is practically insoluble in Ethanol (95%) and Ether, soluble in Water.
Moisture content:	The moisture content is less than 1% w/w. Above 85% relative humidity it rapidly absorbs excessive amounts of water and may start to decompose with loss of CO_2.
Functional categories:	Alkalizing agent; therapeutic agent.
Uses:	Buffer in tablets 10–40 (%); Effervescent tablets 25–50 (%); Isotonic injection/infusion 1.39 (%).
Melting point:	270°C (with decomposition).
Applications:	It is generally used in pharmaceutical formulations as a source of carbon dioxide in effervescent tablets and granules. It is also widely used to produce or maintain an alkaline pH in a preparation. Additionally, sodium bicarbonate is used in solutions as a buffering agent.

4.2.2.7 Potassium Bicarbonate

Table No. 4.2.2.7: Details about Potassium Bicarbonate.

Synonyms:	Carbonic acid monopotassium salt; E501; monopotassium carbonate; potassium acid carbonate; potassium hydrogen carbonate.
Nonpropietary Names:	BP: Potassium bicarbonate**,** PhEur: Kalii hydrogenocarbonas, USP: Potassium bicarbonate.
Chemical Name and CAS Registry No.:	Potassium bicarbonate [298-14-6]
Description:	Potassium bicarbonate occurs as colourless, transparent crystals or as a white granular or crystalline powder. It is odourless, with a saline or weakly alkaline taste.
Empirical Formula:	$KHCO_3$
Molecular Weight:	100.11
Solubility:	Soluble 1 in 4.5 of water at 0°C, 1 in 2.8 of water at 20°C, 1 in 2 of water at 50°C; practically insoluble in ethanol (95%).
Functional categories:	Alkalizing agent; therapeutic agent.
Applications:	Used as an excipient, generally used in formulations as a source of carbon dioxide in effervescent preparations, at conc. of 25-50% w/w. It is of particular use in formulations where sodium bicarbonate is unsuitable, for example, when the presence of Na^+ ions in a formulation needs to be limited or is undesirable.
Storage:	Potassium bicarbonate should be stored in a well-closed container in a cool, dry location.
Incompatibilities:	Potassium bicarbonate reacts with acids and acidic salts with the evolution of carbon dioxide.

4.2.2.8 Tag Powder (Treated Agar Powder)

Table No. 4.2.2.8: Tag Powder, Agar.

Synonyms:	Agar-agar; Bengal isinglass; Ceylon isinglass; Chinese isinglass; E406; gelosa; gelose; Japan agar; Japan isinglass; layor carang.
Nonpropietary Names:	JP: Agar, PhEur: Agar, USPNF: Agar.
Chemical Name and CAS Registry No.:	Agar [9002-18-0]
Description:	It occurs as transparent, odourless, tasteless strips or as a coarse or fine powder. It may be weak yellowish-orange, yellowish-gray to pale-yellow coloured, or colourless. Agar is tough when damp, brittle when dry.
Structural Formula:	Agar is a dried, hydrophilic, colloidal polysaccharide complex extracted from the agarocytes of algae of the Rhodophyceae. The structure is believed to be a complex range of polysaccharide chains having alternating linkages.
Solubility:	It is soluble in boiling water to form a viscous solution practically insoluble in ethanol (95%), and cold water. A 1% w/v aqueous solution forms a stiff jelly on cooling.
Functional categories:	Emulsifying agent; stabilizing agent; suppository base; suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.
Applications:	Agar is widely used as a stabilizing agent. It is used in a handful of oral tablet and topical formulations. It has also been investigated for possessing sustained-release activity in gels, beads, microspheres, and as a disintegrant in tablets.
Storage:	It is mostly stable at pH 4–10 and should be stored in a cool, dry, place.

4.2.2.9 Guar Gum

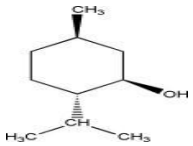
Table No. 4.2.2.9: Guar Gum.

Synonyms:	E412; Galactosol; guar flour; jaguar gum; Meyprogat; Mey-prodor; Meyprofin.
Nonpropietary Names:	BP: Guar galactomannan, PhEur: Guar galactomannanum, USPNF: Guar gum.
Chemical Name and CAS Registry No.:	Galactomannan polysaccharide [9000-300]
Description:	Gaur gum occurs as transparent, odourless, tasteless strips or as a coarse or fine powder. It may be weak yellowish-orange, yellowish-gray to pale-yellow coloured, or colourless.
Emperical Formula:	$(C_6H_{12}O_6)_n$ =220 000
Structural Formula:	It consists of linear chains of (1→4)-b-D-mannopyranosyl units with a-D-galactopyranosyl units attached by (1→6) linkages. The ratio of D-galactose to D-mannose is between 1 : 1.4 and 1 : 2.
Solubility:	It is practically insoluble in organic solvents. In cold or hot water, guar gum disperses and swells almost immediately to

	form a highly viscous, thixotropic sol. The optimum rate of hydration occurs at ph 7.5–9.0. Finely milled powders swell more rapidly and are more difficult to disperse. Two to four hours in water at room temperature are required to develop maximum viscosity.
Functional categories:	Suspending agent; tablet binder; tablet disintegrant; viscosity-increasing agent.
Use:	It is used as emulsion stabilizer up to 1%, tablet binder Up to 10%, thickener for lotions and creams Up to 2.5%
Applications:	Guar gum is a galactomannan, commonly used in cosmetics, food products, and pharmaceutical formulations. It has also been investigated in the preparation of sustained-release matrix tablets in the place of cellulose derivatives such as methylcellulose
Storage:	Guar gum powder should be stored in a well-closed container in a cool, dry place.

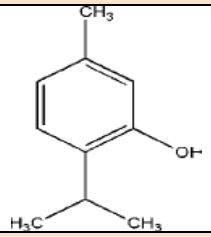
4.2.2.10 Menthol

Table No. 4.2.2.10: Menthol.

Synonyms:	Hexahydrothymol; 2-isopropyl-5-methylcyclohexanol; 4-isopropyl-1-methylcyclohexan-3-ol; 3-p-menthanol; p-menthan 3-ol; dl-menthol; peppermint camphor;
Nonpropietary Names:	BP: Racementhol, JP: dl-Menthol, PhEur: Mentholum racemicum, USP: Menthol.
Chemical Name and CAS Registry No.:	(1RS,2RS,5RS)-()-5-Methyl-2-(1 methylethyl)cyclohexanol [15356-70-4] Note that the following CAS No.s have also been used: [1490-04-6] and [89-78-1].
Description:	Racemic menthol is a mixture of equal parts of the (1R,2S,5R)- and (1S,2R,5S)-isomers of menthol.
Emperical Formula:	$C_{10}H_{20}O$
Molecular Weight:	156.27
Structural Formula:	
Solubility:	Very soluble in ethanol (95%), chloroform, ether, fatty oils and liquid paraffin; soluble in acetone and benzene; very slightly soluble in glycerin; practically insoluble in water.
Functional categories:	Flavouring agent; therapeutic agent.
Melting point:	34°C.
Applications:	It is widely used as a flavouring agent or odour enhancer. It exerts a cooling or refreshing sensation that is exploited in many topical preparations.
Storage:	Menthol should be stored in a well-closed container at a temperature not exceeding 25°C, since it sublimes readily.

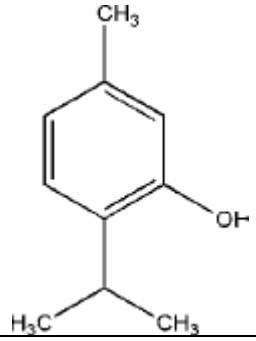
4.2.2.11 Thymol

Table No. 4.2.2.11: Thymol.

Synonyms:	Acido trimico; 3-p-cymenol; p-cymen-3-ol; Flavinol; 3-hydroxy-p-cymene; 3hydroxy-1-methyl-4-isopropylbenzene.
Nonpropietary Names:	Thymol, Thymolum
Chemical Name and CAS Registry No.:	Thymol [89-83-8]
Description:	It occurs as colourless or often large translucent crystal, or as a white crystalline powder and have a pungent caustic taste.
Emperical Formula:	$C_{10}H_{14}O$
Molecular Weight:	150.24
Structural Formula:	
Solubility:	Soluble in chloroform, ethanol (95%), ether, glacial acetic acid, olive oil, water. Freely soluble in essential oils, fixed oils, and fats. Sparingly soluble in glycerine.
Functional categories:	Flavouring agent; therapeutic agent.
Use:	Menthol is used as Inhalation 0.02–0.05 %**,** as an Oral suspension 0.003%**,** Oral syrup 0.005–0.015%, Tablets 0.2–0.4%, Topical formulations 0.05–10.0%**,** Toothpaste 0.4**%,** Mouthwash 0.1–2.0**%,** Oral spray 0.3%.
Storage:	Thymol should be stored in well-closed, light-resistant containers, in a cool, dry, place. Thymol is affected by light.

4.2.2.12 Camphor

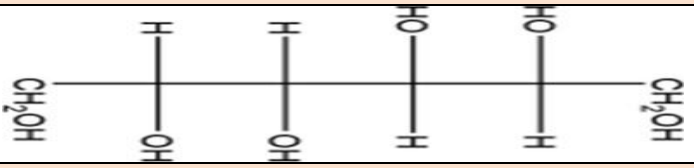
Table No. 4.2.2.12: Camphor.

Synonyms:	2-bornanone,2-camphanone bornan-2-one, Formosa.
Nonpropietary Names:	Camphor
Chemical Name and CAS Registry No.:	1,7,7-trimethylbicyclo [2.2.1]heptan-2-one [464-48-2]
Description:	White or colourless crystals.
Emperical Formula:	$C_{10}H_{16}O$
Molecular Weight:	251.23
Structural Formula:	

Functional categories:	Flavourings agent; therapeutic agent.
Applications:	Modern uses include camphor as a plasticizer for nitrocellulose, as a moth repellent, as an antimicrobial substance.
Storage:	Camphor should be stored in well-closed, light-resistant containers, in a cool, dry, place.

4.2.2.13 Directly Compressible Mannitol

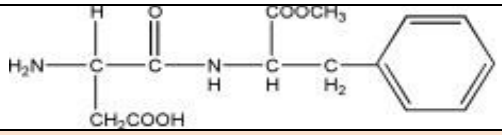
Table No. 4.2.2.13: Directly Compressible Mannitol

Synonyms:	**Cordycepic acid; C PharmMannidex; E421; manna sugar; D-mannite; mannite; Mannogem; Pearlitol.**
Nonpropietary Names:	BP: Mannitol**,** JP: D-Mannitol**,** PhEur: Mannitolum**,** USP:Mannitol
Chemical Name and CAS Registry No.:	D-Mannitol [69-65-8]
Description:	It occurs as a white, odourless, crystalline powder/ 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.
Emperical Formula:	$C_6H_{14}O_6$.
Molecular Weight:	182.17
Structural Formula:	
Functional categories:	Diluent; diluent for lyphilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.
Use:	Menthol is used as Inhalation 0.02–0.05 %**,** as an Oral suspension 0.003%**,** Oral syrup 0.005–0.015%, Tablets 0.2%.
Applications:	It is primarily used as a diluent (10–90%) in tablet formulations.
Storage:	Mannitol is stable in the dry state and in aqueous solutions. The bulk material should be stored in a well-closed container in a cool, dry place.

4.2.2.14 Aspartame

Table No. 4.2.2.14: Aspartame.

Synonyms:	3-Amino-N-(a-carboxyphenethyl)succinamic acid N-methyl ester; 3-amino-N-(a-methoxycarbonylphenethyl)succinamic acid; APM;
Nonpropietary Names:	BP: Aspartame, PhEur: Aspartamum, USPNF: Aspartame
Chemical Name and CAS Registry No.:	N-a-L-Aspartyl-L-phenylalanine 1-methyl ester [22839-47-0]
Description:	Aspartame occurs as an off white, almost odourless crystalline powder with an intensely sweet taste.
Emperical Formula:	$C_{14}H_{18}N_2O_5$.
Molecular Weight:	294.31

Structural Formula:	
Functional categories:	Sweetening agent.
Solubility:	Slightly soluble in ethanol (95%); sparingly soluble in water.
Applications:	Aspartame is used as an intense sweetening agent in beverage products, food products, and table-top sweeteners, and in pharmaceutical preparations including tablets, powder mixes, and vitamin preparations. It is 180–200 times that of sucrose.
Storage:	Aspartame is stable in dry conditions and should be stored in a well-closed container, in a cool, dry place.

4.2.2.15 Talc

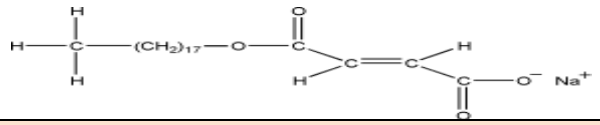
Table No. 4.2.2.15: Talc.

