"FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF PANTOPRAZOLE"

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In Partial fulfillment for the award of the degree of

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In

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Submitted by

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EVALUATION CERTIFICATE

This is to certify that the dissertation work entitled " **FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF PANTOPRAZOLE"** submitted by student bearing **Reg.No.261210253** to **The TamilNadu Dr. M. G. R. Medical University,** Chennai, for the partial fulfilment of the degree of **MASTER OF PHARMACY** was evaluated by us during the examination held on……

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This is to certify that the work embodied in the dissertation "**FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF PANTOPRAZOLE"** submitted to The TamilNadu Dr. M. G. R. Medical University, Chennai, was carried out by **Mr.T.GOBINATH, (Registration No 261210253],** for the partial fulfilment of the degree of Master of Pharmacy in Pharmaceutics under direct supervision of **Mr.V.KAMALAKKANAN, M.Pharm.,** Lecture, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Komarapalayam, during the academic year 2013-2014.

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The work presented in this dissertation entitled, "**FORMULATION AND EVALUATION OF ENTERIC COATED TABLETS OF PANTOPRAZOLE"** was carried out by me, under the direct supervision of **Mr.V. KAMALAKKANNAN**, M.Pharm., Lecturer, Department of Pharmaceutics, J.K.K.Nattraja College of Pharmacy, Kumarapalayam.

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

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ABSTRACT

Pantoprazole is a proton pump inhibitor, belongs to group of benzimidazole, Pantoprazole sodium were prepared by direct compression method using different concentration of, microcrystalline cellulose as filler, mannitol and dicalcium phosphate as diluents, crosscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. Direct compression is economic compare to wet granulation since it requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets. The prepared tablets were evaluated for hardness, weight variation, friability and drug content uniformity and it was found that the results comply with official standards. The prepared tablets were coated using enteric coating polymer such as cellulose acetate phthalate, Eudragit L100 and by dip coating method. The *in vitro* release was studied using acidic buffer pH 1.2 and phosphate buffer pH 6.8. Prepared all batch's C2F9 was found best, with hardness 5.60 ± 0.24 (Kg/cm2**)**, drug content 99.08 ± 0.35(%), disintegration time 7.02± 0.21(min), and percentage cumulative drug released which started after 120 min and reached 99.72 after 180 min. Stability studies indicated that the developed tablets were stable and retained their pharmaceutical properties at room temperature and 40 °C / 75% RH for a period of 3 month.

Key words: Pantoprazole, Direct compression, Proton pump inhibitor, Cellulose acetate phthalate, Eudragit L100

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LIST OF ABBREVIATIONS

BP	British pharmacopoeia
CAP	Cellulose acetate phthalate
CDR	Cumulative drug release
CLA	Cumulative loss
Conc	Concentration
EC	Ethyl cellulose
FTIR	Fourier Transformer Infra red
GERD	Gastroesophageal reflux disease
GIT	Gastro-intestinal Tract
HCl	Hydrochloride
IR	Infra red
KBr	Potassium bromide
MCC	Microcrystalline Cellulose
MS	Mass spectroscopy
NSAID	Non steroidal antiinflamattory disease
PCT	press-coated tablet
PEG	Poly ethylene glycol
pH	Hydrogen ion concentration
PPI	Proton pump inhibitor
PUD	Peptic ulcer diseases
RH	Relative humidity
S.S	Standard Stock solution
SD	Standard Deviation
TEC	Triethyl citrate
USP	United states Pharmacopoeia
UV	Ultra-violet
WHO	World Health Organisation
λmax	Absorption maxima

LIST OF UNITS AND MEASURES

%	Percentage
(^{o})	Degree
°C	Degree centigrade
cm	Centimeter
gm/Kg/day	Gram per kilogram per day
gm	Gram
gm/cm^3	Gram per cube of centimeter
h	Hour
hrs	Hours
Kg/cm^2	Kilogram per square of centimeter
m/v	Mass by volume
mg	micro gram
mg	Milligram
MH_Z	Megha Hertz
min	Minute
mL	milli Litre
mm	milli metre
nm	nano metre
r^2	Regression value
rpm	revolutions per minute
v/v	Volume by volume
w/v	Weight by volume
w/w	Weight by weight
g	micro gram
µg/mL	micro gram per milli Litre

1. INTRODUCTION

More than 50% of pharmaceutical products are orally administered for several reasons. This route of administration is considered as the most widely used route as it offers advantages like ease of administration, versatility, patient compliance and accurate dosing. Undesirable taste is one of the important formulation problems that are encountered with such oral product.

1.1. Structure and functions of the stomach

The stomach is continuous with the oesophagus at the cardiac sphincter and with the duodenum at the pyloric sphincter. It has two curvatures. The stomach is divided into three regions: the fundus, the body and the antrum. At the distal end of the pyloric antrum is the pyloric sphincter, guarding the opening between the stomach and the duodenum. When the stomach is inactive the pyloric sphincter is relaxed and open and when the stomach contains food the sphincter is closed.

Temporary storage allowing time for the digestive, chemical digestion, preparation of iron for absorption, production of intrinsic factor needed for absorption of vitamin B12 in the terminal ileum regulation of the passage of gastric contents into the duodenum. When the chyme is sufficiently acidified and liquefied, the pyloric antrum forces small jets of gastric contents through the pyloric sphincter into the duodenum[1].

1.2. Acid formation

The stomach secretes about 2.5 litres of gastric juice daily. The principal exocrine secretions are proenzymes such as prorennin and pepsinogen elaborated by the chief or peptic cells and hydrochloric acid (HCl) and intrinsic factor secreted by the parietal or oxyntic cells. Mucus-secreting cells abound among the surface cells of the gastric mucosa. Bicarbonate

ions are also secreted and are trapped in the mucus, creating a gel-like protective barrier that maintains the mucosal surface at a pH of 6-7 in the face of a much more acidic environment (pH 1-2) in the lumen[2].

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 (M3, H2, and CCK2 receptors, respectively) are on the basolateral membrane of parietal cells in the body and fundus of the stomach. The H2 receptor is a GPCR that activates the Gs-adenylylcyclase-cyclic AMP-PKA pathway. ACh and gastrin signal through GPCRs that couple to the Gq-PLC-IP3-Ca2+ pathway in parietal cells. In parietal cells, the cyclic AMP and the Ca2+-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 release from postganglionic vagal fibers directly stimulates gastric acid secretion through muscarinic M3 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 H2 receptors. The critical role of histamine in gastric acid secretion is dramatically demonstrated by the efficacy of H2-receptor antagonists in decreasing gastric acid secretion. 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. 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.

1.3. Gastric Defenses Against Acid

The extremely high concentration of H^+ in the gastric lumen requires robust defense mechanisms to protect the esophagus and the stomach. The primary esophageal defense is the lower esophageal sphincter, which prevents reflux of acidic gastric contents into the esophagus. The stomach protects itself from acid damage by a number of mechanisms that require adequate mucosal blood flow, perhaps because of the high metabolic activity and oxygen requirements of the gastric mucosa. One key defense is the secretion of a mucus layer that protects gastric epithelial cells. Gastric mucus is soluble when secreted but quickly forms an insoluble gel that coats the mucosal surface of the stomach, slows ion diffusion, and prevents mucosal damage by macromolecules such as pepsin. Mucus production is stimulated by prostaglandins E2 and I2, which also directly inhibit gastric acid secretion by parietal cells. Thus, alcohol, aspirin, and other drugs that inhibit prostaglandin formation decrease mucus secretion and predispose to the development of acid-peptic disease. A second important part

of the normal mucosal defense is the secretion of bicarbonate ions by superficial gastric epithelial cells. Bicarbonate neutralizes the acid in the region of the mucosal cells, thereby raising pH and preventing acid-mediated damage [3].

Drugs are employed with the following therapeutic aims**:** (1) to relieve pain; (2) to accelerate healing; and (3) to prevent ulcer recurrence. Therapeutic approaches are threefold: (a) to reduce aggressive forces by lowering H+ output; (b) to increase protective forces by means of mucoprotectants; and (c) to eradicate Helicobacter pylori[4].

1.4. Definition of ulcer

Ulcers are crater-like sores (generally 1/4 inch to 3/4 inch in diameter, but sometimes 1 to 2 inches in diameter) which form in the lining of the stomach (called gastric ulcers), just below the stomach at the beginning of the small intestine in the duodenum (called duodenal ulcers) or less commonly in the esophagus (called esophageal ulcers). In general, ulcers in the stomach and duodenum are referred to as peptic ulcers An ulcer is the result of an imbalance between aggressive and defensive factors. On one hand, too much acid and pepsin can damage the stomach lining and cause ulcers. On the other hand, the damage comes first from some other causes, making the stomach lining susceptible to even an ordinary level of gastric acid[5].

An ulcer may arise at various locations:

Stomach (called gastric ulcer), Duodenum (called duodenal ulcer) Oesophagus (called Oesophageal ulcer), Meckel's Diverticulum (called Meckel's Diverticulum ulcer)[6].

1.4.1. Peptic ulcer

A peptic ulcer, also known as ulcus pepticum, peptic ulcer disease (PUD),[7] is an ulcer (defined as mucosal erosions equal to or greater than 0.5 cm) of an area of the gastrointestinal tract that is usually acidic and thus extremely painful. As may as 80% of ulcers are associated with Helicobacter pylori, a spiral-shaped bacterium that lives in the acidic environment of the stomach. Ulcers can also be caused or worsened by drugs such as aspirin and other non-steroid anti-inflammatory drugs (NSAIDs)[8]. The anatomic structure of the stomach and duodenum ulcers is shown in Figure 1.