Synonyms:	Altalc; E553b; hydrous magnesium calcium silicate; hydrousmagnesium silicate; Luzenac Pharma; magnesium hydrogen metasilicate; Magsil Osmanthus; Magsil Star; powdered talc; purified French chalk; Purtalc; soapstone; steatite; Superiore.
Nonpropietary Names:	BP: Purified talc, JP: Talc, PhEur: Talcum, USP: Talc
Chemical Name and CAS Registry No.:	Talc [14807-96-6]
Description:	Talc is a very fine, white to greyish-white, odourless, impalpable, unctuous, crystalline powder. It adheres readily to the skin and is soft to the touch and free from grittiness.
Emperical Formula:	Talc is a purified, hydrated, magnesium silicate, approximating to the formula $Mg_6(Si_2O_5)_4(OH)_4$. It may contain small, variable amounts of aluminium silicate and iron.
Functional categories:	Anticaking agent; glidant; tablet and capsule diluent; tablet and capsule lubricant.
Use:	Used as dusting powder 90.0–99.0%, as a glidant and tablet lubricant 1.0–10.0, tablet and capsule diluent 5.0–30.0
Solubility:	Practically insoluble in dilute acids and alkalis organic solvents, and water.
Applications:	It is widely used as a dissolution retardant in the development of controlled-release products. Talc is also used as a lubricant in tablet formulations; in a novel powder coating for extended-release pellets. Talc is used as a dusting powder,
Storage:	Talc should be stored in a well-closed container in a cool, dry place

4.2.2.16 Sodium Stearyl Fumarate.[61]

Table No. 4.2.2.16: Sodium Stearyl Fumarate

Synonyms:	Fumaric acid, octadecyl ester, sodium salt; Pruv; sodium monostearyl fumarate.
Nonpropietary Names:	Sodium stearyl fumarate, PhEur: Natrii stearylis fumaras,

	USPNF: Sodium stearyl fumarate.
Chemical Name and CAS Registry No.:	2-Butenedioic acid, monooctadecyl ester, sodium salt [4070- 80-8].
Description:	Sodium stearyl fumarate is a fine, white powder with agglomerates of flat, circular-shaped particles.
Emperical Formula:	$C_{22}H_{39}NaO_4$.
Molecular Weight:	390.5
Structural Formula:	
Functional categories:	Tablet and capsule lubricant.
Use:	It is used as lubricant and also as a glident.
Solubility:	Practically insoluble in acetone, chloroform, ethanol. Slightly soluble in methanol. Solubility in water is 1 in 20 000 at 25°C, 1in10at80°C and 1 in 5 at 90°C,
Melting point:	224–245°C (with decomposition)
Applications:	It is widely used as lubricant and also as a glident in tablet or capsule formulations.
Storage:	The bulk material should be stored in a well-closed container in a cool, dry place.

4.3 Instruments

Table No. 4.3: Instruments used for the research work.

Sr. No.	Instruments	Manufacturer
1.	Electronic Weighing Balance (Model No. IND/09/2001/28)	Essae-Teraoka Ltd
2.	UV-Vis Spectrophotometer (UV-1800)	Shimadzu, Japan.
3.	FTIR Spectrophotometer (8400S)	Shimadzu, Japan.
4.	Disintegration Test Apparatus ED-2L	Electrolab.
5.	Dissolution test apparatus TDT-08T	Electrolab.
6.	Digital Vernier Caliper	Mitutoyo, Japan.
7.	Digital pH meter 7007	Dgisun Electronics Hyderabad.
9.	Test Sieve	Scientific Engineering Corp. Delhi.
10.	Hot Air Oven	Servewell Instrument (P) Ltd, Bangalore.
11.	Stability Chamber	Lab Control Equipment Co. Mumbai.
12.	Friabilator USP EF-2	Electrolab.
13.	Tablet punching machine, (Rimek mini press-1) 10- station	Karnavati Engineering Ltd, Mehsana , Gujarat.
14.	Monsanto Hardness Tester	Ketan engineering Ltd, Mumbai
15.	Tap density tester ETD 1020	Electrolab

4.4.Studies Under Taken

4.4.1 Preformulation studies

The goals of preformulation studies are to choose the correct form of the drug substance,

evaluate its physical and chemical properties, and generate a thorough understanding of the material‘s stability under the conditions that will lead to the development of a particular DDS. Preformulation is a science that serves as a big umbrella for the fingerprinting of a drug substance or product both at the early and latter stage of development in pharmaceutical manufacturing. The preformulation phase is a critical learning time about candidate drugs. Typically, it begins during the lead optimization phase and continues through prenomination and into the early phases of development. Decisions made on the information generated during this phase can have a profound effect on the subsequent development of those compounds.[62]

The goals of the preformulation study are:

- To establish the necessary physicochemical characteristics of a new drug substance.
- To determine its kinetic release rate profile.
- To establish its compatibility with different excipients.

Hence, preformulation studies on the obtained sample of drug include colour, taste, solubility analysis, melting point determination and compatibility studies.

4.4.1.1 Identification of Pantoprazole

4.4.1.1.1 Melting point determination

Melting point of Pantoprazole sodium was set to determine by open cup capillary method.

4.4.1.1.2 Infrared absorption spectrum

The infrared absorption spectrum of Pantoprazole was recorded with a KBr disc over the wave No. 4000 to 400 cm^{-1}.

4.4.1.2 Preparation of standard calibration curve

4.4.1.2.1 *Preparation of standard calibration curve of Pantoprazole sodium in 0.1 N Hydrochloric acid.*

Procedure

1 gm of sodium bicarbonate was accurately weigh and transferred it in to 100 ml amber coloured volumetric flask and dissolved in small quantity of 0.1 N HCl. To this a solution 100mg of Pantoprazole sodium dissolved in approximately 2-5 ml of water was added. The volume was made up with the 0.1 N HCl to get a conc. of 1000µg/ml [Standard Stock -I (SS-I)].

From this 1ml was withdrawn and diluted to 100ml to get a conc. of 10µg/ml (SS- II). From SS-II aliquots of 2ml, 4ml, 6ml, 8ml and 10ml were pipetted into 10ml volumetric flasks. The volume was made up with 0.1 N HCl to get the final Conc. of 2, 4, 6, 8, 10 µg/ml respectively. When this solution was scanned in the UV range i.e. from 200nm to 800nm λ_{max} was found to be 281.5 nm for Pantoprazole sodium in 0.1N HCl as a blank in UV-Visible Spectrophotometer (UV-1800 Shimadzu). The absorbance (abs) of each conc. was measured at 281.5 nm.

The same solution was stored at room temperature and abs of the solutions was measured at 281.5 nm using UV-visible spectrophotometer after every half hour.

Beer's range: 2- 100µg/ml.

The conc. was calculated using the following formula:

$$\text{Conc} = \frac{\text{Absorbance}}{\text{Slope}}$$

4.4.1.2.2 Preparation of standard calibration curve of Omeprazole sodium in 0.1 N Hydrochloric acid.

Procedure

1 gm of sodium bicarbonate was accurately weigh and transferred it in to 100 ml amber coloured volumetric flask and dissolved in small quantity of 0.1 N HCl. To this a solution 100mg of Omeprazole sodium dissolved in approximately 2-5 ml of water was added. The volume was made up with the 0.1 N HCl to get a conc. of 1000µg/ml [Standard Stock -I (SS-I)].

From this 1ml was withdrawn and diluted to 100ml to get a conc. of 10µg/ml (SS- II). From SS-II aliquots of 2ml, 4ml, 6ml, 8ml and 10ml were pipetted into 10ml volumetric flasks. The volume was made up with 0.1 N HCl to get the final conc. of 2, 4, 6, 8, 10 µg/ml respectively. When this solution was scanned in the UV range i.e. from 200nm to 800nm λ_{max} was found to be 301nm for Omeprazole sodium in 0.1N HCl as a blank in UV-Visible Spectrophotometer (UV-1800 Shimadzu). The abs of each conc. was measured at 301 nm.

The same solution was stored at room temperature and abs of the solutions was measured at 301 nm using UV-visible spectrophotometer after every half hour.

Beer's range: 2- 100µg/ml.

The conc. was calculated using the following formula:

$$\text{Conc} = \frac{\text{Absorbance}}{\text{Slope}}$$

4.4.1.3 Compatibility studies of drug and polymers

4.4.1.3.1 *FTIR Studies*

Compatibility of the pantoprazole with superdisintegrants and other polymers used to formulate ODTs where studied by FTIR analysis. FTIR spectral analysis of pantoprazole sodium, superdisintegrants and excipients and combination of the pantoprazole sodium and superdisintegrants and excipients were carried out to investigate the changes in chemical composition of the drug after combining it with the excipients.

The compatibility study on IR was carried by Shimadzu 8400S IR spectra of pure pantoprazole sodium, superdisintegrants, physical mixtures and optimized formulation were obtained by adding potassium bromide 100 times the quantity of the sample to be studied.

4.4.2. Post formulation Studies

4.4.2.1 Formulation of Orodispersible Tablets of Pantoprazole Sodium

Pantopraozle sodium ODT where prepared by using three approaches of Direct Compression method.

Approach 1: Super disintigrant addition method.
Approach 2: Combination of different superdisintegrants method.
Approach 3: Sublimation method.
Approach 4: Combination of superdisintegrants and sublimationmethod.
Approach 5: Treated Natural gums used as superdisintegrants.

4.4.2.1.1 Preparation of Pantoprazole Orodispersible tablets using Superdisintegrant *Addition method*

Pantoprazole ODTs were prepared by direct compression. All the ingredients were passed through 60# mesh sieve separately and collected. The drug was weighed along with the other excipients and was mixed in geometrical order. This mixture was shaken for few mins to ensure proper mixing of all the ingredients. The tablets were compressed using flat face 16.4 X 8 mm flat oval shaped punch to get tablets of 1300 mg weight using ten stations Rimek

tablet compression machine (Karnavati Engineering Ltd. Ahmadabad, India).

4.4.2.1.2 Preparation of Orodispersible tablets using combination of different superdisintegrants method

In this approach pantoprazole Sodium ODTs were prepared by direct compression using a combination of two different superdisintegrants in the ratio of 1:1. All the ingredients were passed through 60# mesh sieve separately and collected. The drug was weighed along with the other excipients and was mixed in geometrical order. This mixture was shaken for few mins to ensure proper mixing of all the ingredients. The tablets were compressed using flat face 16.4 X 8 mm flat oval punch to get tablets of 1300 mg weight using ten stations Rimek tablet compression machine.

4.4.2.1.2 Preparation of Orodispersible tablets using sublimation method

Sublimating agents resulted in rapid disintegration of tablets due to the phenomenon of sublimating which improves dissolution. Pantoprazole sodium ODTs were prepared by direct compression.[63] All the ingredients were passed through 60# mesh sieve separately and collected. The drug was weighed along with the other excipients and was mixed in geometrical order. This mixture was shaken for few mins to ensure proper mixing of all the ingredients. The tablets were compressed using flat face 16.4 X 8 mm flat oval size punches to get tablets of 1300 mg weight using ten stations Rimek tablet compression machine (Karnavati Engineering Ltd. Ahmadabad, India). The tablets were dried at 60^0 C in oven till constant weight was obtained.

4.4.2.1.4 Preparation of Orospersible tablets using combination of Superdisintegrants and Sublimation method

Pantoprazole ODTs were prepared by direct compression. In this approach one superdisintegrants and one sublimating agents where used. All the ingredients were passed through 60# mesh sieve separately and collected. The drug was weighed along with the other excipients and was mixed in geometrical order. This mixture was shaken for few mins to ensure proper mixing of all the ingredients. The tablets were compressed using flat face 16.4 X 8 mm flat oval shaped punch to get tablets of 1300 mg weight using ten stations Rimek tablet compression machine (Karnavati Engineering Ltd. Ahmadabad, India).

4.4.2.1.5 Treated natural gums used as superdisintegrants

Natural gums are getting a lot of importance due to their properties. Treated agar gum (TAG)

powder has shown having superdisintegration property. Pantoprazole sodium ODTs using natural gums as superdisintegrants were prepared by direct compression. The gums like agar, gaur gum, gum acacia etc where taken.

10gm of the gums was accurately weighed and added to 250 ml beaker containing 100 ml distilled water and then stirred for few minis. This was kept aside for 2 days and then dried until it form dry powered. This mass was pulverised and pass throw 60# sieve. All the other ingredients were also passed through 60# mesh sieve separately and collected. The drug was weighed along with the other excipients and was mixed in geometrical order. This mixture was shaken for few mins to ensure proper mixing of all the ingredients. The tablets were compressed using flat face 16.4 X 8 mm flat oval size punch to get a tablets of 1300 mg weight using ten station Rimek tablet compression machine (Karnavati Engineering Ltd. Ahmadabad, India).

Table No. 4.4.2.1.1: Formulations of Orodispersible tablets using superdisintigrant addition method.

Sr. No	Ingredients	Quantity used in mg															
		F1	F2	F3	F4	F5	F6	F7	F8	F9	F10	F11	F12	F13	F14	F15	F16
1.	Pantoprazole	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20	20
2.	CP	-	13	39	65	-	-	-	-	-	-	-	-	-	-	-	-
3.	SSG	-	-	-	-	13	39	65	-	-	-	-	-	-	-	-	-
4.	CCS	-	-	-	-	-	-	-	13	39	65	-	-	-	-	-	-
5.	L-HPC	-	-	-	-	-	-	-	-	-	-	13	39	65	-	-	-
6.	Pregelatinized Starch	-	-	-	-	-	-	-	-	-	-	-	-	-	13	39	65
7.	Treated Agar	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
8.	Treated Gaur	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-
9.	Aspartame	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52	52
10.	Mannitol DC	77.5	64.5	38.5	12.5	64.5	38.5	12.5	64.5	38.5	12.5	64.5	38.5	12.5	64.5	38.5	12.5
11.	Talc	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26	26
12.	SSF	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13	13
13.	Sodium Bicarbonate	585	585	585	585	585	585	585	585	585	585	585	585	585	585	585	585
14.	Potassium Bicarbonate	520	520	520	520	520	520	520	520	520	520	520	520	520	520	520	520
15.	Flavour	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5	6.5

Table No.4.4.2.1.2: Formulations of Orodispersible tablets using combination of superdisintigrants.

Sr. No.	Chemical Used	Quantity used in mg			
		F17	F18	F19	F20
1.	Pantoprazole	20	20	20	20
2.	CP	-	32.5	32.5	32.5
3.	SSG	32.5	32.5	-	-
4.	CCS	32.5	-	32.5	-
5.	L-HPC	-	-	-	32.5
6.	Aspartame	52	52	52	52
7.	Mannitol DC	12.5	12.5	12.5	12.5
8.	Talc	26	26	26	26
9.	SSF	13	13	13	13
10.	Sodium bicarbonate	585	585	585	585
11.	Potassium bicarbonate	520	520	520	520
12.	Flavour	6.5	6.5	6.5	6.5

Table No 4.4.2.1.3: Formulations of Orodispersible tablets using subliming agent.

Sr.No.	Chemical used	Quantity used in mg		
		F21	F22	F23
1.	Pantoprazole	20	20	20
2.	Camphor	65	-	-
3.	Menthol	-	-	65
4.	Thymol	-	65	-
5.	Aspartame	52	52	52
6.	Mannitol DC	12.5	12.5	12.5
7.	Talc	26	26	26
8.	Sodium steryl fumerate	13	13	13
9.	Sodium bicarbonate	585	585	585
10.	Potassium bicarbonate	520	520	520
11.	Flavour	6.5	6.5	6.5

Table No. 4.4.2.1.4: Formulations of Orodispersible tablets using a combination of superdisintegrants and sublimation method.

Sr. No.	Chemical used	Quantity used in mg	
		F24	F25
1.	Pantoprazole	20	20
2.	CP	32.5	32.5
3.	Camphor	32.5	-
4.	Menthol	-	32.5
5.	Aspartame	52	52
6.	Mannitol DC	12.5	12.5
7.	Talc	26	26
8.	Sodium steryl fumerate	13	13
9.	Sodium bicarbonate	585	585
10.	Potassium bicarbonate	520	520
11.	Flavour	6.5	6.5

Table No. 4.4.2.1.5: Formulations of Orodispersible tablets using Natural gums as superdisintegrants.

Sr. No.	Chemical used	Quantity used in mg	
		F26	F27
1.	Pantoprazole	20	20
2.	Gum Agar	-	32.5
3.	Gaur gum	32.5	-
5.	Aspartame	52	52
6.	Mannitol DC	12.5	12.5
7.	Talc	26	26
8.	Sodium steryl fumerate	13	13
9.	Sodium bicarbonate	585	585
10.	Potassium bicarbonate	520	520
11.	Flavour	6.5	6.5

4.5 Evaluation of Tablets

4.5.1 Pre-compression Parameters

4.5.1.1 Angle of Repose (θ)

Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and horizontal plane. If more material is added to the pile, it slides down the sides until the mutual friction of the particles, producing a surface at an angle is in equilibrium with the gravitational force; the tangent of the angle of repose is equal to the coefficient of friction, μ, between the particles. The frictional force in a loose powder or granules can be measured by using this angle of repose.

$\tan \theta = h / r$

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

Where, θ is the angle of repose h is height of pile

r is radius of the base of pile[64]

Different ranges of flow ability in terms of angle of repose are given in table no.4.5.1.1

Table No 4.5.1.1 Relationship between Angle of Repose (θ) and flow properties.

Angle of Repose (θ) (degrees)	Flow
<25	Excellent
25=30	Good
30-40	Passable
>40	Very poor

METHOD

A funnel was filled to the brim and the test sample was allowed to flow smoothly through the orifice under gravity. From the cone formed on a graph sheet was taken to measure the area of pile, thereby evaluating the flowability of the granules. Height of the pile was kept constant to 2cm measured.

4.5.1.2 Bulk Density

Bulk density is defined as the mass of a powder divided by the bulk volume. The bulk density of a powder depends primarily on particle size distribution, particle shape, and the tendency of the particles to adhere to one another. The bulk density of a powder depends on particle packing and changes as the powder consolidates. A consolidated powder is likely to have a greater arch strength then a less consolidated one and may therefore be more resistant to powder flow. The ease with which a powder consolidates can be used as an indirect method of quantifying powder flow.[65]

Method

Both loose bulk density (LBD) and tapped bulk density (TBD) were determined by tap density tester. A quantity of accurately weighed powder from each formula, previously shaken to break any agglomerates formed was introduced into a measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 seconds interval. The taping was continued until no further change in volume was noted. LBD and TBD were calculated using following formula;

$$LBD = \frac{\text{weight of the powder}}{\text{volume of the packing}} \quad \text{--------- (a)}$$

$$TBD = \frac{\text{weight of the powder}}{\text{volume of the packing}} \quad \text{---------- (b)}$$

4.5.1.3 Carr's Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index. Grading of the powders for their flow properties according to CI is given in Table 4.5.1.3

Table No 4.5.1.3: Grading of the powders for their flow properties according to Carr's Index.

Consolidation Index (Carr's %)	Flow
5 – 15	Excellent
12-16	Good
18-21	Fair to passable
23-35	Poor
33-38	Very poor
>40	Very very poor

(%) CI can be calculated by using the following formula CI (%) $\frac{TBD - LBD}{TBD}$ x 100---------- (c)

4.5.1.4 Hausners Ratio:

Hausner found that the ratio bulk density by tapped density war related to interparticle friction and, as such, could be used to predict powder flow property. He showed that powders with low interparticle friction, such as coarse spheres, have ratios of approximately 1.2. Where more cohesive, less free-flowing powders such as flakes have Hausner ratios greater than 1.6.[70]

$$HR = \frac{\text{Tapped density}}{\text{Bulk density}}$$

Table No 4.5.1.4 Grading of the powders for their flow properties according to Hausners Ratio

HR	Flow
<1.2	Free flowing powder
>1.6	Less free flowing

4.5.2 Post-Compression Parameters

4.5.2.1 *Shape and colour*

The tablets were examined under a lens for the shape of the tablet and colour by keeping the tablets in light.

4.5.2.2. *Uniformity of thickness*

The crown thickness of individual tablet may be measured with a vernier caliper, which permits accurate measurements and provides information on the variation between tablets.

Other technique employed in production control involves placing 5 or 10 tablets in a holding tray, where their total crown thickness may be measured with a sliding caliper scale. The tablet thickness was measured using vernier caliper.

4.5.2.3 Hardness test

Tablets require a certain amount of strength, or hardness and resistance to friability, to withstand mechanical shocks of handling in manufacture, packaging and shipping. The hardness of the tablets was determined using Monsanto Hardness tester. It is expressed in Kg/cm^2. Three tablets were randomly picked from each formulation and the mean and standard deviation values were calculated.

4.5.2.4 Friability test

It is the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. The friability of tablets was determined by using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed [W (initial)] and transferred into friabilator. The friabilator was operated at 25 rpm for 4 mins or run up to 100 revolutions. The tablets were weighed again [W (final)]. The percentage friability was then calculated by,

$$F = \frac{\text{W (initial)} - \text{W (final)} \times 100}{\text{W (initial)}}$$

Table No. 4.5.2.4 Acceptable limit of Friability

Percent Friability	Acceptable limit
<1	Acceptable
>1	Not acceptable

4.5.2.5 Weight variation test

The tablets were selected randomly from each formulation and weighed individually to check for weight variation. The U.S Pharmacopoeia allows a little variation in the weight of a tablet. The percentage deviation in weight variation is shown in table no 4.5.2.5.

Table No. 4.5.2.5 Percentage deviation in weight variation

Average weight of a tablet	Percentage deviation
130 mg or less	10
More than 130 mg and less than 324 mg	7.5
324 mg and above	5

In all the formulations the tablet weight was above 324 mg and, hence 5% maximum difference was allowed.

4.5.2.6 Drug Content Uniformity

The content uniformity test is used to ensure that every tablet contains the amount of drug substance intended with little variation among tablets within a batch. Due to increased awareness of physiological availability, the content uniformity test has been included in the monographs of all coated and uncoated tablets intended for oral administration where the range of size of the dosage form available includes 50 mg or smaller sizes. For content uniformity test, representative samples of 30 tablets are selected and 10 are assayed individually. At least 9 must assay within ± 15% of the declared potency and none may exceed ± 25%.

The amount of active ingredient(s) is determined by the method described in assay and amount of active ingredient is calculated. Since active ingredient of present investigation is not official in any pharmacopoeia the following method was used for determination of drug content.

Twenty tablets were weighed and powdered. The blend equivalent to 20 mg of pantoprazole sodium was weighed and dissolved in sufficient quantity of 0.1N HCl. The solution was filtered through Whatmann filter paper (No.41), suitably diluted with 0.1N HCl and assayed at 281.5 nm, using a UV-Visible double beam spectrophotometer (UV- 1800 Shimadzu).

4.5.2.7 In vitro disintegration time

The process of breakdown of a tablet into smaller particles is called as disintegration. The *in vitro* disintegration time of a tablet was determined using a modified disintegration test used only for fast disintegrating agents.

Method

For a drug to be absorbed from a solid dosage form after oral administration, it must first be in solution, and the first important step toward this condition is usually the break-up of the tablet; a process known as disintegration.

The disintegration time of the water dispersible tablets was determined in accordance with the official European Pharmacopoeia monograph _Dispersible tablets‘, stating a maximum disintegration time of 3 min for dispersible tablets (European Pharmacopoeia, 2001). The

disintegration apparatus (Pharma Test, Hainburg, Germany) had to be modified, since the standard glass tube is 21.5 mm in internal diameter and the tested tablets have, however, a mean diameter of 25 mm.[57] The disintegration was carried out in a beaker consisting of a 200 ml medium. The medium consisted of water at a temperature between 15 and 25°C. Only one tablet at a time was tested and considered disintegrated when completely dispersed fragments were obtained.

4.5.2.8 In vitro dissolution studies

In vitro release studies were carried out using a modified USP XXIII dissolution test apparatus. Two objectives in the development of *in vitro* dissolution tests was to show that,

i) Release of the drug from the tablet is as close as possible upto 100%.

ii) Rate of drug release is uniform from batch to batch and is the same as the release rate from those proven to be bioavailable and clinically effective.

iii) Modification

The normal USP XXIII dissolution apparatus was chosen in which a beaker was placed. This beaker is an elongated one generally used for TLC and other purpose. Another modification was that basket was used in place of paddles because of the narrow mouth opening of the beaker. Outside this beaker water was putted at a level till the dissolution fluid in the beaker reaches. The temperature was validated and kept at 40.1°C and the rotation of the basket was kept at 75 RPM. Only 190 ml dissolution fluid was used. Summary of general *in vitro* dissolution conditions employed throughout the study to determine the *in vitro* dissolution rate for all the formulation is given in the following table.

Table No.4.5.2.8 Summary of general dissolution conditions

Sr. No.	Parameter	Specification
1.	Dissolution medium	190 ml 0.1 N HCl
2.	Temperature	40.1°C ± 5°C
3.	Rotation speed	75 rpm
4.	Volume withdrawn	5 ml every 30 seconds for 10 mins
5.	□max	281.5nm
6.	Beer‘s range	2 – 100□g/ml
7.	Tablet taken	1 tab (known drug content)

Fig No. 4.5.2.8: Modification done in the dissolution apparatus.

Stability studies

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutic and toxicological specifications. Stability studies was conducted as per the specified ICH guidelines the selected best formulation. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and enables recommended storage conditions, re-test periods and shelf lives to be established.

In the present study, the ODTs where packed in suitable packaging material and stored under the following conditions for a period of 90 days at 40 ± 1 ^{0}C and RH 75 ± 5%

The tablets were withdrawn after period of 15, 45 and 90days and analyzed for physical characterization (Visual defects, hardness, friability, disintegration, dissolution etc) and drug content.