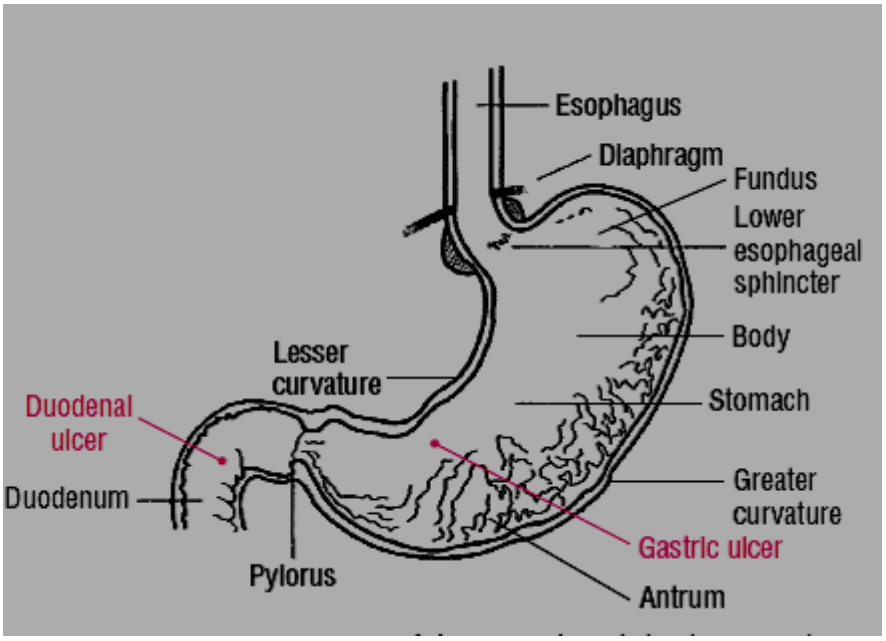


Figure 1. Structure of the stomach and duodenum ulcers

1.4.2. Types of peptic ulcer

Type I: Ulcer along the lesser curve of stomach

Type II: Two ulcers present - one gastric, one duodenal

Type III: Prepyloric ulcer

Type IV: Proximal gastroesophageal ulcer

Type V: Anywhere along gastric body, NSAID induced

1.4.3. Epidemiology

The lifetime risk for developing a peptic ulcer is approximately 10%. In Western countries the prevalence of *Helicobacter pylori* infections roughly matches age. Prevalence is higher in third world countries. Transmission is by food, contaminated groundwater and through human saliva.

1.4.4. Pathophysiology of peptic ulcer

Classical causes of ulcers (tobacco smoking, blood groups, spices and a large array of strange things) are of relatively minor importance in the development of peptic ulcers. A major causative factor (90% of gastric and 75% of duodenal ulcers) is chronic inflammation due to Helicobacter pylori, a spirochete that inhabits the antral mucosa and increases gastric production. Gastric, in turn, stimulates the production of gastric acid by parietal cells.

Smoking leads to, atherosclerosis and vascular spasms causing vascular insufficiency and promoting the development of ulcers through ischemia. A family history is often present in duodenal ulcers, especially when blood group O is also present. Inheritance appears to be unimportant in gastric ulcers[9].

1.5. Gastroesophageal reflux disease (GERD)

It is a very common problem presenting as 'heartburn', acid eructation, sensation of stomach contents coming back in foodpipe, especially after a large meal, aggravated by stooping or lying flat. Some cases have an anatomical defect (hiatus hernia) but majority are only functional (LES relaxation in the absence of swallowing). Repeated reflux of acid gastric contents into lower one third of esophagus causes esophagitis, erosions, ulcers, pain on swallowing, dysphasia strictures, and increases the risk of esophageal carcinoma[10].

Endoscopy is used to evaluate mucosal damage from gastroesophageal reflux disease (GERD) and assess for the presence of Barrett's esophagus (BE); 24-hour ambulatory pH testing or a therapeutic trial of a proton pump inhibitor are useful for diagnosing GERD in patients with persistent symptoms or atypical symptoms; manometry is useful in evaluating motility and before antireflux surgery. The goals of treatment of GERD are to alleviate symptoms, to decrease the frequency of recurrent disease, to promote healing of mucosal injury, and to prevent complications. Treatment of GERD involves a stepwise approach determined by disease severity and includes lifestyle changes and patient-directed therapy (Phase I); pharmacologic treatment with nonprescription and prescription medications (Phase II); and interventional approaches such as antireflux surgery or endoluminal therapies (Phase III). Patients with typical GERD symptoms should be treated with lifestyle modifications and a trial of empiric acid suppression therapy. Those who do not respond to empiric therapy or who have more complicated symptoms should undergo diagnostic tests.

1.5.1. Epidemiology

Gastroesophageal reflux disease occurs in both adults and children. Although mortality associated with GERD is rare (1 death per 100,000 patients), GERD symptoms have a greater impact on quality of life than do duodenal ulcers, untreated hypertension, mild congestive heart failure, angina, or menopause. The true prevalence and incidence of GERD

is difficult to assess because (a) many patients do not seek medical treatment, (b) symptoms do not always correlate well with severity of disease, and (c) there is no standardized definition or universal gold standard method for diagnosing the disease.

1.5.2. Pathophysiology

The key factor in the development of GERD is the retrograde movement of acid or other noxious substances from the stomach into the esophagus.9 In some cases, gastroesophageal reflux is associated with defective lower esophageal sphincter (LES) pressure or function. Patients may have decreased gastroesophageal sphincter pressures related to (a) spontaneous transient LES relaxations, (b) transient increases in intra-abdominal pressure, or (c) an atonic LES—all of which may lead to the development of gastroesophageal reflux. Problems with other normal mucosal defense mechanisms such as anatomic factors, esophageal clearance, mucosal resistance, gastric emptying, epidermal growth factor, and salivary buffering may also contribute to the development of GERD. Aggressive factors that may promote esophageal damage upon reflux into the esophagus include gastric acid, pepsin, bile acids, and pancreatic enzymes. Thus the composition and volume of the refluxate as well as duration of exposure are the most important aggressive factors in determining the consequences of gastroesophageal reflux. Rational therapeutic regimens in the treatment of gastroesophageal reflux are designed to maximize normal mucosal defense mechanisms and attenuate the aggressive factors[11].

1.6. Treatment of acid-related diseases

1.6.1. Antacids

Antacids are alkali preparations that neutralize hydrochloric acid in the stomach. Antacids can contain aluminium, magnesium, calcium or combined substances. Antacids are indicated for dyspepsia, GERD, reflux oesophagitis and gastritis. Their onset of action is fast,

but they require frequent administration (4 to 6 times a day) because of their short duration of action.

1.6.2. H2-receptor antagonists

Parietal cells in the stomach express receptors for acetylcholine, gastric and histamine. Stimulation of these receptors results in gastric acid production. H2-receptor antagonists (H2RAs) inhibit acid production by reversibly competing with histamine for binding to H2-receptors on the parietal cells. Four different H2RAs are available: cimetidine, famotidine, nizatidine and ranitidine. H2RAs are indicated for reflux-oesophagitis, ulcus duodeni, ulcus ventriculi, prevention of recurrent peptic ulcers and the treatment of NSAID related ulcers. These agents are primarily effective in decreasing basal acid production and nocturnal acid breakthrough. They are however less effective in controlling food-stimulated acid secretion during daytime. In general, H2RAs are administered twice a day. Although H2RAs have reasonable efficacy, patients develop tolerance in particular with continuous therapy.

1.6.3. Proton pump inhibitors

Proton pump inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the H+/K+- ATPase in the gastric parietal cell. This process starts with absorption of the PPI in the parietal cell. PPIs are weak bases, so protonation takes place in the acidic region of the secretory canaliculus of the parietal cell.

PPIs are indicated for the treatment of GERD, reflux oesophagitis, peptic ulcers and Zollinger-Ellison syndrome. In addition, PPIs are used for gastroprotection in patients using NSAIDs. In combination with two suitable antibiotics, PPIs are also used for the eradication of *H. pylori* infection. In the Netherlands five PPIs are available:

esomeprazole, lansoprazole, omeprazole, pantoprazole and rabeprazole[12].

1.7. Proton pump inhibitor

Since their introduction in the late 1980s, these efficacious acid inhibitory agents have rapidly assumed the major role for the treatment of acid-peptic disorders.. The mechanism of action of various proton pump inhibitors is shown in **Figure 2.** [13].

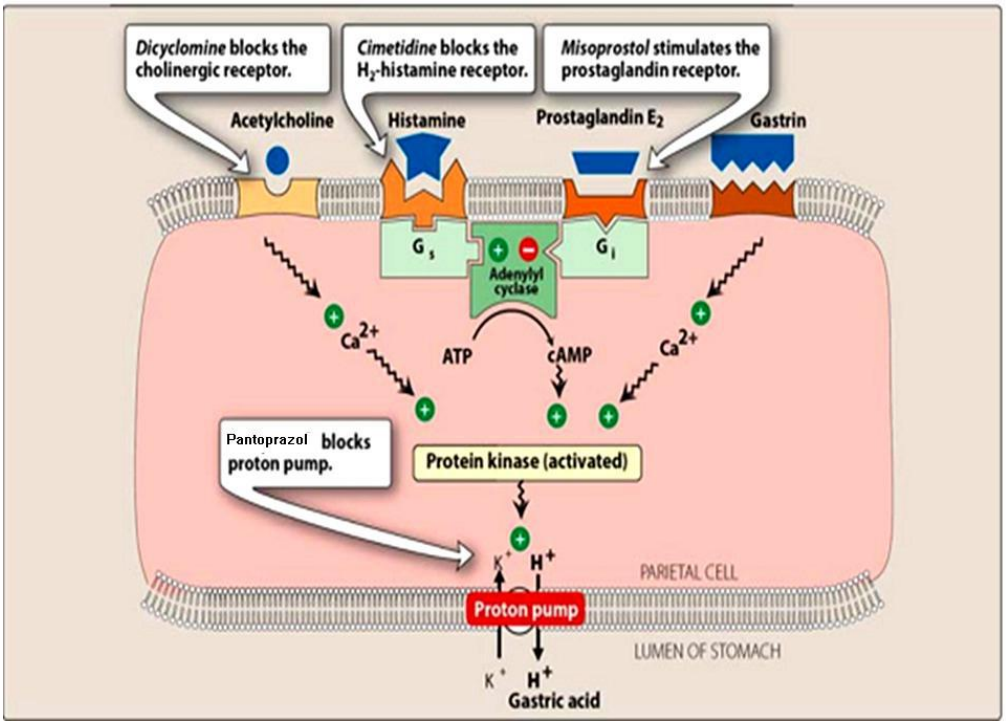


Figure 2. The mechanism of action of various proton pump inhibitors

1.7.1. Chemistry and pharmacokinetics

Five proton pump inhibitors are available for clinical use: omeprazole, lansoprazole, rabeprazole, pantoprazole, and esomeprazole. All are substituted benzimidazoles that resemble H2 antagonists in structure but have a completely different mechanism of action. To

protect the acid-labile prodrug from rapid destruction within the gastric lumen, they are formulated as acid-resistant enteric-coated. After passing through the stomach into the alkaline intestinal lumen, the enteric coatings dissolve and the prodrug is absorbed. These prodrugs are lipophilic weak bases (pKa 4–5) and therefore diffuse readily across lipid membranes into acidified compartments (such as the parietal cell canaliculus). Within the acidified compartment the prodrug rapidly becomes protonated and is concentrated > 1000-fold within the parietal cell canaliculus. There, it rapidly undergoes a molecular conversion to the active, reactive thiophilic sulfonamide cation. The sulfonamide reacts with the H+/K+ ATPase, forms a covalent disulfide linkage, and irreversibly inactivates the enzyme[14].

1.8. Tablet

Tablets are solid dosage forms containing medicinal substances with or without suitable diluents. They are the most widely preferred form of medication both by pharmaceutical manufacturer as well as physicians and patients. They offer safe and convenient ways of active pharmaceutical ingredients (API) administration with excellent physicochemical stability in comparison to some other dosage forms, and also provide means of accurate dosing. They can be mass produced with robust quality controls and offer different branding possibilities by means of colored film coating, different shapes, sizes or logos. The method for the preparation of tablet is shown in **Table 1.**

Table 1. Tablet manufacturing methods - advantages and limitations

Method	Advantages	Limitations
Direct compression	Simple, economical process. No heat or moisture, so good for unstable compounds	Not suitable for all API Generally limited to lower dose compounds Segregation potential Expensive excipients
Wet granulation	Robust process suitable for most compounds Imparts flowability to a formulation Can reduce elasticity problems Coating surface with hydrophilic polymer can improve wettability Binds API with excipient, thus reducing segregation potential.	Expensive: time and energy consuming process Specialized equipment required Stability issues for moisture sensitive and thermolabile API with aqueous granulation
Wet granulation (non-aqueous)	Suitable for moisture sensitive API Vacuum drying techniques can remove/reduce need for heat.	Expensive equipment Needs organic facility Solvent recovery issues Health and environment issues
Dry granulation (slugging or roll compaction)	Eliminates exposure to moisture and drying	Dusty procedure Not suitable for all compounds Slow process

1.8.1. Types of tablets

The tablet dosage form is a versatile drug delivery system. Different types of tablet formulations are available, which could be broadly classified based on: (1) route of administration such as tablets for oral delivery, sublingual delivery, buccal delivery,

rectal delivery or vaginal delivery, and (2) formulation characteristics such as immediate release tablets, effervescent tablets, melt-in mouth or fast dissolving tablets, delayed release or extended release tablets[15].

1.8.2. Coated tablets

Enteric coated dosage forms, such as coated tablets, sugar-coated tablets, soft and hard gelatin capsules, granulates or pellets, have their firm place in the medical arsenal. The preparations most commonly provided with enteric coatings contain pancreatin and other proteolytic enzymes, diclofenac, cardiac glycosides, electrolyte preparations with sodium, potassium and magnesium salts as well as calcium, iron and manganese preparations. Bisacodyl preparations, preparations containing valproic acid as well as formulations with plant extract or terpenes are also common. Nowadays, enteric coatings are particularly used to

- Protect active substances destroyed by the acidic gastric juice
- Improve tolerability of medicaments irritating the stomach by only releasing them in the small intestine
- Making active substances available after a time delay (sustained release),
- Achieving targeted release and concentration in the small intestine[16]

1.8.2.1 Techniques

Generally three methods are used for tablet coating

- Sugar coating
- Film coating
- Enteric coating

1.8.2.1.1 Sugar coating process involves five separate operations

- Sealing / Water proofing: provides a moisture barrier and harden the tablet surface
- Subcoating causes a rapid buildup to round off the tablet edges

- Grossing/Smoothing: smoothes out the subcoated surface
- Predetermine dimension
- Colouring gives the tablet its color and finished size
- Polishing produces the characteristics gloss

1.8.2.1.2 Development of film coating formulations

- If the following questions are answered then one can go for film coating:
- Is it necessary to mask objectionable taste, color and odor
- Is it necessary to control drug release
- What tablets size, shape, or color constrains must be placed on the developmental work

1.8.2.2 Materials used in film coating

- Film formers, which may be enteric or no enteric
- Solvents
- Plasticizers
- Colourants
- Opaquant-Extenders
- Miscellaneous coating solution components

1.8.2.2.1 Film formers

Ideal requirements of film coating materials are summarized below:

- Solubility in solvent of choice for coating preparation
- Solubility requirement for the intended use e.g. free water-solubility, pH -dependent solubility
- Capacity to produce an elegant looking product
- High stability against heat, light, moisture, air and the substrate being coated
- No inherent colour, taste or odor
- High compatibility with other coating solution additives
- Nontoxic with no pharmacological activity
- High resistance to cracking
- Film former should not give bridging or filling of the debossed tablet
- Compatible to printing procedure

Commonly used film formers are as follow

- Hydroxy Propyl Methyl Cellulose (HPMC)
- Methyl Hydroxy Ethyl Cellulose (MHEC)
- Ethyl Cellulose (EC)
- Hydroxy Propyl Cellulose (HPC)
- Povidon

- Sodium carboxy methyl cellulose
- Polyethylene glycols (PEG)[17]

1.8.2.2.2 Solvents

Solvents are used to dissolve or disperse the polymers and other additives and convey them to substrate surface.

Ideal requirement of solvents used for enteric coatings are summarized below

- Should be either dissolve/disperse polymer system
- Should easily disperse other additives into solvent system
- Small concentration of polymers (2-10%) should not in an extremely viscous solution
- Should be colorless, tasteless, odorless, inexpensive, inert, nontoxic and nonflammable.
- Rapid drying rate
- No environmental pollution

1.8.2.2.3 Plasticizers

Phthalate esters , Phosphate esters, Stearates, Sebacate.

1.8.2.2.4 Colorants

1.8.2.3 Ideal properties of enteric coating material are summarized as below

- Resistance to gastric fluids
- Susceptible/permeable to intestinal fluid
- Compatibility with most coating solution components and the drug substrate
- Formation of continuous film

- Nontoxic, cheap and ease of application
- Ability to be readily printed

Polymers used for enteric coating are as follow

- Cellulose acetate phthalate (CAP)
- Acrylate polymers
- Hydroxy propyl methyl cellulose phthalate
- Polyvinyl acetate phthalate

1.8.2.4 New materials used for tablet coating[18]

- Zein
- Aqua-Zein®, which is an aqueous zein formulation containing no alcohol
- Amylose starch and starch derivatives
- Dextrins

1.9 Directly compression

The International Pharmaceutical Excipients Council (IPEC) defines excipients as "Substances, other than the Active Pharmaceutical Ingredient (API) in finished dosage form, which have been appropriately evaluated for safety and are included in a drug delivery system to either aid the processing or to aid manufacture, protect, support, enhance stability, bioavailability or patient acceptability, assist in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or

use". Solvents used for the production of a dosage form but not contained in the final product are considered to be excipients, i.e. the granulation fluids, which might be dried off later, should comply with relevant requirements of Pharmacopoeia unless adequately justified**.** Excipients no longer maintain the initial concept of "inactive support" because of the influence they have both over biopharmaceutical aspects and technological factors. The desired activity, the excipients equivalent of the active ingredient's efficacy, is called its Functionality[19]. **Figure 3** indicating the direct compression process of tablet manufacturing[20] and **Table 2** shows the ideal requirements, advantages and limitations of direct compression.

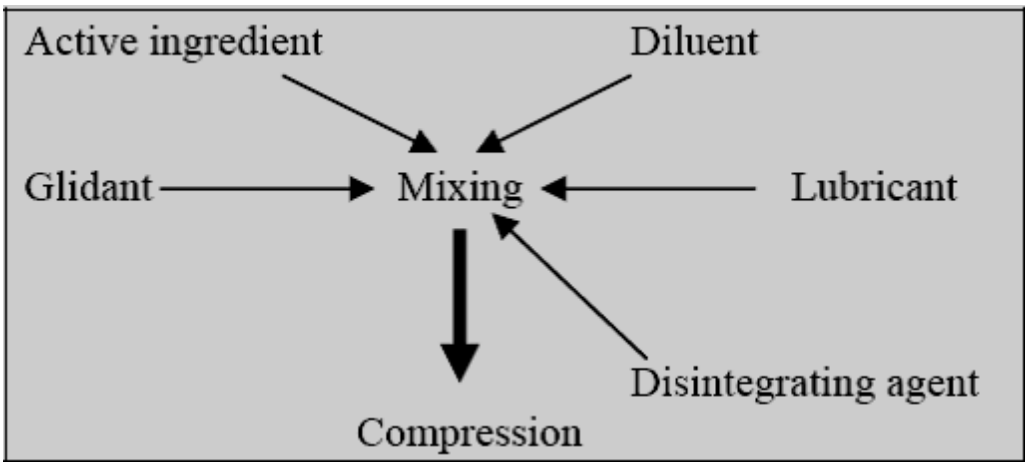


Figure 3. The direct compression process of tablet manufacturing

Table 2. Ideal requirements, advantages and limitations of direct compression

Ideal requirement	Advantage	Limitation
Flowability	Cost effective production	Segregation
Compressibility	Better stability of API	Variation in functionality
Dilution potentia	Faster dissolution	Low dilution potential
Rework ability	Less wear and tear of punches	Rework ability
Stability	Simplified validation	Poor compressibility of API
Controlled particle size	Lower microbial contamination	Lubricant sensitivity

1.9.1 Advantages of direct compression

- Direct compression is economic compare to wet granulation since it requires fewer unit operations. This means less equipment, lower power consumption, less space, less time and less labour leading to reduced production cost of tablets
- More suitable for moisture and heat sensitive APIs, since it eliminates wetting and drying steps and increases the stability of active ingredients by reducing detrimental effects
- Changes in dissolution profiles are less likely to occur in tablets made by direct compression on storage than in those made from granulations. This is extremely important because the official compendium now requires dissolution specifications in most solid dosage forms

- Disintegration or dissolution is the rate-limiting step in absorption in the case of tablets of poorly soluble API prepared by wet granulation. The tablets prepared by direct compression disintegrate into API particles instead of granules that directly come into contact with dissolution

- The high compaction pressure involved in the production of tablets by slugging or roller compaction can be avoided by adopting direct compression

- The chances of wear and tear of punches and dies are less[21-22]

1.9.2 Factors in formulation development

Many factors influence the choice of the optimum direct-compression filler to be used in a tablet formulation.