4.5.2.9 Similarity factor

Moore and Flanner proposed two new indices (f_1 and f_2) to compare dissolution profiles of a test and a reference formulations . The concept of similarity factor (f_2) has been endorsed by Food and Drug Administration (FDA); therefore, it is widely adopted in formulation and development and dossier preparation. The equation of similarity factor proposed by Moore

and Flanner is represented in Eqn

$$f_2 = 50 \times \log \{[1 / (1 + (\Sigma (R_t - T_t)^2) / N)]^{1/2} \times 100\}$$

Where, N = Number of experimental data.

This is a widely used factor used to determine the similarity between two formulations. It is widely used when you have to check your formulation is similar to that of the marketed formulation. Values of f_2 between 50 and 100 can be considered as superimposed dissolution profiles.[66]

6. RESULTS

The present study was aimed at formulating ODTs of PPIs. This is a novel approach for increasing the patient compliance with a faster onset of action as compared to the conventional formulation mainly used at present.

5.1 Identification of Pantoprazole Sodium

5.1.1 FTIR Studies

FTIR is one of the most widely used methods for checking the compatability between substances and for the identification of the drug. Pantoprazole sodium, excipients and the selected formulations where analysed using infrared spectrophotometer (Shimadzu FTIR 8-400, S model).

All the samples were scanned at the resolution of 4 cm^{-1} over the wave number region 4000-400 cm^{-1} using KBr disk method. This KBr disks are formed by taking drug and KBr in a ratio of 1:100 respectively. Then this mixture was mixed well in mortar for three to five mins. A very small amount of this mixture was uniformly spread and sandwich between the pellets and pressed using KBr pellet press at a pressure of 20,000 psi for 1 mins. The pressure was then released and pellet was placed into the pellet holder and thus scanned in the IR region.

The selected formulation shows the characteristics peak similar to that obtained in the pure pantoprazole sodium indicating that there is no incompatability between the drug and the excipients used.

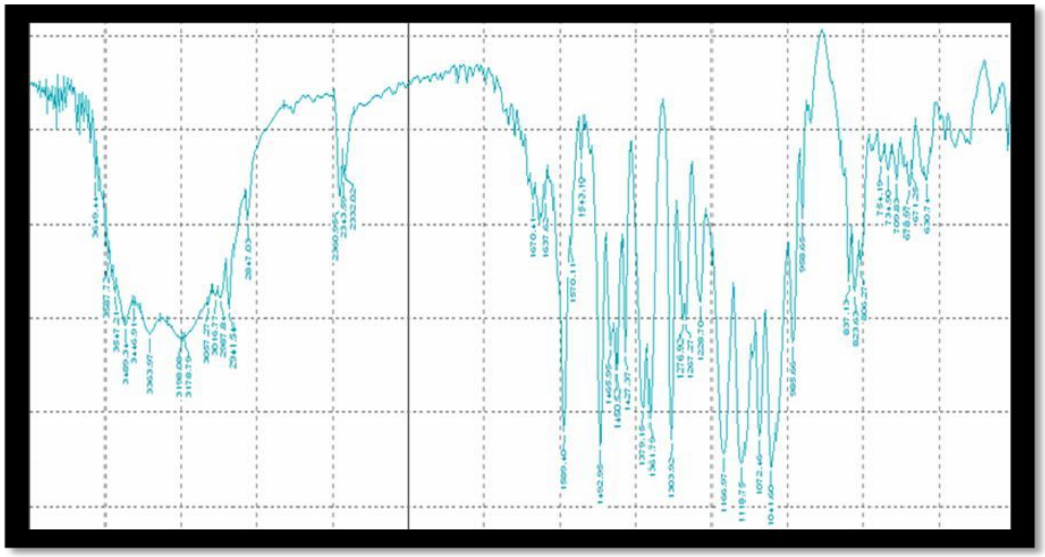


Fig No. 5.1.1.1: FTIR scan of Pantoprazole sodium.

Table no.5.1.1.1: Different IR peaks for Pantoprazole Sodium.

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
N-H	3500-3300 cm^{-1}	1500 cm^{-1}	3363.97cm^{-1} & 3489.94 cm^{-1}	1450 cm^{-1}
C-N	1350-1000 cm^{-1}		1303.92 cm^{-1}	
C=C	16000-1400cm^{-1}		1585.54 cm^{-1} & 1469.81cm^{-1}	
AromaticC-H	3150-3050 cm^{-1}	900-690 cm^{-1}	3057.27 cm^{-1}	823.63 cm^{-1}& 806.37cm^{-1}
C-O	1100-1300 cm^{-1}		1166.97 cm^{-1}	
C-F	1400-1000 cm^{-1}		1303.92 cm^{-1}	

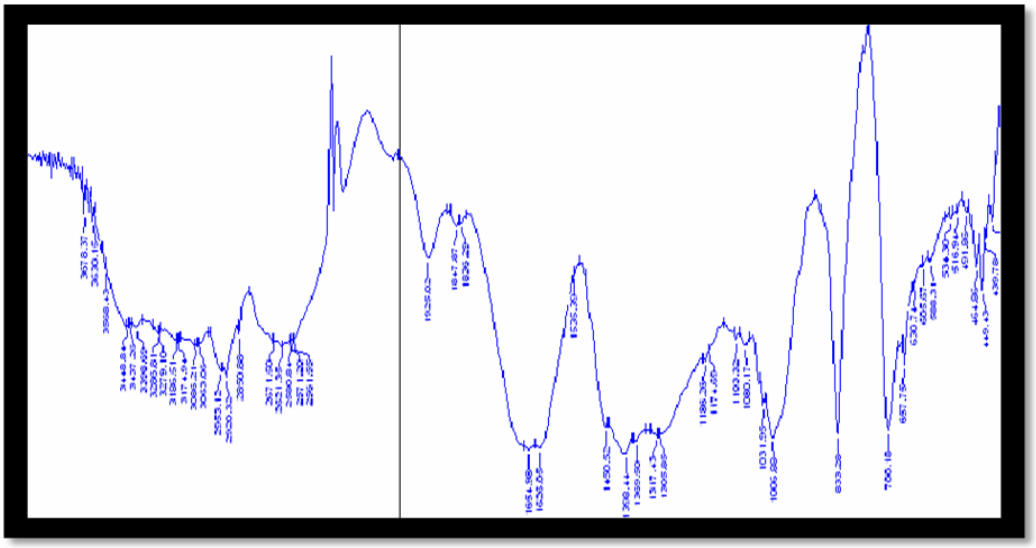


Fig no. 5.1.1.2: FTIR scan of formulation code F4.

Table no. 5.1.1.2: Different IR peaks for formulation code F4.

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
N-H	3500-3300cm^{-1}	1500 cm^{-1}	3398.69 cm^{-1}	1450.52 cm^{-1}
C-N	1350-1000 cm^{-1}		1317.43 cm^{-1}	
C=C	16000-1400cm^{-1}		1535.39 cm^{-1}	
AromaticC-H	3150-3050cm^{-1}	900-690 cm^{-1}	3063.40 cm^{-1}	833.28 cm^{-1}
C-O	1100-1300cm^{-1}		1174.69 cm^{-1}	
C-F	1400-1000cm^{-1}		1305.85 cm^{-1}	

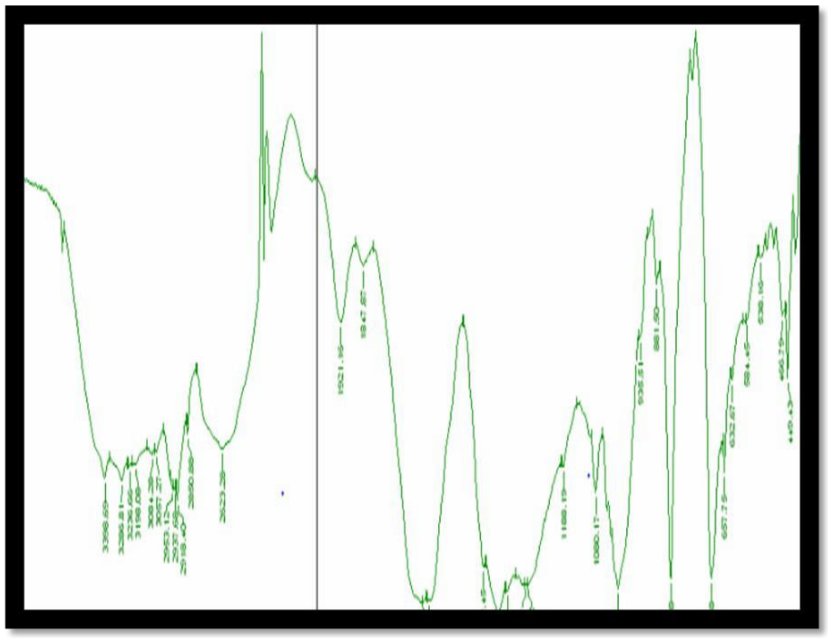


Fig no. 5.1.1.3: FTIR scan of formulation code F3.

Table no. 5.1.1.3: Different IR peaks for formulation code F3.

Functional group	Characteristic peak		Observed peak	
	Stretching	Bending	Stretching	Bending
N-H	3500-3300 cm^{-1}	1500 cm^{-1}	3398.69 cm^{-1}	1452.45 cm^{-1}
C-N	1350-1000 cm^{-1}		1317.43 cm^{-1}	
C=C	16000-1400cm^{-1}		1549.90 cm^{-1}	
Aromatic C-H	3150-3050 cm^{-1}	900-690 cm^{-1}	3084.28 cm^{-1}	833.28 cm^{-1}
C-O	1100-1300 cm^{-1}		1188.19 cm^{-1}	
C-F	1400-1000 cm^{-1}		1306.88 cm^{-1}	

5.2 Standard Calibration Curve

5.2.1 Standard calibration curve of Pantoprazole sodium.

Table No. 5.2.1: Calibration Curve of Pantoprazole sodium in 0.1N Hydrochloric acid.

Sr. No.	Concentration (µg/ml)	Absorbance at 281.5 nm
1.	0	0
2.	5	0.1535
3.	10	0.32583
4.	15	0.505
5.	20	0.6525
6.	25	0.81783

* Absorbance shown as mean of 6 replicates

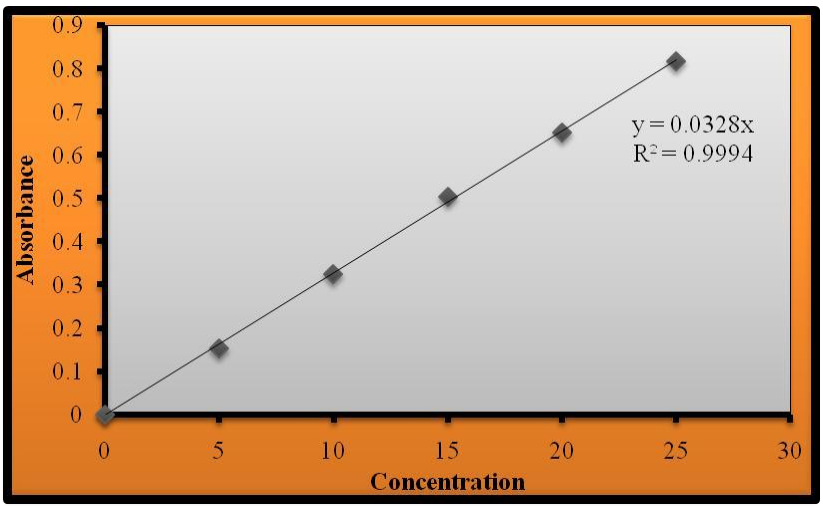


Fig. No. 5.2.1a: Calibration Curve of Pantoprazole sodium in 0.1N Hydrochloric Acid.

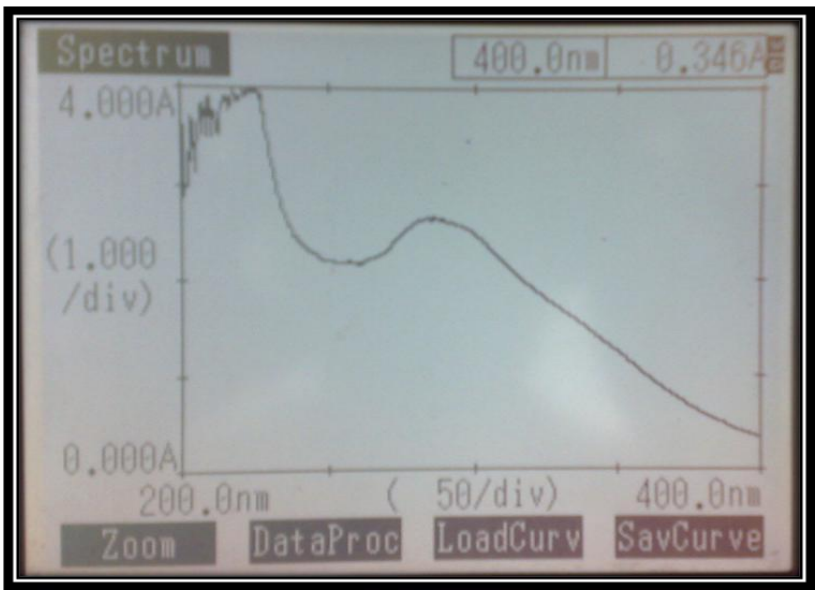


Fig No. 5.2.1b: Ultravoilet Scan of Pantoprazole sodium at 1.2 pH.