More than in any other type of tablets, successful formulations of direct compression tablets depend on careful consideration of excipient properties and optimization of the compressibility, fluidity, and lubricability of powder blends. The importance of standardizing the functional properties of the component raw materials and the blending parameters cannot be overstressed. Preformulation studies are essential in direct-compression tableting even for what would appear to be a simple formulation[23].

2. AIM & OBJECTIVE OF WORK

The tablet enteric coating is perhaps one of the oldest pharmaceutical processes still in existence. Enteric refers to the small intestine; therefore enteric coatings prevent release of medication before it reaches the small intestine.

Enteric-coated dosage forms do not release the active ingredient until they have been transported down to the neutral reacting part of the small intestine; hence they offer the best possibilities for the protection of unstable drugs at low pH values. The most important reasons for enteric coating can be summarized as follows: - to protect acid-labile drugs from gastric fluid (e.g. enzymes and certain antibiotics), - to prevent gastric distress or nausea due to irritation from a drug (e.g. sodium salicylate), - to deliver drugs intended for local action in the intestines (e.g. intestinal antiseptics could be delivered to their site of action in a concentrated form and bypass systemic absorption in the stomach), - to deliver drugs that are optimally absorbed in the small intestine to their primary absorption site in their most concentrated form, - to provide a delayed-release component for repeat action .

The modified enteric-coated Pantoprazole sodium formulation that provide immediate release in the small intestine and simultaneously provide sustained input of drugs that have an absorption window and at the same time may improve or maintain bioavailability of the formulation.

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%. Available PPI’s for clinical use: Omeprazole, esomeprazole, lansoprazole, pantoprazole, rabeprazole.

The primary treatment goal patients with peptic ulcer and GERD are relief of symptoms, prevention of complications related to the disease and healing of ulceration.

Pantoprazole is a substituted benzimidazole derivative that targets gastric acid proton pumps ,the final common pathway for gastric acid secretion. The drug covalently binding to the proton pumps, causing prolonged inhibition of gastric acidsecretion. But the drug causes irritation to gastric mucosa which may lead to nausea and vomiting. The stability of pantoprazole is rapidly degrades in acid medium of the stomach, but has acceptable stability in alkaline conditions. Therefore, pantoprazole should be delivered into the intestine. Hence, formulation of pantoprazole as an enteric coated tablet may solve the stability problem of drug in the stomach and release the drug in the intestine.

The main objectives of the present study was

- To formulate and evaluate enteric coated tablets Pantoprazole sodium by direct compression method
- Selection of suitable coating material to develop the dosage form
- To overcome the drug degradation by the gastric enzymes as well as the acidic environment of the stomach

3.PLAN OF THE WORK

1.Pre-compression parameters

- Bulk density
- Tapped density
- Carr's index
- Haussner ratio
- Angle of repose

2. Formulation of core tablets, by direct compression

3. Post compression parameters

- Weight variation
- Hardness test
- Friability test
- Drug content
- Disintegration time

4. Tablets coating

- Filmthickness
- Film solubility
- In-vitro dissolution studies

5. Stability studies

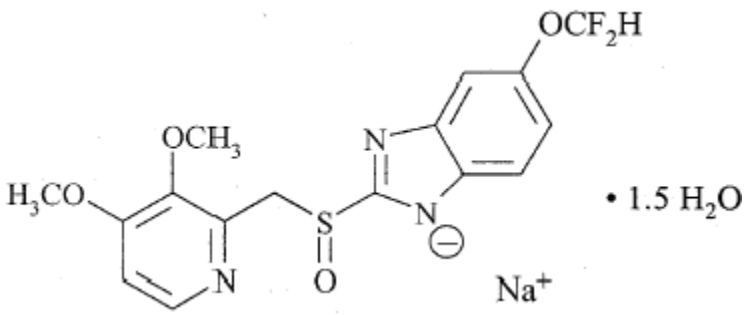
4. DRUG AND EXCIPIENTS PROFILE

4.1 PANTOPRAZOLE[24, 25, 26]

Chemistry: Chemically, pantoprazole sodium sesquihydrate, is a sodium 5- (difluoromethoxy)-2[[(3,4,dimethoxy-2pyridinyl)methyl] sulfinyl] -1H benzimidazole sesquihydrate.

Molecular formula: $C_{16}H_{15}F_2N_3O_4S.\ 1.5\ H_2O$

Molecular weight: 432.4 gm/mol.



Mechanism of action: Pantoprazole is a proton pump inhibitor (PPI) that suppresses the final step in gastric acid production by covalently binding to the (H^+,K^+) - ATPase enzyme system at the secretory surface of the gastric parietal cell. This effect leads to inhibition of both basal and stimulated gastric acid secretion irrespective of the stimulus. The binding to the (H^+, K^+)- ATPase results in a duration of antisecretory effect that persists longer than 24 h for all doses tested.

Pharmacokinetics: Pantoprazole sodium is prepared as an enteric-coated tablet so that absorption of pantoprazole begins only after the tablet area under the serum concentration time curve (AUC) increase in a manner proportional to oral and intravenous doses from 10 mg to 80 mg. Pantoprazole does not accumulate and its pharmacokinetics are unaltered with multiple daily dosing.

Absorption: The absorption of pantoprazole is rapid, with a Cmax of 2.5 μg/ml that occurs approximately 2.5 h after administration of a single or multiple oral 40 mg doses of pantoprazole sodium delayed release tablets. Pantoprazole is well absorbed; it undergoes little first-pass metabolism resulting in an absolute bioavailability of approximately 77%. Administration with food may delay its absorption.

Distribution: The apparent volume of distribution of pantoprazole is approximately 11.0 to 23.6L, distributing mainly in extracellular fluid. The serum protein binding of pantoprazole is about 98%, primarily to albumin.

Metabolism: Pantoprazole is extensively metabolized in the liver through the cytochrome P450 (CYP) system. Pantoprazole metabolism is independent of the route of administration (intravenous or oral).

Elimination: After a single oral or intravenous dose of pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through biliary excretion.

Drug-drug interactions: Pantoprazole given with atazanavir, indinavir, nelfinavir may be reduce the plasma concentrations. Coadministration with atazanavir is not recommended. Plasma levels of certain azole antifungal (e.g. itraconazole, ketoconazole) may be reduced, avoid this combination if possible.

Contraindications: Pantoprazole sodium delayed-release tablets are contraindicated in patients with known hypersensitivity to any component of the formulation.

Precautions: Generally, daily treatment with any acid-suppressing medications over a long period of time (eg, longer than 3 years) may lead to malabsorption of cyanocobalamin (vitamin B-12).

Side effects: The common side effects are abdominal pain, blurred vision, dry mouth, fatigue, flushed, dry skin, increased hunger, increased thirst, increased urination, nausea, sweating.

Uses: Pantoprazole is used to treat erosive esophagitis or "heartburn" caused by gastroesophageal reflux disease (GERD). Pantoprazole may also be used to treat Zollinger- Ellison syndrome, stomach produces too much acid.

Dose: It is administered orally dose of 40 mg once daily.

Storage: Store the medicine in a closed container at room temperature, away from heat, moisture, and direct light.

4.2MICROCRYSTALLINE CELLULOSE[27]

Non-proprietary names: Cellulosum microcristallinum, microcrystalline cellulose

Synonyms: Avicel, Emcocel and Tabulose, Crystalline cellulose

Chemical Name: Cellulose

Empirical formula: (C6H10O5) n, Where n=220

Molecular weight: Approximately 36,000

Description: white, odorless, tasteless, crystalline powder

Functional category: Adsorbent; suspending agent; tablet and capsule diluent; tablet disintegrant.

Solubility: Slightly soluble in 5% w/v sodium hydroxide solution; practically insoluble in water, dilute acids, and most organic solvents.

Applications: Adsorbent-20 to 90%, Antiadherent–5 to 20%, Capsule binder/diluents -20 to90%, Tablet disintegrant-5 to 15%, Tablet binder/diluents-20 to 90%.

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

Incompatibilities: Incompatible with strong oxidizing agents.

Safety: It is not absorbed systemically following oral administration and thus has little toxic potential.

4.3 MAGNESIUM STEARATE[27]

Non-proprietary names: Magnesium stearate, Magnesii stearas.

Synonyms: Magnesium octadecanoate; octadecanoic acid, magnesium salt; stearic acid, magnesium salt

Chemical Name: Octadecanoic acid magnesium salt

Empirical formula: C36H70MgO4

Molecular weight: 591.34

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste.

Functional category: Tablet and capsule lubricant.

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

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

Stability and Storage Conditions: Magnesium stearate is stable and should be stored in a well closed container in a cool, dry place.

Incompatibilities: Incompatible with strong acids, alkalis, and iron salts.

Safety: Oral consumption produce a laxative effect. No toxicity information is available.

4.4 TALC[27]

Non-proprietary names: Purified talc, Talc, Talcum.

Synonyms: Altalc, hydrous magnesium calcium silicate.

Chemical Name: Talc

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

Description: Talc is a very fine, white to greyish-white, odorless, impalpable unctuous, crystalline powder.

Functional category: Anticaking agent; glidant diluent; tablet and capsule lubricant.

Solubility: practically insoluble in dilute acids and alkalis, organic solvents, and water.

Applications: Talc was once widely used in oral solid dosage formulations as a lubricant, diluent and lubricant.

Stability and Storage Conditions: Talc is a stable material and may be sterilized by heating at 160 ºC for not less than 1 hour. Talc should be stored in a well-closed container in a cool, dry place.

Incompatibilities: Incompatible with quaternary ammonium compounds.

Safety: Talc is not absorbed systemically following oral ingestion and is therefore regarded as an essentially nontoxic material. However intranasal or intravenous

abuse of products containing talc can cause granulomas in body tissues.

4.5 CROSCARMELLOSE SODIUM[27]

Synonyms: Ac-Di-Sol; Cross-linked carboxymethyl cellulose sodium;

Description: It occurs as white, odourless powder.

Functional categories Tablet and capsule disintegrate.

Solubility: Insoluble in water, but rapidly swells to 4-8 times its original volume on contact with water. Practically insoluble in acetone, ethanol and toluene.

Stability and storage: Croscarmellose sodium is stable, though it is a hygroscopic material. It should be stored in airtight container in a cool and dry place.