5.2.2 Standard calibration curve of Omeprazole sodium

Omeprazole sodium was used for the determination of the standard curve. The marketed product, **"Omez Insta"** label claim states that it contains only omeprazole. Therefore a correction with respect to the weight of sodium was performed and omeprazole sodium used was expressed in terms of pure omeprazole alone.

METHOD

Molecular weight of omeprazole: 345.4

Molecular weight of omeprazole sodium: 345.4+23= 368.4

Therefore, 368.4 gm of omeprazole sodium contains 345.4 gm of omeprazole.

Using the above relationship, the concentration of omeprazole was calculated from the actual obtained concentrations of omeprazole sodium, as recorded in the table 5.2.2a below.

Table No. 5.2.2a Concentration of Omeprazole in Omeprazole sodium

Sr. No.	Conccentration of Omeprazole Sodium	entration of Omeprazole in Omeprazole Sodium
1	0 µg/ml	0 µg/ml
2.	2 µg/ml	1.875 µg/ml
3.	4 µg/ml	3.750 µg/ml
4.	6 µg/ml	5.625 µg/ml
5.	8 µg/ml	7.501 µg/ml
6.	10 µg/ml	9.376 µg/ml

* Absorbance shown as mean of 6 replicates

Table No. 5.2.2b Calibration Curve of Omeprazole in 0.1N Hydrochloric acid.

Sr. No.	Concentration (µg/ml)	Absorbance at 301nm
1.	0	0
2.	1.875	0.05275
3.	3.750	0.10575
4.	5.625	0.16025
5.	7.501	0.21125
6.	9.376	0.261

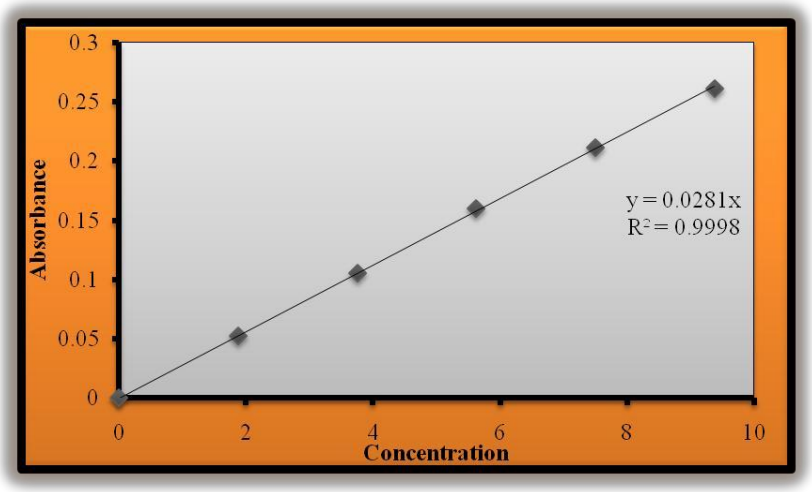


Fig. No. 5.2.2 Calibration Curve of Omeprazole in 0.1N Hydrochloric Acid.

5.3 Evaluation

5.3.1 Pre compression evaluation parameters

Table No. 5.3.1.1 Evaluation of powder blend prepared by superdisintegrants addition method.

FC	*Angle of repose*	*LBD(gm/cm^3)*	*TBD(gm/cm^3)*	*CI (%)*	*HR*
F 1	25.82	0.71	0.81	12.84	1.15
F 2	27.35	0.70	0.80	12.50	1.14
F 3	24.28	0.72	0.81	11.32	1.13
F4	25.11	0.69	0.79	12.73	1.15
F 5	29.05	0.69	0.81	14.53	1.17
F 6	26.76	0.70	0.82	14.55	1.17
F 7	25.12	0.68	0.78	12.50	1.14
F 8	25.29	0.71	0.83	14.55	1.17
F 9	29.51	0.69	0.80	14.29	1.17
F 10	26.76	0.70	0.81	12.73	1.15
F 11	25.12	0.70	0.81	12.73	1.15
F12	27.76	0.69	0.81	14.29	1.17
F 13	27.15	0.69	0.80	14.29	1.17
F 14	28.83	0.69	0.79	12.49	1.14
F 15	26.57	0.71	0.83	14.29	1.17
F 16	26.38	0.71	0.81	12.73	1.15

Table No. 5.3.1.2: Evaluation of different powder blend prepared by combination of different superdisintegrants.

FC	*Angle of repose*	*LBD(gm/cm^3)*	*TBD(gm/cm^3)*	*CI (%)*	*HR*
F 17	25.11	0.69	0.80	14.28	1.17
F 18	28.18	0.690	0.79	12.48	1.14
F 19	26.19	0.70	0.81	12.72	1.14
F20	23.50	0.67	0.78	14.54	1.17

Table No. 5.3.1.3: Evaluation of different powder blend prepared by sublimation method.

FC	*Angle of repose*	*LBD(gm/cm^3)*	*TBD(gm/cm^3)*	*CI (%)*	*HR*
F 21	24.44	0.70	0.82	14.54	1.17
F 22	27.35	0.70	0.80	12.50	1.14
F 23	24.12	0.70	0.80	11.33	1.13

Table No. 5.3.1.4: Evaluation of different powder blend prepared by combination of superdisintegrants and sublimationmethod.

FC	*Angle of repose*	*LBD(gm/cm^3)*	*TBD(gm/cm^3)*	*CI (%)*	*HR*
F 24	24.12	0.71	0.83	14.55	1.17
F 25	24.78	0.72	0.81	11.11	1.13

Table No. 5.3.1.5: Evaluation of different powder blend prepared by treated natural gums used as Superdisintegrants.

FC	*Angle of repose*	*LBD(gmc/m^3)*	*TBD(gm/cm^3)*	*CI (%)*	*HR*
F 26	25.46	0.70	0.81	12.73	1.15
F 27	24.94	0.70	0.81	12.72	1.15

5.3.2 Post compression evaluation parameters

Table No. 5.3.2.1: Evaluation of Orodispersible tablet formulations prepared by using superdisintegrant addition method.

FC	*Uniformity of Thickness(mm)*	*Hardness (kg/cm^2)*	*Friability %*	*Weight Variation (mg)*
F 1	6.98±0.04	3.37±0.15	0.30±0.13	1303±65.15
F 2	7.01±0.025	3.57±0.06	0.58±0.35	1315.5 ± 65.78
F 3	6.89±0.32	3.43±0.06	0.44±0.43	1293.5 ± 64.68
F4	7.01±0.03	3.57±0.06	0.35±0.24	1295± 58.75
F 5	6.89±0.071	3.77±0.06	0.30±0.08	1306.5±65.33
F 6	6.86±0.04	4.2±0	0.61±0.34	1303.5±65.18
F 7	6.95 ± 0.03	3.47±0.06	0.43±0.19	1309±65.45
F 8	6.96±0.03	4.17±0.06	0.52±0.19	1296.5±64.83
F 9	6.96±0.03	4.23±0.06	0.17±0.11	1316.5±70.58
F 10	6.95±0.05	3.83±0.06	0.15±0.077	1298.5±64.95
F 11	6.97 ± 0.01	3.7±0.54	0.56±0.31	1304.5±65.25
F12	7.03±0.05	3.4±0	0.21±0.045	1297±69.6
F 13	7.04 ± 0.03	3.4±0.1	0.39±0.28	1301.5±65.08
F 14	6.95 ± 0.04	3.13±0.06	0.45±0.09	1288.5±69.18
F 15	7.00±0.02	3.23±0.12	0.64±0.42	1296±64.8
F 16	6.94±0.01	3.47±0.06	0.51±0.42	1299±60

*All the parameters shown above are based on 3 replicates and are expressed as Mean ± S.D

Table No. 5.3.2.2: Evaluation of Orodispersible tablet formulations prepared by using combination of different superdisintegrants.

FC	*Uniformity of Thickness(mm)*	*Hardness (kg/cm^2)*	*Friability %*	*Weight Variation (mg)*
F 17	7.03±0.01	3.3±0.1	0.38±0.20	1307.5±65.38
F 18	7±0.01	3.5±0	0.39±0.20	1299.5±64.98
F 19	7.05±0.01	3.47±0.06	0.33±0.09	1303.5±65.18
F20	6.99±0.01	3.27±0.06	0.355±0.11	1306.5+65.38

* All the parameters shown above are based on 3 replicates and are expressed as Mean ±S.D

Table No. 5.3.2.3: Evaluation of Orodispersible tablet formulations prepared by using Sublimation method.

FC	*Uniformity of Thickness(mm)*	*Hardness (kg/cm^2)*	*Friability %*	*Weight Variation (mg)*
F 21	6.96±0.03	3.37±0.058	0.30±0.07	1308.5±65.43
F 22	7.01±0.01	3.43±0.058	0.51±0.19	1305±65.25
F 23	7.04+ 0.03	3.53±0.058	0.20±0.048	1308±65.4

* All the parameters shown above are based on 3 replicates and are expressed as Mean ±S.D

Table No. 5.3.2.4: Evaluation of Orodispersible tablet formulations prepared by using combination of superdisintegrants and sublimationmethod.

FC	*Uniformity of Thickness(mm)*	*Hardness (kg/cm^2)*	*Friability %*	*Weight Variation (mg)*
F 24	6.99±0.02	3.3±0.1	0.46±0.24	1308±65.4
F 25	6.98±0.01	3.3±0	0.38±0.22	1308±65.4

* All the parameters shown above are based on 3 replicates and are expressed as Mean ±S.D

Table 5.3.2.5: Evaluation of Orodispersible tablet formulations prepared by using formulations using treated natural gums used as Superdisintegrants.

FC	*Uniformity of Thickness(mm)*	*Hardness (kg/cm^2)*	*Friability %*	*Weight Variation (mg)*
F 26	7.02±0.012	3.3±0.1	0.55±0.17	1310.5±65.53
F 27	6.98±0.01	3.3±0.1	0.45±0.18	1299.5±64.98

* All the parameters shown above are based on 3 replicates and are expressed as Mean ±S.D

5.3.3 Disintegration test

Disintegration plays an important role for ODTs as the drug release and its pattern purely depends on the disintegration time. For ODTs shortest disintegration time is desired as the

dosage form should be capable of being immediately absorbed with the disintegrated portion reaching the gastric fluid in seconds without the requirement of water, for ingestion.

Disintegration time of 3 min (180 sec) was fixed as the upper limit for branding formulations as ODTs as specified by European Pharmacopoeia. Therefore, formulations having disintegration time greater than 180 sec were not selected for further studies such as drug content, *in vitro* dissolution etc.

Approaches such as sublimation methods, combination of superdisintegrants and subliming agents, and treated natural gums to be used as superdisintegrants did not yield favourable results with respect to the disintegration test.

Table No. 5.3.3: *In vitro* Disintegration Time.

FC	Approach	disintegration time (Seconds)
F1	Superdisintegrants addition	Above 180 sec
F2	Superdisintegrants addition	96.67 ± 5.03
F3	Superdisintegrants addition	56.33 ±5.03
F4	Superdisintegrants addition	24.33 ± 3.79
F5	Superdisintegrants addition	Above 180 sec
F6	Superdisintegrants addition	166.67 ± 10.41
F7	Superdisintegrants addition	87 ± 3.06
F8	Superdisintegrants addition	Above 180 sec
F 9	Superdisintegrants addition	172.33 ± 2.52
F 10	Superdisintegrants addition	115.67 ± 4.04
F 11	Superdisintegrants addition	Above 180 sec
F 12	Superdisintegrants addition	Above 180 sec
F13	Superdisintegrants addition	170.67 ± 8.02
F14	Superdisintegrants addition	Above 180 sec
F15	Superdisintegrants addition	Above 180 sec
F16	Superdisintegrants addition	166 ± 5.03
F17	Combination of different superdisintegrants	149.67 ± 1.53
F18	Combination of different superdisintegrants	97.33 ± 3.06
F19	Combination of different superdisintegrants	77.67 ± 5.51
F20	Combination of different superdisintegrants	143.33 ± 9.87
F21	Addition of Sublimating agent	Above 180 sec
F22	Addition of Sublimating agent	Above 180 sec
F23	Addition of Sublimating agent	Above 180 sec
F24	Combination of superdisintegrants and sublimation method	Above 180 sec
F25	Combination of superdisintegrants and sublimation method	Above 180 sec
F26	Addition of treated natural gums used as superdisintegrants	Above 180 sec
F27	Addition of treated natural gums used as superdisintegrants	Above 180 sec

All the parameters shown above are based on 3 replicates and are expressed as Mean ±S.D

Drug content.