Safety: It is nontoxic and non-irritant material and widely used in oral pharmaceuticals.

Application: It is used in oral pharmaceutical formulations as a disintegrate for capsules and tablets. In tablet formulations, croscarmellose sodium may be used in both direct-compression and wet-granulation processes. Croscarmellose sodium at concentrations up to 5% w/w may be used as a tablet disintegrant, although normally 2% w/w is used in tablets prepared by direct compression and 3% w/w in tablets prepared by a wet-granulation process.

Incompatibilities: Not compatible with strong acids. *Drug and Excipients Profile Dept. of Pharmaceutics, Gautham College of Pharmacy Bangalore 32* 30

4.6 MANNITOL[27]

Non proprietary name:	Mannitol, D-Mannitol ,Mannitolum
Synonyms:	Cordycepic acid; C*PharmMannidex; E421; manna sugar;
Chemical name:	D-Mannitol
Category:	Diluents, diluents for lyophilized preparations; sweetening agent; tablet and capsule diluent; tonicity agent.
Description:	Mannitol occurs as white, odourless, crystalline powder, or free-flowing granules. It has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose.
Solubility:	Soluble in water, alkalies, ethanol, glycerine and propane.
Stability and storage:	Mannitol is stable in the dry state and in aqueous solutions. Solutions may be sterilized by filtration or by autoclaving and if necessary may be autoclaved repeatedly with no adverse physical or chemical effects.
Safety:	Mannitol is a naturally occurring sugar alcohol found in animals and plants; it is present in small quantities in almost all vegetables. Laxative effects may occur if mannitol is consumed orally in large quantities. If it is used in foods as a bodying agent and daily ingestion of over 20 g is foreseeable, the product label should bear the statement ‘excessive consumption may have a laxative effect.

4.7 CELLULOSE ACETATE PHTHALATE[27]

Nonproprietary names: Cellacephate; Cellacefate

Synonyms: CAP, Cellulose acetophthalate

Chemical name: Cellulose, acetate, 1,2-benzenedicarboxylate.

Category: Pharmaceutical aid (for enteric coating of tablets).

Description: White, free-flowing powder or colorless flakes; odorless or with a faint odor of acetic acid; hygroscopic.

Solubility: Freely soluble in acetone; soluble in diethylene glycol and in dioxan; practically insoluble in water, in ethanol (95%), in toluene and in chlorinated and non chlorinated aliphatic hydrocarbons. It dissolves in dilute solutions of alkalis.

Storage: To be stored in tightly-closed containers at a temperature between 8° and 15 °C.

Viscosity: 50-90 cps good coating solution with a honey like consistency, but the viscosity is influenced by the purity of the solvent.

Applications: CAP is used as an enteric coating material for tablets or capsules.

Incompatibilities: Cellulose acetate phthalate is incompatible with ferrous sulfate, ferric chloride, silver nitrate, sodium citrate, aluminum sulfate, calcium chloride, mercuric chloride, barium nitrate, acetate, and strong oxidizing agents such as strong alkalis and acids.

4.8 EUDRAGIT L-100 [27]

Synonyms:	Methacrylic acid
Functional category:	Film former, tablet binder
Description:	White powders with a faint characteristic odor.
Solubility:	1 gm of Eudragit L-100 dissolves in 7 g methanol, ethanol, in aqueous isopropyl alcohol and acetone. Insoluble in ethyl acetate, methylene chloride, petroleum ether and water.
Stability and storage conditions:	Eudragit and L 100 polymers are stable at room temperature.
Safety:	Acute toxicity studies have been performed in rats, rabbits and dogs. No toxic effects were observed. Chronic toxicity studies were performed in rats over a period of 3 months. No significant changes were found in the animal organs.
Applications:	Eudragit L 100 and S 100 are employed as film coating agents resistant to gastric fluid with solubility above pH 6.0 and pH 7.0 respectively, for enteric coating of formulations. Eudragit L and S, also referred to as methacrylic acid copolymers in the USP32–NF27 monograph, are anionic copolymerization products of methacrylic acid and methyl methacrylate. The ratio of free carboxyl groups to the ester is approximately 1 : 1 in Eudragit L (Type A) and approximately 1 : 2 in Eudragit S (Type B).

4.9 CALCIUM PHOSPHATE[27]

Nonproprietary Names: Anhydrous Calcium Hydrogen Phosphate, Anhydrous Dibasic Calcium Phosphate

Chemical Name: Dibasic calcium phosphate

Molecular Weigh: 136.06

Functional Category: Tablet and capsule diluent.

Applications: Anhydrous dibasic calcium phosphate is used both as an excipient and as a source of calcium in nutritional supplements. It is used particularly in the nutritional/health food sectors. It is also used in pharmaceutical products because of its compaction properties, and the good flow properties of the coarse-grade material.

Description: Anhydrous dibasic calcium phosphate is a white, odorless, tasteless powder or crystalline solid. It occurs as triclinic crystals.

Stability and Storage Conditions: Dibasic calcium phosphate anhydrous is a nonhygroscopic, relatively stable material. Under conditions of high humidity it does not hydrate to form the dihydrate.

Incompatibilities: Dibasic calcium phosphate should not be used to formulate tetracyline antibiotics.

5. REVIEW OF LITERETURE

Sumit *et al* (2009)., formulated pantoprazole enteric coated tablets, in aqueous media more acidic than pH 4 it suffers a practically complete decomposition within a period shorter than 10 minutes. Even in solid state it is sensitive to heat, humidity, light and especially to substances containing an acidic group. Pantoprazole which have an irritant effect on the stomach, can be coated with a substance that will only dissolve in the small intestine, hence such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestines pH 5.5 and above) where they do not degrade, and give their desired action. This stimulate us to formulate and evaluate pantoprazole as an enteric coated tablet[28].

Anroop et al (2010)., developed and evaluated enteric coated tablets for esomeprazole magnesium trihydrate, with different enteric coating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propyl methylcellulose phthalate, cellulose acetate phthalate and Acryl-EZE® to achieve 5% weight gain. Disintegration studies showed that the formulations failed in 0.1 N HCl media. Hence the quantity of enteric coating was increased to 8% w/w. *In vitro* analysis of the developed tablets was carried out. Results from disintegration time and dissolution rate studies indicate that all the esomeprazole enteric tablets prepared possess good integrity, desirable for enteric coated tablets. Among the polymers studied, the methacrylic polymers exhibited better dissolution rate than the cellulose polymers. Therefore stability studies indicate that the prepared formulations were stable for a period of three months. This study concluded that enteric coated tablets of esomeprazole can be prepared using any of the enteric coating polymer studied using a minimal weight gain of 8%[29].

Saffar et al (2007)., studied on *in vitro* evaluations (hardness, friability, weight variation, assay, disintegration and dissolution tests) of marketed pantaprazole tablets (2 batches of each) from WHO GMP certified Nepalese companies ,non-GMP certified Nepalese companies and multinational companies were done. The result of hardness, friability, weight variation, and assay and disintegration tests of all marketed products comply with pharmacopoeial limit. However, BP-02-A2 showed the fastest disintegration. Moreover, the comparison of percentage drug release of these companies on the basis of dissolution study demonstrated that BP-02-A2 (90 % drug release) complied best with standard RDRL protocol while BP-02-B2 (78% drug release) does not comply with above specification[30].

Chanchal et al (2011)., made an attempt to perform various prototype trials were taken and evaluated with respect to the various quality parameters such as disintegration, tablet weight, thickness; diameter, gastric resistance test, drug uniformity and dissolution also determine optimum polymer concentration for enteric coating. Pantoprazole enteric coated tablets prepared by direct compression. Because of its instability in acidic environment decided to give it alkaline environment with the help of alkaliser and also protective seal coating between core tablet and acid resistant enteric coat. The primary aim of using delayed release is to protect the drug from an unfavorable environment in the gastrointestinal tract, to protect the gastrointestinal tract from high, local concentrations of an irritating drug compound, or to target a specific region of absorption or action[31].

Putta et al (2011)., prepared directly compressible esomeprazole magnesium trihydrate enteric coated tablets to deliver drug in upper GIT. Different tablets were prepared with super disintegrates like Ac-Di-Sol, Crospovidone, sodium starch glycolate and diluents like Pharmatose DCL11, Mannogem EZ. Tablets were enteric coated using Acryl-EZE. The tablets were evaluated for hardness, disintegration time and *in vitro* drug release. The powder bed showed good rheological properties and enteric coated tablets showed acid uptake value

<5 indicates significant protection of acid liable drug. The compressional parameters were within the limits, the drug content in all formulations was found to be uniform and consistent. *In vitro* dissolution studies indicated there is no drug loss during gastric phase[32].

Bozdag et al (1999)., studied omeprazole, , is a specific and noncompetitive inhibitor of the enzyme H+/K+-ATPase, known as the gastric proton pump. It is unstable in conditions of low pH and must be protected from the effects of gastric acid when given orally; thus, it is administered in the form of enteric-coated dosage/arms. In this present study, various coating solutions were prepared in different concentrations and appliedto previously subcoated omeprazole tablets to examine whether this coating prevented omeprazolefrom degrading in acidic media. Dissolution tests were conducted in acidic and basic media to determine the appropriate coating ratio. For stability evaluation, an accelerated stability test was performed on developed tablet formulations and commercially obtained capsules[33].

Mohamed et al (2009)., evaluated the bioequivalence of two commonly prescribed enteric coated formulations of 20 mg omeprazole, Omez (test) and Losec (reference). *In vitro* studies were adopted to determine and compare the dissolution behavior of both products. Both brands met the requirements specified by the United States pharmacopoeia for omeprazole delayed release capsules. *In vivo* study was conducted according to a single dose, standard two-way, crossover design with a washout period of one week. Twelve healthy adult Egyptian male volunteers were randomly allocated to receive a single 20 mg dose of either test or reference product. Blood samples were collected at specified time intervals, plasma was separated and analyzed for omeprazole concentration using an HPLC assay[34].