Table No. 5.3.4 Drug Content

FC	Approach	Drug content in mg
`F2	Superdisintegrants addition	18.88 ± 0.38
F3	Superdisintegrants addition	18.19 ± 0.33
F4	Superdisintegrants addition	19.96 ± 0.34
F6	Superdisintegrants addition	18.47 ± 0.35
F7	Superdisintegrants addition	19.19 ± 0.50
F9	Superdisintegrants addition	19.94 ± 0.60
F10	Superdisintegrants addition	19.90 ± 0.18
F13	Superdisintegrants addition	20.19 ± 0.33
F 16	Superdisintegrants addition	18.69 ± 0.33
F 17	Combination of different superdisintegrants	19.71 ± 0.67
F 18	Combination of different superdisintegrants	18.44 ± 0.33
F 19	Combination of different superdisintegrants	19.52 ± 0.49
F20	Combination of different superdisintegrants	18.40 ± 0.46

* All the parameters shown above are based on 3 replicates and are expressed as Mean ±S.D

No limits for the drug content are presently available in the pharmacopoeias for PPI prepared as ODTs. Therefore, IP 2010 limits of 90 to 110% for enteric coated tablets were used in this study as a standard for comparison.

The drug content in the selected formulation was found to be in the range of 90.94% to 100.94% with a standard deviation of ± 0.18 to ± 0.60. This lies within the IP limits for enteric coated pantoprazole tablets.

5.3.4 Drug dissolution profile

Drug dissolution profile is one of the important aspects in development of all the dosage forms. In this research project dissolution time of 10 min was chosen since the expected dissolution time for ODT was around 5 min. In addition, IP has prescribed a dissolution time of 10 min for Ondansetron DTs. Certain modification where done as explained in the 4.5.2.8 *In vitro* dissolution studies under the topic called methodology.

All the formulation which passed the *in vitro* disintegration where subjected to *in vitro* dissolution studies. This study also plays an important part in the selection of the best formulation among all.

5.3.4.1 Dissolution drug profile of ODT formulations prepared by superdisintegrant addition method.

Table No. 5.3.5.1: Cumulative percent drug release from Orodispersible tablets prepared by superdisintegrant addition method.

Time (mins)	F2	F3	F4	F6	F7	F9	F10	F13	F16
0	0 ± 0	0 ±0	0 ±0	0 ±0	0 ±0	0 ±0	0 ±0	0 ±0	0 ±1.523
0.5	33.03 ± 3.18	87.65 ±2.17	95.35 ±0.72	20.69 ±5.73	40.91 ±2.78	37.18 ±1.57	47.00 ±1.78	3.97 ±1.93	8.10 ±1.5
1	44.52 ±1.40	93.59±2.10	102.52±0.23	31.06 ±2.24	75.77 ±3.26	60.45±5.28	67.64 ±4.05	7.60 ±1.70	11.81 ±1.96
1.5	73.11 ±3.35	97.34 ±.084	102.12±0.60	45.14±1.89	87.96 ±2.64	78.42 ±3.78	82.74 ±4.63	18.46 ±1.94	25.22 ±1.01
2	82.14 ±3.06	98.87 ±1.25	101.80±0.70	52.25 ±2.55	98.64 ±1.06	89.76 ±5.01	84.84 ±5.58	24.82 ±3.82	30.80 ±1.10
2.5	87.26 ±1.82	92.99 ±0.91	100.46±0.91	59.28 ±2.99	102.18±3.13	94.51±2.40	84.55 ±1.37	20.62±10.88	40.71 ±2.52
3	90.35 ±1.61	88.14 ±1.55	99.81 ±1.49	69.67 ±3.40	99.71 ±3.21	89.42 ±2.49	85.54 ±2.22	23.57±12.65	46.10 ±2.26
3.5	92.75 ±1.63	83.57 ±2.13	98.39 ±2.06	80.87 ±6.78	98.65 ±1.98	87.58 ±3.50	85.76 ±3.42	34.84 ±3.90	51.36 ±2.70
4	91.93 ±0.58	76.23 ±2.95	97.12 ±3.10	94.17 ±1.48	98.05 ±0.65	86.52 ±2.27	83.47 ±2.57	38.41 ±3.99	59.99 ±3.07
4.5	92.69 ±0.85	71.00 ±1.27	96.30 ±3.27	97.06 ±0.91	97.99 ±1.46	85.75 ±2.15	81.51 ±4.41	42.42 ±3.66	66.20 ±2.96
5	91.60 ±2.51	68.99 ±1.67	93.97 ±3.27	96.42 ±1.95	97.80 ±1.13	85.35 ±1.86	79.53 ±2.82	48.94 ±1.04	82.70 ±8.15
5.5	90.03 ±2.72	66.43 ±1.40	92.41 ±2.75	95.70 ±1.28	97.16 ±0.85	85.71 ±1.66	79.32 ±3.31	54.28 ±2.28	85.37 ±3.37
6	90.73 ±1.95	63.66 ±2.15	89.92 ±2.82	94.99 ±1.19	96.37 ±0.84	84.52 ±1.82	78.98 ±2.83	59.95 ±2.29	84.72 ±4.68
6.5	88.97 ±2.16	61.16 ±1.78	87.61 ±2.46	94.13 ±1.44	97.37 ±1.69	84.64 ±2.31	79.11 ±3.62	66.11 ±0.99	89.73 ±1.08
7	88.52 ±2.18	58.49 ±2.10	84.96 ±1.57	92.95 ±2.40	95.62 ±2.08	85.90 ±1.69	77.94 ±2.36	70.70 ±1.55	92.11 ±1.15
7.5	88.64 ±2.35	55.34 ±3.18	85.06 ±1.34	91.36 ±2.14	95.10 ±1.68	85.53 ±1.43	77.89 ±2.35	75.89 ±1.57	90.38 ±1.78
8	89.20 ±2.81	53.65 ±2.15	84.04 ±1.14	90.33 ±1.60	94.29 ±2.64	84.85 ±1.30	77.21 ±1.79	82.56 ±1.46	92.20 ±2.76
8.5	87.92 ±2.87	51.47 ±2.95	83.30 ±1.56	90.18 ±1.87	93.33 ±2.71	84.36 ±0.98	75.72 ±1.36	84.30 ±2.35	90.04 ±1.95
9	88.68 ±2.36	49.30 ±3.27	82.10 ±1.50	88.63 ±1.80	93.39 ±4.62	85.20 ±1.27	75.80 ±1.78	84.93 ±3.79	90.41 ±3.76
9.5	88.16 ±2.61	47.55 ±3.49	81.14 ±0.86	87.63 ±3.29	92.55 ±5.36	85.46 ±1.59	74.88 ±2.17	84.79 ±3.03	87.39 ±4.20
10	88.224±2.72	45.27 ±3.78	80.56 ±1.21	87.76 ±4.44	90.88 ±4.58	85.06 ±1.68	75.99 ±2	86.52 ±3.12	84.34 ±3.43

* Here n=6 for F3 and F4 formulations and n=4 for rest of all formulations (F2, F6, F7, F9, F10, F13, F16

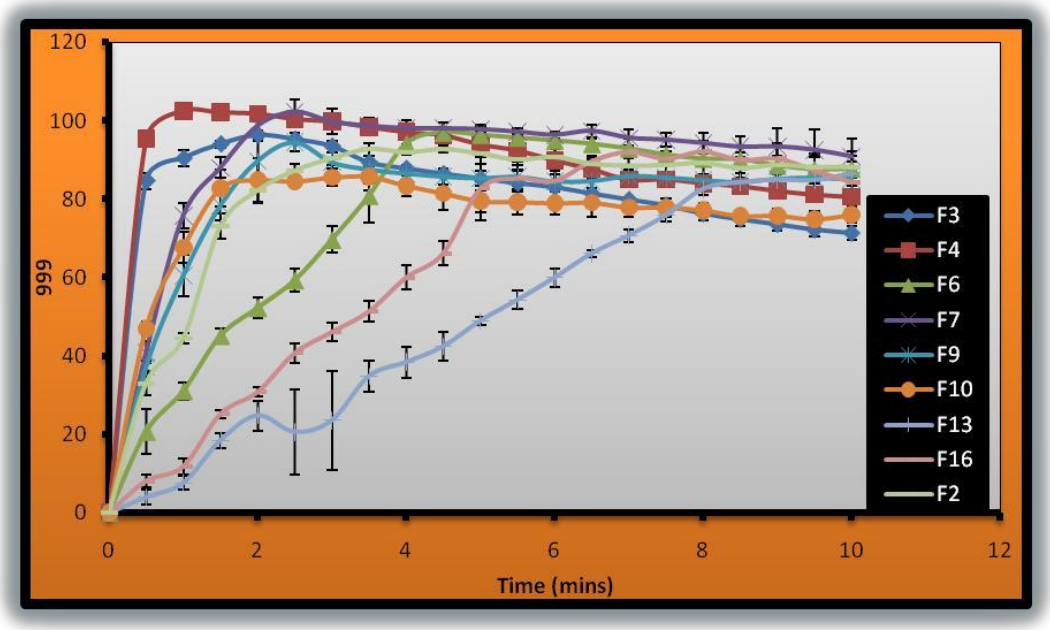


Fig No. 5.3.5.1: Cumulative percentage drug released from Orodispersible tablet formulations prepared by superdisintegrant addition method.

5.3.4.2 Dissolution profile study of Orodispersible tablet formulations prepared by combination of different superdisintegrants

Table No. 5.3.5.2: Cumulative percent drug released from Orodispersible tablet formulations prepared by combination of different superdisintegrants.

Time (min)	F17	F18	F19	F20
0	0 ±0	0 ±0	0 ±0	0 ±0
0.5	2.79±1.29	33.09 ±0.97	22.96 ±4.28	36.15 ±2.25
1	34.49 ±2.70	57.63 ±5.58	43.03 ±2.2	50.01 ±1.11
1.5	49.86 ±1.56	79.65 ±3.99	80.96 ±3.39	77.28 ±7.86
2	61.99 ±0.42	85.95 ±2.52	92.70 ±1.95	86.85 ±2.30
2.5	72.60 ±1.57	90.60 ±3.19	98.08 ±2.20	93.134 ±2.50
3	81.64 ±1.73	92.57 ±2.74	98.14 ±0.86	94.53 ±1.68
3.5	88.01 ±1.50	95.17 ±1.09	98.37 ±1.36	95.42 ±1.08
4	84.10 ±2.72	94.65 ±1.42	96.26 ±1.39	94.98 ±0.97
4.5	89.14 ±1.30	93.25 ±3.31	94.34 ±0.80	95.19 ±1.75
5	89.30 ±1.73	92.57 ±2.99	94.21 ±0.91	96.41 ±1.28
5.5	89.78 ±1.47	92.21 ±2.91	93.57 ±0.78	95.99 ±1.73
6	90.82 ±1.30	92.68 ±4.43	92.70 ±0.95	95.01 ±2.70
6.5	91.85 ±1.22	92.31 ±6.21	92.45 ±1.85	94.77 ±3.03
7	92.32 ±1.47	91.15 ±4.54	91.15 ±1.74	94.95 ±2.51
7.5	93.05 ±1.45	90.63 ±4.68	91.14 ±2.83	94.36 ±2.73
8	93.68 ±1.26	90.22 ±3.83	90.55 ±2.99	93.31 ±3.09
8.5	94.20 ±2.93	89.92 ±3.63	91.03 ±3.30	93.47 ±2.40
9	94.38 ±1.74	88.99 ±3.22	91.19 ±3.08	91.33 ±3.19

9.5	93.93 ±2.17	89.30 ±3.12	91.31 ±3.41	91.27 ±3.86
10	93.71 ±1.84	90.62 ±4.10	91.47 ±3.30	90.85 ±3.79

*Here n=4 replicates for formulation F17, F18, F19 and F20

5.3.4.3 Dissolution profile study of Orodispersible tablet formulations prepared by combination of different superdisintegrants

Table No. 5.3.5.2: Cumulative percent drug released from Orodispersible tablet formulations prepared by combination of different superdisintegrants.