Devraj et al (2010)., studied time released drug delivery of metronidazole. Metronidazole containing matrix tablets coated with 3,4,5 & 6% w/v cellulose acetate phthalate in acetone were examined for applicability as timed release tablets with a

predetermined lag time of 4-5 hrs. Different types of enteric coated tablets were prepared and there drug dissolution profile was studied in 0.1 N HCl (0 to 2hr) and PBS 6.8 (2- 24 hr) as dissolution media at 37±0.5 ºC,100 rpm by USP Apparatus-1(Basket assembly). The result indicated that the tablets with timed release functions could be prepared and, that the lag time were increased as the coat concentrations increased (3% to 6%w/v).The different kinds of timed release enteric coated tablets that showed lag time of 2 to 5.4 hrs in in- vitro dissolution in 2% w/v rat caecal\ content in 6.8 PBS(Phosphate buffer saline). The lag time showed a good agreement between the in- vitro test in PBS 6.8 and in -vitro test in 2% w/v rat caecal content. However the lag times were 4.5 hrs in in-vitro test in 2%w/v rat caecal content medium[35].

Dhruba et al (2010)., made an attempt to decrease dosing frequency by prepare a mucoadhesive tablets. Various hydrophilic polymers such as HPMC, Sodium alginate, Tragacanth, Sodium CMC and hydrophobic polymer EC are used to prepare mucoadhesive tablets and EC is use for enteric coating were subjected to friability, content uniformity, surface pH, wash-off test and dissolution study. The results of friability tests carried out for all the formulations are within the official limit and acceptable. According to *in vitro* drug release study the formulation containing HPMC (81.17897%) before coating and (68.93494% after coating with ethyl cellulose), ethyl cellulose (83.91042% before coating and 51.06213% after coating with ethyl cellulose) and tragacanth (83.75215% before coating and 73.24184% after coating with ethyl cellulose) gives better result than the other formulation. Among these three formulations, the formulation containing ethyl cellulose gives better result[36].

Durriya et al (2009)., reviewed that, tablet coating is perhaps one of the oldest pharmaceutical processes still in existence. It offers many benefits namely: improving the aesthetic qualities of the dosage form, masking unpleasant odour or taste, easing ingestion, improving product stability and modifying the release characteristics of the drug. It is widely

used in enteric coating, controlled release system and osmotic pump systems. Enteric coated dosage forms are designed to resist the destructive action of the gastric fluid and to disintegrate in the higher pH environment of the intestinal fluid. Polymer for enteric coating can be applied to solid dosage forms (i.e. granules, pellets, or tablets) from aqueous solutions of alkali salts, or organic solvent solutions. The most commonly used pH sensitive enteric coating polymers today include: cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropyl methyl cellulose phthalate (HPMCP) and methacrylic acid copolymers. In recent years, acrylic copolymers have evolved as the most preferred materials for designing enteric coating formulations in terms of performance and global acceptability[37].

Senthil et al (2010)., developed enteric coated tablets of didanosine by wet granulation technique using polymer Ethyl Cellulose std 100 FP, Ethyl Cellulose Med 70 P, Ethyl Cellulose Med 50 P and other excipients are povidone micro crystalline cellulose in different ratios. These polymers and excipients are used for sustained the drug release. And 20% solution of Eudragit L 100 with Iso propyl alcohol used for enteric coat. And Di Ethyl Phthalate added as polishing agent in enteric coat solution. Tablets were evaluated for physical characteristics, weight variation, hardness, drug content, and further tablets were evaluated for *in vitro* drug release for 12 hrs i.e. first 2 hrs no drug release was observed and gradually drug release was increased up to 12 hrs by using Ethyl Cellulose std 100 P 20% with other excipients[38].

Muhammad et al (2011)., studied direct compression is the simplest and most economical method f or the manufacturing of tablets because it requires less processing steps than other techniques. In early 1960's, the introduction of spray dried lactose (1960) and Avicel (1964) had changed the tablet manufacturing process and opened avenues of direct compression tableting. The simplicity of the direct compression process is apparent from a comparison of the steps involved in the manufacture of tablets by wet granulation, roller

compaction and direct compression techniques . It has been estimated that less than 20 percent of pharmaceutical materials can be compressed directly into tablets due to lack of flow, cohesion properties and lubrication. Therefore, they must be blended with other directly compressible ingredients to manufacture satisfactory tablets[39].

Vivek et al (2011)., studied enteric coated tablets of didanosine using different polymers as release retarding agent to overcome the gastric juice incompatibility. Preformualtion study was done initially and results directed for the further course of formulation . Based on preformualtion studies different formulation batches of didanosine was prepared using selected excipient. Granules were evaluated for tests loss on drying , bulk density , tapped density, compressibility index, hausner ratio. Tablets were tested for weight variation, thickness, hardness, friability and in vitro drug release as per official procedure. Change in dissolution parameter study made it suitable for minute physiological variables[40].

Singh et al (2009)., made an attempt to formulate a delayed release solid dosage forms. Prepared the conventional diclofenac sodium tablets by wet granulation method (non-aqueous) using granulating fluid (isopropyl alcohol). Developed the aqueous coating formula using shacryl and non-aqueous coating formula using HPMCP and optimized the best aqueous coating formula. Coating was performed in a mini coating pan at 107 rpm using low-pressure air atomized liquid spray techniques. Comparative dissolution, disintegration and antiulcer studies were performed on the best products and marketed products. The Comparative antiulcer studies were performed on wister albino rats using conventional, dummy and enteric-coated tablets[41].

Rupesh et al (2010)., prepared enteric coated tablets of Ketorolac Tromethamine by direct compression method using EudragitL100 as coating polymer. *In vitro* release profiles of batches F1-F4 shows that Ketorolac Tromethamine in drug :polymer ratio with Guar gum,

Xanthan Gum, Ethyl cellulose and Sodium alginate give 79.32%, 91.52%, 88.35% and 92.19% drug release respectively in 12 hours. In vitro release profile of batches F5-F8 shows that Ketorolac Tromethamine in ratio 1:4 with Guar gum, Xanthan Gum, Ethyl cellulose and Sodium alginate gives release of 85.21%, 95.52%, 93.50%, 97.24% respectively in 12 hours. In vitro release profile of batches F9-F12 shows that Ketorolac Tromethamine in ratio 1:3 with Guar gum, Xanthan Gum, Ethyl cellulose and Sodium alginate gives release of 89.50%, 98.25%, 95.22%, 100.27% respectively in 12 hours[42].

Rabia et al (2010)., developed enteric coated ibuprofen tablets in order to avoid gastric mucosal irritation, diffusion of drug across mucosal lining and to let active ingredient be absorbed easily in small intestine. The formulation was developed and manufactured through the direct compression process, the simplest, easiest and most economical method of manufacturing. Enteric coating was done using an Opadry white subcoating and an aqueous coating dispersion of Acryl-Eze. Enteric coated formulation was subjected to disintegration and dissolution tests by placing in 0.1 M hydrochloric acid for 2 h and then 1 h in phosphate buffer with a pH of 6.8. About 0.04% of drug was released in the acidic phase and 99.05% in the basic medium. These results reflect that ibuprofen can be successfully enteric coated in order to prevent its release in the stomach and facilitate rapid release of the drug in the duodenum, due to the presence of superdisintegrant. Formulating this enteric coated tablets could increase patient compliance by decreasing adverse drug reactions (ADRS) associated with Ibuprofen therapy[43].

Mominurl et al (2010)., formulated diclofenac sodium (DS) microspheres with two different polymers, ethyl cellulose (EC) and cellulose acetate phthalate (CAP). Emulsification-solvent evaporation method was used to prepare the microspheres. Liquid paraffin containing 1.5% (w/w) span 80 was the external phase and acetone-polymer solution was the internal phase. EC and CAP, both as single and as mixture, were used to encapsulate

DS. EC microspheres were more spherical in shape and showed more entrapment efficiency than CAP microspheres. The size of the microspheres varied between 560-920 μm and as high as 90% loading efficiency was obtained. In vitro release study was carried out in 0.1 N hydrochloric acid solution (pH 1.2) for first 2 hours followed by in phosphate buffer solution (pH 6.8) for next 4 hours. After first 2 hours of dissolution in 0.1 N hydrochloric acid, EC microspheres released 24% of DS whereas CAP microspheres released only 2% DS. After 4 hours of dissolution in phosphate buffer, 60% DS was released from EC microspheres and almost all drug was released from CAP microspheres. Combination of EC and CAP showed more sustaining action than the individual polymer in both the dissolution media. DS release from EC microspheres followed Higuchi model whereas CAP microspheres followed first order model[44].

Rakesh et al (2012)., prepared enteric-coated drug multiparticulates with single polymeric coatings (acrylic or cellulosic) were compared with two different polymeric layer coatings to evaluate the effectiveness of latter coatings in more effectively producing a better rabeprazole sodium delayed-release pellet product The pH-dependent, enteric acrylic, and cellulosic polymers were used either alone, in combination, or applied one over the other to impart delayed-release properties to the core drug pellets. It was demonstrated that dual delayed-release coating with two different enteric polymers-an inner acrylic coating followed by an outer cellulosic coating-yields the best product that provide all the desired physicochemical and drug dissolution characteristics[45].

Subramaniam et al (2010)., formulated and evaluated aspirin (75mg) delayed release tablet to provide a controlled and predictable release of Aspirin and which is used in the treatment of Coronary Thrombosis (heart disease) for Once in Day administration. The half life of Antiplatelet agent is 6 Hours which makes it suitable candidate for delayed release formulation. The present work aims to avoid degradation of drug in acidic environment of

stomach. So due to enteric coating drug releases in to the small intestine so that drug gets larger surface area for absorption. Micro crystalline cellulose, maize starch, cross carmilose Sodium is a disintegrent used to prepare a blend for direct compaction method[46].

Gohel et al (2005)., the present review outlines the importance of the functionality of the directly compressible adjuvants in the formulation of tablets. The co-processing is the most widely explored method for the preparation of directly compressible adjuvants because it is cost effective and can be prepared in-house based on the functionality required. Hence, the present review focuses on the properties of the co-processed directly compressible adjuvants available in the market[47].

Rajeshwar et al (2010)., developed gastroresistant drug delivery system for pantoprazole, is a proton pump inhibitor, this is alsoan acid labile drug, which can be degraded in the tomach. Therefore, the drug should be targeted to intestine; to bypass the stomach the gastroresistant double walled microspheric drug delivery system was adopted. The formulations were developed consisting of double wall. The primary wall composed of mucoadhesive polymer sodium CMC and a release controlling polymer sodium alginate. The second wall coating the primary microspheres was composed of eudragit S-100. The effect of polymer concentration onthe particle size, shape drug entrapment efficiency,mucoadhesive property, release study of core microspheres were evaluated[48].

6. METHODOLOGY

6.1. Preformulation studies

6.1.1.Preparation of standard graph for pantoprazole sodium using acidic buffer (pH 1.2)

6.1.1.1. Determination of absorption maxima (λmax)

100 mg of pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 100 mL of pH 1.2 acidic buffer in 100 mL volumetric flask (stock solution). 2 mL was taken from the stock solution and transferred into 100 mL volumetric flask and diluted up to 100 mL with pH 1.2 acidic buffer. The resulting solution was labeled as standard working Solution. 2 mL of the working solution was withdrawn and diluted up to 10 mL with pH 1.2 acidic buffer in 10 mL volumetric flask. The spectrum of this solution was run in 200 to 400 nm range in UV-visible spectrophotometer. The λ max of the pantoprazole sodium sesquihydrate was found to be 283 nm.

6.1.1.2. Preparation of standard graph

From above standard working solution, 1, 2, 3, 4, 5 and 6 mL was withdrawn and diluted up to 10 mL with pH 1.2 acidic buffer in 10 mL volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 283 nm using the pH 1.2 acidic buffer as blank.

6.1.2. Preparation of standard graph for pantoprazole sodium using phosphate buffer (pH 6.8)

6.1.2.1. Determination of absorption maxima (λmax)

100 mg of pantoprazole sodium sesquihydrate was weighed accurately and dissolved in 100 mL of pH 6.8 phosphate buffer in 100 mL volumetric flask (stock solution). 2 mL was

taken from the stock solution and transferred into 100 mL volumetric flask and diluted up to 100 mL with pH 6.8 phosphate buffer. The resulting solution was labeled as standard working Solution. 2 mL of the working solution was withdrawn and diluted up to 10 mL with pH 6.8 phosphate buffer in 10 mL volumetric flask. The spectrum of this solution was run in 200 to 400 nm range in UV-visible spectrophotometer. The λ max of the pantoprazole sodium sesquihydrate was found to be 288 nm.

6.1.2.2. Preparation of standard graph

From standard working solution, 1, 2, 3, 4, 5 and 6 mL has withdrawn and diluted up to 10 mL with pH 6.8 phosphate buffer in 10 mL volumetric flask to get concentration of 2 µg, 4 µg, 6 µg, 8 µg, 10 µg and 12 µg respectively. The absorbance of each solution was measured by UV-visible spectrophotometer at 288 nm using the phosphate buffer (pH 6.8) as blank.

6.1.3. FTIR spectra study

This was carried out to find out the compatibility between the drug pantoprazole sodium sesquihydrate and the croscarmellos sodium, MCC, manito and other exicipients. 10 mg of the sample and 400 mg of KBr were taken in a mortar and triturated. A small amount of the triturated sample was taken into a pellet maker and was compressed at10 Kg/cm2 using a hydraulic press. The pellet was kept on to the sample holder and

scanned in Bruker FT-IR spectrophotometer. The spectra obtained were compared and interpreted for the functional group peaks.

6.2. Evaluation

6.2.1. Precompression parameters

6.2.1.1. Bulk density (Db)

Accurately weighed granules were carefully transferred into graduated measuring cylinder. The granules bed was then made uniform and the volume occupied by the granules was noted as per the graduation marks on the cylinder as mL. It is expressed in gm/mL and is calculated using the following formula[49,50].

6.2.1.2. Tapped density (Dt)

It is the ratio of total mass of granule to the tapped volume of granule. The graduated measuring cylinder containing accurately weighed granule was manually tapped for 50 times. Volume occupied by the granule was noted. It is expressed in gram/mL and is calculated by following formula[49,50].

6.2.1.3. Compressibility index (I) and Hausner's ratio

Carr's index and Hausner's ratio measure the propensity of granule to be compressed and the flow ability of granule. Carr's index and Hausner's ratio were calculated using following formula[49,50].

$$I = \frac{D_t - D_b}{D_t} \times 100$$

$$\text{Hausner's ratio} = D_t / D_b$$

Where, D_t – Tapped density of the powder

D_b – Bulk density of the powder

6.2.1.4. Angle of repose (θ)

The frictional forces in a loose powder can be measured by the angle of repose. This is the maximum angle possible between the surface of a pile of powder and the horizontal plane. Sufficient quantities of pantoprazole granules were passed through a funnel from a particular height (2 cm) onto a flat surface until it formed a heap, which touched the tip of the funnel. The height and radius of the heap were measured. The angle of repose was calculated using the formula[49,50].

Angle of repose (θ) = $\tan^{-1}$ (h/r)

Where, h – Height of the pile in cm

r – Radius of the pile

6.3. Formulation studies

6.3.1. Preparation of pantoprazole sodium tablets

6.3.1.1. Preparation of powder blend

Pantoprazole sodium sesquihydrate powder blend for tabletting were prepared by direct compression method. Specified quantity of pantoprazole, croscarmellos sodium, manitol, calcium phosphate, and MCC were weighed according to the formula (**Table 3**) and transferred in a mortar and pestle and mixed thoroughly. The powder was passed through sieve no 80 to obtain the granules. The specified quantity of magnesium stearate and talc were finally added and mixed for the compression of tablets.

6.3.1.2. Preparation of pantoprazole sodium tablets

An ideal mixture of granules were directly punched into tablets weighing about 200 mg containing 40 mg of pantoprazole sodium sesquihydrate, using rotary tablet compression

machine (Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India), using 8 mm diameter concave punches. The different batches of pantoprazole tablets were collected and stored in air tight containers.

Table 3. Composition of pantoprazole sodium enteric coated sodium tablets

Composition	F1	F2	F3	F4	F5	F6	F7	F8	F9
Pantoprazole sodium (mg)	40	40	40	40	40	40	40	40	40
Croscarmellose sodium (mg)	2	4	6	2	4	6	2	4	6
Microcrystalline cellulose(mg)	27	25	23	27	25	43	80	50	23
Mannitol (mg)	50	75	100	40	85	80	43	50	75
Dicalcium phosphate (mg)	75	50	25	85	40	25	75	50	50
Talc (mg)	2	2	2	2	2	2	2	2	2
Magnesium stearate (mg)	4	4	4	4	4	4	4	4	4
Total weight (mg)	200	200	200	200	200	200	200	200	200

6.4. Post compression parameters

6.4.1. Hardness test

The prepared tablets were subjected to hardness test[28,38]. It was carried out by using hardness tester and expressed in kg/cm2.

6.4.2. Friability test

The friabilit was determined using friabilator and expressed in percentage (%). 20 tablets from each batch were weighed separately (Winitial) and placed in the friabilator, which was then operated for 100 revolutions at 25 rpm. The tablets were reweighed (Wfinal) and the percentage friability (F) was calculated for each batch by using the following formula[28,38].

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

6.4.3. Weight variation test

Twenty tablets were selected at random from the lot, weighed individually and the average weight was determined. The percent deviation of each tablets weight against the average weight was calculated[28,38]. The test requirements are met, if not more than two of the individual weights deviate from the average weight by more than 5% and none deviates more than 10%. IP limit for weight variation in case of tablets weighing more than 80 mg but less than 250 mg is ± 7.5 %.

6.4.4. Drug content uniformity

The prepared pantoprazole sodium sesquihydrate tablets were tested for their drug content. Three tablets of each formulation were weighed and finely powdered. About 40 mg equivalent of pantoprazole sodium sesquihydrate was accurately weighed and completely dissolved in pH 6.8 phosphate buffer and the solution was filtered. 1 mL of the filtrate was further diluted to 100 mL with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured by UV spectrophotometer at 288 nm[28].

6.4.5 Disintegration time of Pantoprazole sodium core tablets

Disintegration test was carried out using the tablet disintegration test apparatus (Servewell Instruments pvt. Ltd., Electrolab ED-2L, India) pH 6.8 phosphate buffer at 37 ± 0.5 ºC was used as the disintegration media and the time in second taken for complete disintegration of the tablet

6.5 Coating of compressed pantoprazole sodium tablets

6.5.1. Preparation of enteric coating solution

The enteric coating solution was prepared by simple solution method. It was prepared by 6% w/w and 8% W/W of Eudragit L100 (E1 and E2)or cellulose acetate phthalate (C1 and C2) as an enteric polymer, PEG 1.5% w/w as plasticizer and acetone and isopropyl acetone was used as solvent. Diethyl phthalate was added and made up the volume with rest of the solvent mixture; this mixture was constantly stirred for 1h with paddle mechanical stirrer at the rate of 1000 rpm and the stirred coating solution was again filtered through muslin cloth, a coating solution was obtained38,42.

Table 4. Composition of coating solution

Ingredients	Quantity (%)
Cellulose acetate phthalate/ Eudragit L100	6.0 / 8.0
PEG	1.5
Acetone	59.4

6.5.2. Enteric coating of pantoprazole sodium compressed tablets by dipping method

The compressed tablets were coated with enteric coating polymer (Eudragit L100 or cellulose acetate phthalate) solution by dipping method. Desired tablet coating continued the dipping and weight gain was achieved. The coated tablets were studied for its weight variation, thickness, uniformity of drug content and *in vitro* dissolution study[38,42].

6.5.3. Physicochemical evaluation of coating films

The same polymer solution was used to prepare the polymeric films and was subjected for film thickness, film solubility.

The polymeric films were prepared by casting the acetone with PEG the polymer solution was poured on the glass plate. The film was dried for 24 h at room temperature under a special cover with reduced solvent evaporation to obtained smooth homogenous films. The dried films were cut in to $1cm^2$ area the prepared polymeric film was studied for film thickness, and film solubility. The thickness of dried films was determined by thickness Digital micrometer. The film solubility was studied with pH 1.2 and pH 6.8. The 1×1 cm^2 coating film was selected, weighed and transferred in a beaker containing 20 mL of specified pH medium, which was mixed in a magnetic stirrer for 1 h at 37 ± 1°C and finally film solubility was examined.

6.5.4 *In vitro* drug release studies

USP dissolution apparatus type II (Electrolab TDT-08L,Mumbai,India) was employed to study the *in vitro* drug release from various formulations prepared. The dissolution medium used was 900 mL of acidic buffer of pH 1.2 for 2 h and phosphate buffer of pH 6.8

for 1 hrs. The tablet was kept in to the basket. The temperature was maintained at 37 ± 0.5°C and the stirring rate was 100 rpm. Samples were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured by UV spectrophotometer at 283 nm (pH 1.2) and at 288 nm (pH 6.8) against a blank. The release studies were conducted in triplicate and the mean values were plotted versus time[28].