Time (min)	F17	F18	F19	F20
0	0 ±0	0 ±0	0 ±0	0 ±0
0.5	2.79±1.29	33.09 ±0.97	22.96 ±4.28	36.15 ±2.25
1	34.49 ±2.70	57.63 ±5.58	43.03 ±2.2	50.01 ±1.11
1.5	49.86 ±1.56	79.65 ±3.99	80.96 ±3.39	77.28 ±7.86
2	61.99 ±0.42	85.95 ±2.52	92.70 ±1.95	86.85 ±2.30
2.5	72.60 ±1.57	90.60 ±3.19	98.08 ±2.20	93.134 ±2.50
3	81.64 ±1.73	92.57 ±2.74	98.14 ±0.86	94.53 ±1.68
3.5	88.01 ±1.50	95.17 ±1.09	98.37 ±1.36	95.42 ±1.08
4	84.10 ±2.72	94.65 ±1.42	96.26 ±1.39	94.98 ±0.97
4.5	89.14 ±1.30	93.25 ±3.31	94.34 ±0.80	95.19 ±1.75
5	89.30 ±1.73	92.57 ±2.99	94.21 ±0.91	96.41 ±1.28
5.5	89.78 ±1.47	92.21 ±2.91	93.57 ±0.78	95.99 ±1.73
6	90.82 ±1.30	92.68 ±4.43	92.70 ±0.95	95.01 ±2.70
6.5	91.85 ±1.22	92.31 ±6.21	92.45 ±1.85	94.77 ±3.03
7	92.32 ±1.47	91.15 ±4.54	91.15 ±1.74	94.95 ±2.51
7.5	93.05 ±1.45	90.63 ±4.68	91.14 ±2.83	94.36 ±2.73
8	93.68 ±1.26	90.22 ±3.83	90.55 ±2.99	93.31 ±3.09
8.5	94.20 ±2.93	89.92 ±3.63	91.03 ±3.30	93.47 ±2.40
9	94.38 ±1.74	88.99 ±3.22	91.19 ±3.08	91.33 ±3.19
9.5	93.93 ±2.17	89.30 ±3.12	91.31 ±3.41	91.27 ±3.86
10	93.71 ±1.84	90.62 ±4.10	91.47 ±3.30	90.85 ±3.79

*Here n=4 replicates for formulation F17, F18, F19 and F20

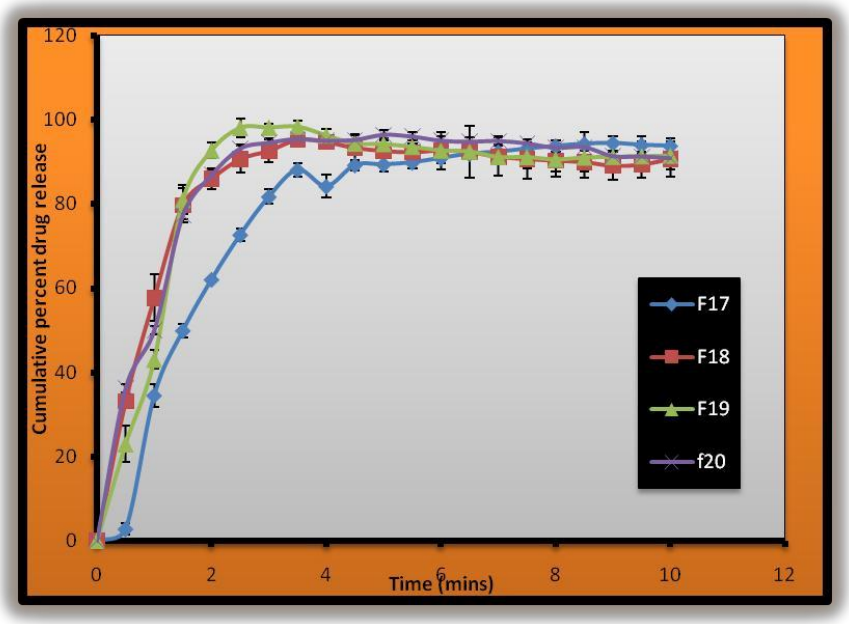


Fig No. 5.3.5.2: Cumulative percentage drug released from Orodispersible tablet formulations prepared by combination of different superdisintegrants.

Based on the disintegration time and the release patterns, formulations coded F4 and F3 were selected as the optimum formulations which fulfil best the criteria for ODTs.

5.3.4.4 Dissolution profile of reference marketed product

OMEZ INSTA was used as a reference for the evaluation of the similarity in drug release of the reference and the selected formulations.

Table no. 5.3.5.3: Dissolution profile of OMEZ INSTA.

Time (mins)	Cumulative percent drug release*
0	0 ±0
0.5	89.90 ±3.43
1	98.11 ±2.71
1.5	100.27 ±1.29
2	101.95 ±1.92
2.5	101.57 ±1.58
3	101.12 ±0.84
3.5	100.36 ±1.57
4	101.42 ±0.98
4.5	100.36 ±2.14
5	100.53 ±2.13
5.5	99.22 ±3.13
6	99.07 ±3.22
6.5	98.62 ±2.4
7	98.89 ±2.65
7.5	98.40 ±2.25

8	98.26 ±2.77
8.5	97.12 ±2.53
9	96.39 ±3.56
9.5	93.98 ±5.64
10	90.15 ±2.70

* Here for Omez Insta n=6 replicates

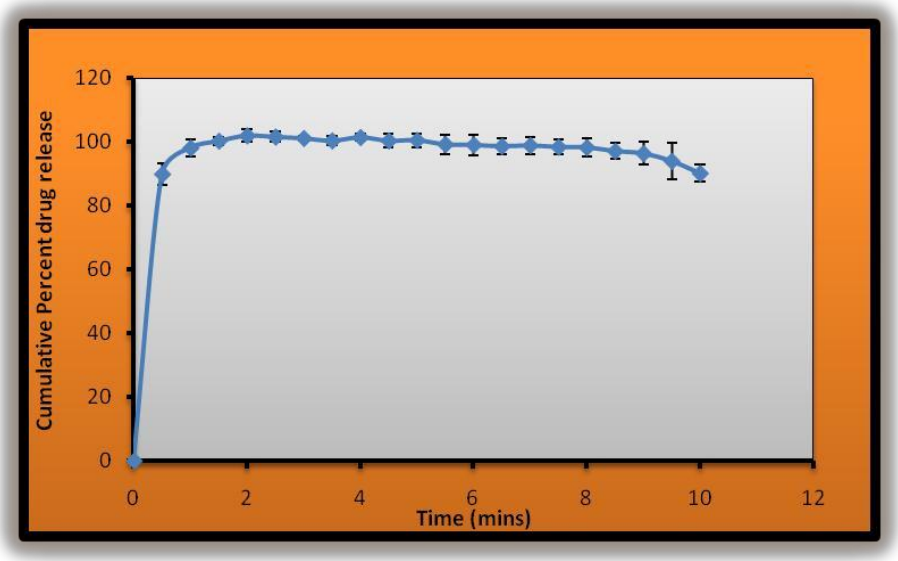


Fig No. 5.3.5.3: Cumulative percent drug release of OMEZ INSTA.

5.3.4.5 Comparison of dissolution profile between selected F4 and F3 formulations with marketed OMEZ INSTA

Table No.5.3.5.4: Comparative table showing cumulative percent drug release of the selected formulations F4 and F3 with marketed formulation OMEZ INSTA.

Time (mins)	F3	Standard Formulation	F4
0	0 ±0	0 ±0	0 ±0
0.5	87.65 ±2.17	89.90 ±3.43	95.35 ±0.72
1	93.59±2.10	98.11 ±2.71	102.52±0.23
1.5	97.34 ±.084	100.27 ±1.29	102.12±0.60
2	98.87 ±1.25	101.95 ±1.92	101.80±0.70
2.5	92.99 ±0.91	101.57 ±1.58	100.46±0.91
3	88.14 ±1.55	101.12 ±0.84	99.81 ±1.49
3.5	83.57 ±2.13	100.36 ±1.57	98.39 ±2.06
4	76.23 ±2.95	101.42 ±0.98	97.12 ±3.10
4.5	71.00 ±1.27	100.36 ±2.14	96.30 ±3.27
5	68.99 ±1.67	100.53 ±2.13	93.97 ±3.27
5.5	66.43 ±1.40	99.22 ±3.13	92.41 ±2.75
6	63.66 ±2.15	99.07 ±3.22	89.92 ±2.82
6.5	61.16 ±1.78	98.62 ±2.4	87.61 ±2.46
7	58.49 ±2.10	98.89 ±2.65	84.96 ±1.57

7.5	55.34 ±3.18	98.40 ±2.25	85.06 ±1.34
8	53.65 ±2.15	98.26 ±2.77	84.04 ±1.14
8.5	51.47 ±2.95	97.12 ±2.53	83.30 ±1.56
9	49.30 ±3.27	96.39 ±3.56	82.10 ±1.50
9.5	47.55 ±3.49	93.98 ±5.64	81.14 ±0.86
10	45.27 ±3.78	90.15 ±2.70	80.56 ±1.21

* n=6 replicates for all the 3 formulations.

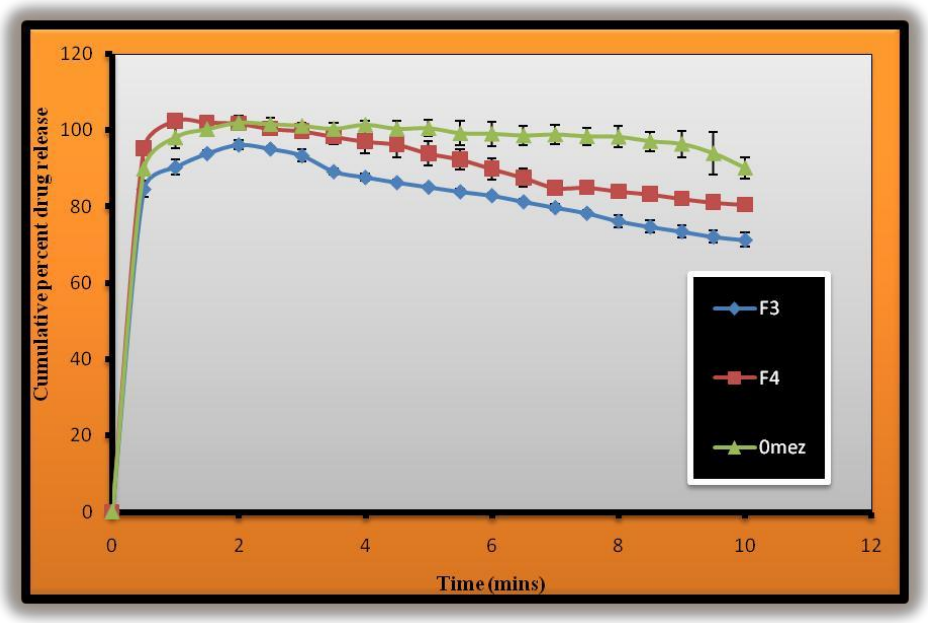


Fig No. 5.3.5.4: table showing cumulative percent drug release of the selected formulation F4 and F3 and marketed formulation OMEZ INSTA.

5.3.6 Similarity factor

Table No 5.3.6: similarity factor of formulation F3 and F4.

Similarity factor with respect to standard formulation "OMEZ INSTA"	
F3	**F4**
50.6033	72.0016

Since the similarity factors of the formulations F3 and F4 are both greater than 50, as per the USP guidelines, both these formulations are similar to the reference formulation.

5.4 Stability Studies

Results of the stability studies are tabulated in table 5.4

Table No. 5.4: Stability studies.

FC	Time	Parameters					
		Hardness (Kg/cm^2)	Drug content	CPDR	DT (sec)	Friability	Appearance
F3	15 days	3.47	19.58	93.08	53.33	0.56	Same as Day 0
F3	45 days	3.4	19.22	93.25	55	0.39	Same as Day 0
F3	90 days	3.53	18.75	94.68	53.67	0.33	Same as Day 0
F4	15 days	3.53	19.79	100.8	25	0.35	Same as Day 0
F4	45 days	3.57	19.58	101.27	25.67	0.21	Same as Day 0
F4	90 days	3.47	19.54	102.40	26	0.39	Same as Day 0

* Here n=3 replicates for all the above parameters

Thus the selected formulations pass the stability test since none of the examined parameters are outside the respective acceptance limits prescribed by ICH guidelines.

DISCUSSION

In the present work, an attempt was made to prepare an ODTs of PPIs. ODTs have an advantage over the conventional tablets in elderly, pediatric and patients with dysphagia. Pantoprazole sodium was used as a model drug to represent the class of PPIs. The main challenge of this research was to deal with the stability of the drug. All PPIs are unstable at a pH below 5 and the project involved delivery of the drug into stomach with a pH of 1.2. The degradation half life of the drug in the stomach is 1-2 min. No UV spectrophotmetric method was reported to be developed in gastric stomach pH 1.2.

The pre and post compression parameters of all the formulation were evaluated. The effect of formulation variables, such as different classes of superdisintegrants in varying ratios on various pre and post parameters were evaluated using parameters such as disintegration time, uniformity of weight, content uniformity, friability, hardness, thickness and stability studies..

6.1 Identification of Pantoprazole Sodium

6.1.1 Melting Point Determination

Melting point of pantoprazole sodium was to be determined by open cup capillary method. However, pure pantoprazole sodium degrades at higher temperatures, which is a specific characteristic of PPIs. A similar observation was also made in this set of experiments confirming the well known degradation of PPIs at higher temperatures. Thus, determination of the melting point of pantaprazole sodium was not possible as expected.

6.1.2 Solubility

Pantoprazole sodium was found to be soluble in ethanol, water, and in phosphate buffer of 6.8 and 7.4. pantoprazole sodium shows a clear solution in stimulated gastric pH 1.2 but also show a characteristic yellow coloration when PPIs are dissolved in acidic pH. The coloration intensifies as the pH decreases. Thus this yellow coloration could possibly be associated with degradation in the acidic medium.

Fig. no 6.1.2: Solubility of Pantoprazole Sodium in different medium.

6.2 Standard Calibration Curve

Although seemingly easy, preparation of standard calibration curves is a very tricky and complex procedure for PPIs. Many methods were tried but the main problem associated with the standard curve preparation was its stability. As stated in the introduction, to discussion (Section 6), the degradation half-life of pantoprazole sodium is just 1 to 2 mins. Therefore, as soon as the drug was added into the acidic medium degradation sets in. Thus it was contemplated to add buffer along with it but then a new problem arose. When buffer was dissolved in1.2 pH the drug was not getting solubilized even after sonication for 1 hr. A different method was adopted by adding of 5 ml of purified water into 100 ml of solution of HCl, pH 1.2. The pH of the solution remained unchanged around 1.2; within the expected limits. Thus a method involving dissolution of the drug in 5ml of the purified water, followed by addition of this solution to the bicarbonate dissolved in 1.2 pH, and further making up the volume to 100 ml using 1.2 pH HCl (SS-I) was followed. Other stock solutions were prepared by dilution of SS-I using 1.2 pH HCl solutions.

6.2.1 Standard Calibration Curve of Pantoprazole sodium

The scanning of drug solution was done in the UV region (200–400 nm) to find out the wavelength of maximum absorption (λ_{max}) in the gastric fluid pH 1.2. The λ_{max} was found to be at 281.5 nm. The standard calibration curve of pantoprazole sodium was developed at this wavelength. The calibration curve was linear between 1–100 µg/ml conc. ranges. The standard calibration was obtained by plotting absorbance against conc. at 281.5 nm, and it follows the Beer's law. Results were tabulated in Table No.5.1.2 and plotted in Fig. no.5.1.2 The r^2 was found to be 0.9994 and slope was found to be 0.032 in
0.1 N HCl.

6.2.2 Standard Calibration Curve of Omeprazole sodium

The scanning of drug solution was done in the UV region (200–400 nm) to find out the wavelength of maximum absorption (λ_{max}) in the gastric fluid pH 1.2. The λ_{max} was found to be at 301 nm. The standard calibration curve of omeprazole sodium was developed at this wavelength. The standard calibration was obtained by plotting absorbance against conc. at 301 nm, and it follows the Beer's law. Results were tabulated in Table No.5.1.3 and plotted in Fig. no.5.1.3 The r^2 was found to be 0.9998 and slope was found to be 0.028 in 0.1 N HCl.

6.3 Compatability Studies

6.3.1 FTIR Studies

Drug- excipient interactions play a crucial role with respect to the stability and- potency of the drug. FTIR techniques have been used here to study the physical and chemical interaction between drug and excipients used.

Compatibility studies were performed using FTIR spectrophotometer. The IR spectrum of pure pantoprazole sodium and physical mixture of drug and polymers were studied. The FTIR scan shows characteristic absorption peaks of pantoprazole sodium at 3363.97 cm^{-1}, 1450.52 cm^{-1} (N-H stretching and bending vibrations); 1303.92 cm^{-1} (C-N stretching vibration); 1589.40 cm^{-1} and 823.63 cm^{-1} (C=C stretching vibration); 3057.27cm^{-1} (Aromatic C-H stretching and bending vibrations), 1041.60 cm^{-1} (S=O stretching vibration) respectively.

The FTIR spectrum of pure drug and different excipients and the tablet formulation where studied and is tabulated in table no. 5.1.1.1 to 5.1.1.3.

The peaks obtained in the spectra of the pure drug have a correlation with the peaks obtained when the drug and excipients were scanned together, thus indicating that the drug was compatible with the formulation excipients.

Based on this study it was concluded that there is no chemical interaction between drug and the excipients used and thus it can be safely used in the formulations.

6.4 Precompression Parameters

6.4.1 Loose Bulk Density

LBD of the formulation blend plays an important role in the compression of the powder the LBD of the formulation was found to be in the range of 0.679 g/cm^3 to 0.719 g/cm^3.

6.4.2 Tapped Bulk Density

TBD also plays an important role in knowing the compressibility of the formulation blend it was found to be in the range of 0.69g/cm^3 to 0.83 g/cm^3. It was noted that the TBD of all the formulation where greater than their respective LBD thus indicating that all the powder formulation had a good compressibility.

6.4.3 Angle of Repose (θ).

The angle of repose for the formulated blend was carried out and the results were shown in Table no. 5.2.2.1 to 5.2.2.5. It was concluded that the entire formulations blend were in the range 23^{0}491' to 29^{0}511' thus falling in the official limit range of 25^0 to 30^0 which indicates that all the formulation blend have good flow property.

Carr's Index

CI was calculated on the basis of the LBD and TBD and the results were shown in table 5.2.2.1 to 5.2.2.5. It was found to be in the range of 11.32% to 14.55% which lies in the official limits i.e. 5% to 15%, indicating the granules blend has excellent flow property for compression.

6.4.4 Hausners Ratio

HR was calculated on the basis of the LBD and TBD. It is an ratio between TBD and LBD and was found to be in the range of 1.127 to 1.17 thus indicating that formulation blend have free flowing property which is ideal for ODTs.

6.5 Formulation of Orodispersible Tablets

For the formulation of ODTs the most easy and economical method direct compression, was selected. This is one of the most widely used methods. Five approaches were designed to be used for this research work: superdisintegrant addition, combination of different superdisintegrants, sublimation method and combination of both superdisintegrants and sublimation methods and using treated natural gums as superdisintegrants. Thus a wide variety of superdisintegrants were used for the preparation of ODTs. Mannitol DC, SSG and other excipients were chosen based on the review done for ODTs.

Due to the use of high amount of buffer which is always associated with bad taste, Orange DC100 was incorporated as a flavour in the concentration of 0.5% to mask this effect. All the superdisintegrants were used in the concentration of 2%, 3%, and 5% respectively.

Blending time was carefully controlled since SSF was used. Long mixing times can result in the formation of hydrophobic powder beds which do not disperse easily. Therefore, SSF was added and mixed for a period of only 2 to 5 minutes. An increase in the coefficient of variation of mixing and a decrease in the dissolution rate have been observed following long mixing periods of SSF with a tablet powder. Tablet dissolution rate and crushing strength is decreased as the time of blending is increased; and SSF may also increase tablet friability.

The uniform blends of tablet were directly compressed by keeping tablet press setting constant for all the formulations. Proper lubrication of powder blends was essential for ease of ejection of compressed tablets as well as for free movement of lower punch during compression cycle. The tablets were compressed using flat face 16.4 X 8 mm flat oval size punches to get tablets of 1300 mg weight using ten stations Rimek tablet compression machine (Karnavati Engineering Ltd. Ahmadabad, India). The hardness for the tablets was set at a lower level of 3 Kg/cm^2.

6.6 Modification of The Dissolution Apparatus

During the course of this research, a lot of questions arose due to various perspectives of this research work. First the traditional method was considered for performing the dissolution in 900 ml of dissolution media, but the results were unsatisfactory. The quantity of buffer used was then considered. Further review showed that in IP 2010 in the assay for Ondansetron orally disintegrating tablets dissolution was performed in 500 ml of dissolution medium. Based on this information it was decided to use 500 ml of dissolution medium. The

percentage of drug released using 500 ml of dissolution medium was more than that obtained using 900 ml, although the cumulative percent released was less than 72%. Further review of the literature revealed that a marketing pamphlet existed for –OMEZ INSTA which quoted that the marketed product will increase the pH of the stomach above 6.

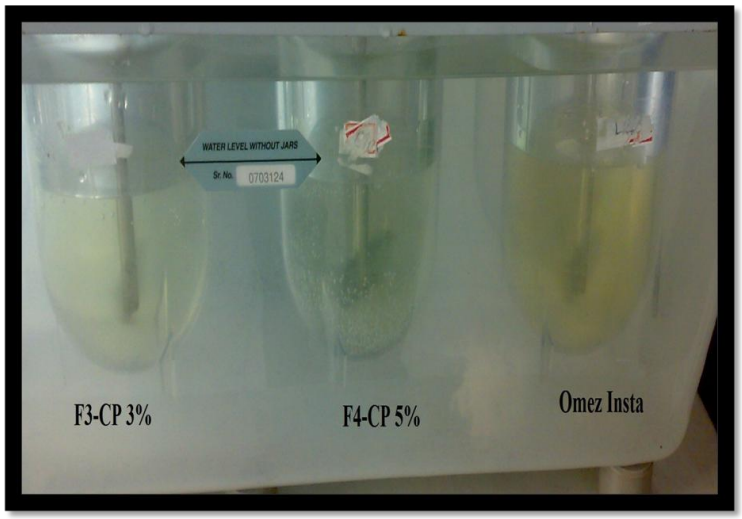


Fig. no 6.5: Study performed in 500 ml of 1.2 pH of OMEZ INSTA, F4 and F3.

Thus based on back calculation it was determined that 190 ml of acid should be present to increase the pH above 6.Further it was seen that good similarity existed between the dissolution profiles obtained with the test formulations and the marketed formulation of OMEZ INSTA when both 900 ml and 500 ml of dissolution medium was used. The temperature was validated and kept at 40.1°C and the rotation of the basket was kept at 75 RPM.

The photograph shown above (fig. 6.5) of the dissolution study done in 500 ml dissolution medium for OMEZ INSTA clearly shows the yellow colouration indicating that it may be due to the degradation.

6.7 Quantity of Bicarbonates

A combination of two buffers i.e. Sodium and potassium bicarbonate were used for stabilizing agents so that the level of sodium will be maintained. The quantity of 1.1 gm of the buffer mixture consisting of sodium and potassium bicarbonate was arrived at by a series of *in vitro* dissolution tests. The least amount of buffer mixture required to prevent the drug from degradation was selected.

Comparison of the three formulations, F3, F4 and OMEZ-INSTA clearly indicates that the intensity of the yellow colouration is minimal with both the F3-CP 3% and F4- CP 5% as compared to OMEZ INSTA. This could be explained by possible decreased degradation of PPIs indicating the correct choice of the optimum amount of buffer.

Evaluation of Tablets

6.7.1 Shape of the tablets

All the tablets have common flat oval shape.

6.7.2 Colour of the tablets

The colour of the tablet was white and formulation prepared by addition of treated natural gums shows specific brown to black colouration depending on the colour of the dried treated gum powder.

6.7.3 Thickness

Thickness of all the tablets was found to be between 6.86 mm to 7.05.

6.7.4 Tablet Hardness

The crushing strength of the tablets of each batch ranged between 3.13 to 4.23 kg/cm^2. This ensures good handling characteristics of all batches.

6.7.5 Friability Test

The values of friability test were in the range from 0.21 to 0.64% the percent friability of all the formulation was less than 1% ensuring that the tablets were mechanically stable.

6.7.6 Weight Variation Test

The percentage weight variations for all formulations were done. All the formulated tablets passed weight variation test as the percent weight variation was withinthe pharmacopoeial limits as the formulation blend of all the formulations have a good flow thus the percent weight deviation was in between □5% of the average weight. The weights of all the tablets were found to be uniform with low standard deviation values.

6.7.7 Drug Content Uniformity

The percentage of drug content for all formulation was found to 91.98% to 100.94% which lies in the IP limit for enteric coated formulation of 90 to 110% which was taken into consideration as ODTs of pantoprazole sodium is not official in any pharmacopoeia.

CONCLUSION

In this research work ODTs of PPIs were successfully formulated by direct compression method using superdisintegration addition method, combination of different superdisintegrants, sublimation method, combination of superdisintegrants and sublimation method, and treated natural gums used as Superdisintegrants.

The flow properties of the formulation powder have good flow property which is an important aspect for the ODT formulations.

Direct compression method is the best method for the formulation of ODTs. This method is also very economical and time saving. CP was found to be the best superdisintegrant among all with 5 percent concentration yielding the best results. It was also concluded that 1.1 gm of bicarbonate is required for the stability of the PPIs in acidic conditions.

Stability studies reviled that the formulation F3 and F4 i.e. formulation with 3% and 5% CP have good stability in accelerated stability testing.

SUMMARY

Mankind has lived with peptic ulcers since ancient times. Perhaps the first description of this malady is the one inscribed on the pillars of the temple of Aesculapius of Epidaurus from around fourth century B.C.

PPIs are the most potent suppressors of gastric acid secretion and are inhibitors of the gastric H^+/K^+-ATPase. The usual dose of pantoprazole is 20 to 40 mg. In typical doses, these drugs diminish the daily production of acid (basal and stimulated) by 80% to 95%. PPIs are widely used for treating acid induced inflammation, ulcers of the stomach and duodenum, GERD, erosive esophagitis, heartburn, upper gastrointestinal bleeding in critically ill patients, and Zollinger-Ellison Syndrome. They are also used in combination with antibiotics for eradicating H. pylori infection of the stomach.

Administration of conventional tablets of PPIs has been reported to exhibit longer lag time as they are enteric coated and fluctuations in the plasma drug levels, resulting either in reduction in drug cocn. in the blood.

Thus ODTs can act as a dosage form which can nullify all the drawbacks and problems related to conventional enteric coated formulation with additional advantages of increased

patient compliance and quick relief.

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