6.6. Stability studies

Stability studies were performed as per the ICH guidelines. Selected formulations of Pantoprazole sodium tablet were sealed in aluminum foil cover and stored at (40 ± 2 °C / 75 ± 5 % R.H) for a period of 3 months. Samples from each formulation which are kept for examination were withdrawn at definite time intervals. The withdrawn samples were evaluated for physical appearance, hardness, drug content [29].

LIST OF CHEMICALS USED

SL. No.	Materials	Manufacturer / Supplier
1	Acetone	SD Pharma, Mumbai, India
2	Calcium phosphate	Fine Chem Industries, India
3	Disodium hydrogen phosphate	Fine Chem Industries, India
4	Potassium dihydrogen phosphate	Cipla Pharma, Mumbai, India
5	Cellulose acetate phthalate	SD Pharma, Mumbai, India
6	Micro crystalline cellulose	Cipla Pharma, Mumbai, India
7	Mannitol	Signet Chemical Corporation
8	Croscarmellose sodium	SD Chemical Corporation
9	Pantoprazole sodium sesquihydrate	Signet Chemical Corporation
10	Talc	Spectrochem Pvt. Ltd. Mumbai.
11	Magnesium stearate	Spectrochem Pvt. Ltd. Mumbai.
12	Eudragit L-100	Sd fine Chem. Ltd., Mumbai, India.
13	Potassium dihydrogen Phosphate	Spectrum reagent and chemicals Pvt. Ltd., India.
14	Hydrochloric acid	Swastik Pharmaceuticals, Mumbai, India.

SL. NO	Equipment	Manufacturer / Supplier
1	Rotary tablet punching machine	Ridhi Pharma machinery, Ahmedabad, India
2	UV Spectrophotometer	Shimadzu 1800, Japan
3	Digital Electronic Balance	Citizon, India.
4	Monsanto Hardness tester	Labtech, India
5	Friability apparatus	Ketan, Koshish Industries, India
6	Digital pH meter	Hanna, India
7	Vernier calipers	Mitutoyo. Japan
8	Disintegration test apparatus	Electrolab ED-2L,Servewell Industries, India
9	Dissolution test apparatus	Electrolab TDT-08L Servewell Industries, India
10	FTIR Spectrophotometer	Bruker,Japan.
11	Hot air oven	Servewell Industries, India

7. RESULTS AND DISCUSSIONS

Present study was done on enteric coating tablets with different formulation F1 to F9. Pantoprazole sodium sesquihydrate were prepared by direct compression method using different concentration of, microcrystalline cellulose, mannitol, dicalcium phosphate, croscarmellose sodium, magnesium stearate and talc, CAP and Eudragit L100 were used as enteric coating polymer, which prevent drug form gastric pH and release in intestinal pH.

7.1. Preformulation studies

7.1.1. Preparation of standard graphs

Standard graph for the drug pantoprazole sodium was done separately in pH 1.2 acidic buffer and pH 6.8 phosphate buffer. **Table 5 and 6** show the concentrations of pantoprazole sodium in pH 1.2 acidic and pH 6.8 phosphate buffers and the respective absorbance. The Figure 4 and 5 show the calibration curves of pantoprazole sodium in pH 1.2 acidic buffer and pH 6.8 phosphate buffer respectively.

Table 5. Calibration data of pantoprazole sodium in 0.1N HCl (pH 1.2)

SL. NO.	Concentration (mg /mL)	Absorbance* (nm)
1	0	0
2	2	0.082+0.0005
3	4	0.145+0.0015
4	6	0.231+0.0101
5	8	0.289+0.0023
6	10	0.361+0.0025
7	12	0.459+0.0047

Figure 4. Standard graph of pantoprazole sodium in 0.1N HCl (pH 1.2)

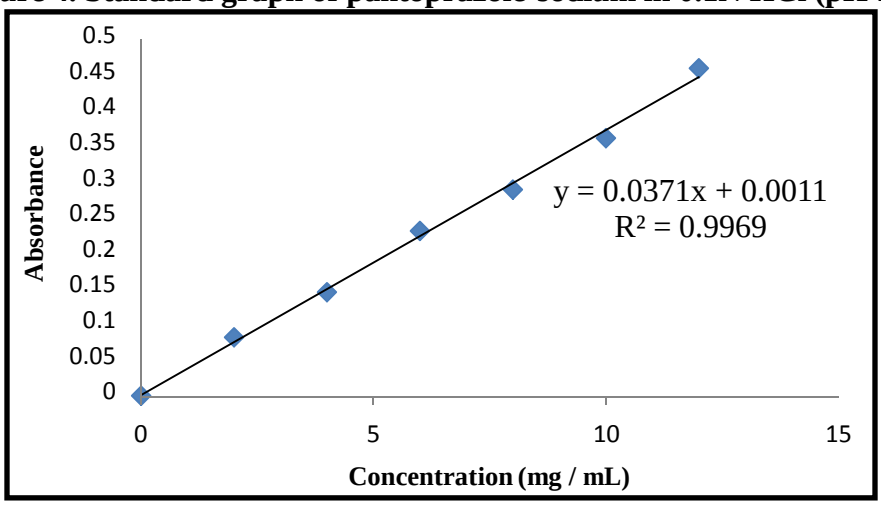
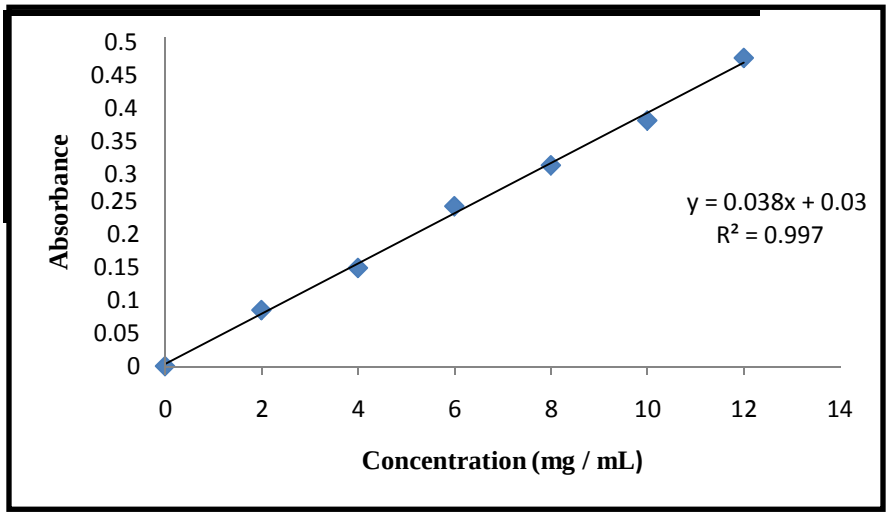


Table 6. Calibration data of pantoprazole sodium in phosphate buffer (pH 6.8)

SL. NO.	Concentration (mg /mL)	Absorbance*(nm)
1	0	0
2	2	0.085±0.0040
3	4	0.149±0.0036
4	6	0.243±0.0015
5	8	0.305±0.0075
6	10	0.373±0.0051
7	12	0.468±0.0020

*Mean±SD, *n* = 3

Figure 5. Standard graph of pantoprazole sodium in phosphate buffer (pH 6.8)



7.1.2. FTIR spectral study

FT-IR spectroscopy study was carried out separately to find out the compatibility between the drug pantoprazole and Microcrystalline cellulose, mannitol, dicalcium phosphate, croscarmellose sodium. The FT-IR was performed for drug, polymer and the physical mixture of drug-polymer. The spectral obtained from FT-IR spectroscopy studies shows in **Table 7 and Figures 6-9**

The peaks obtained in the spectra of drug and polymers mixtures correlates with each other. This indicates that the drug was compatible with the formulation components. IR studies indicated no interaction between drug and polymers.

Figure 6. FTIR Spectrum of pantoprazole sodium

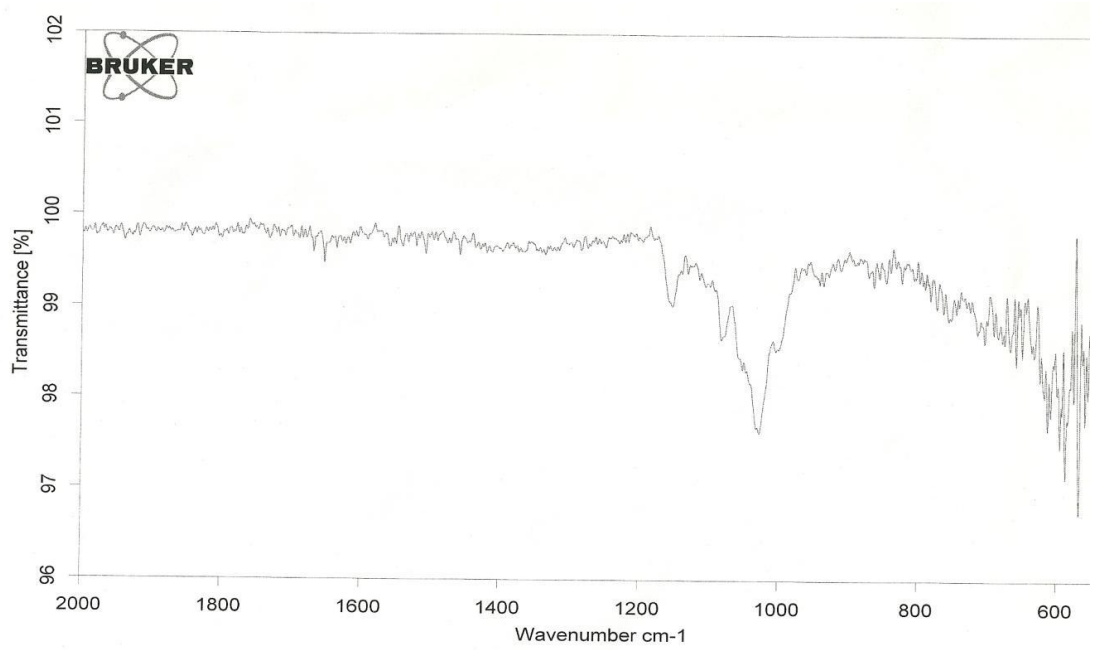


Figure 7. FTIR Spectrum of physical mixture of pantoprazole sodium with mannitol

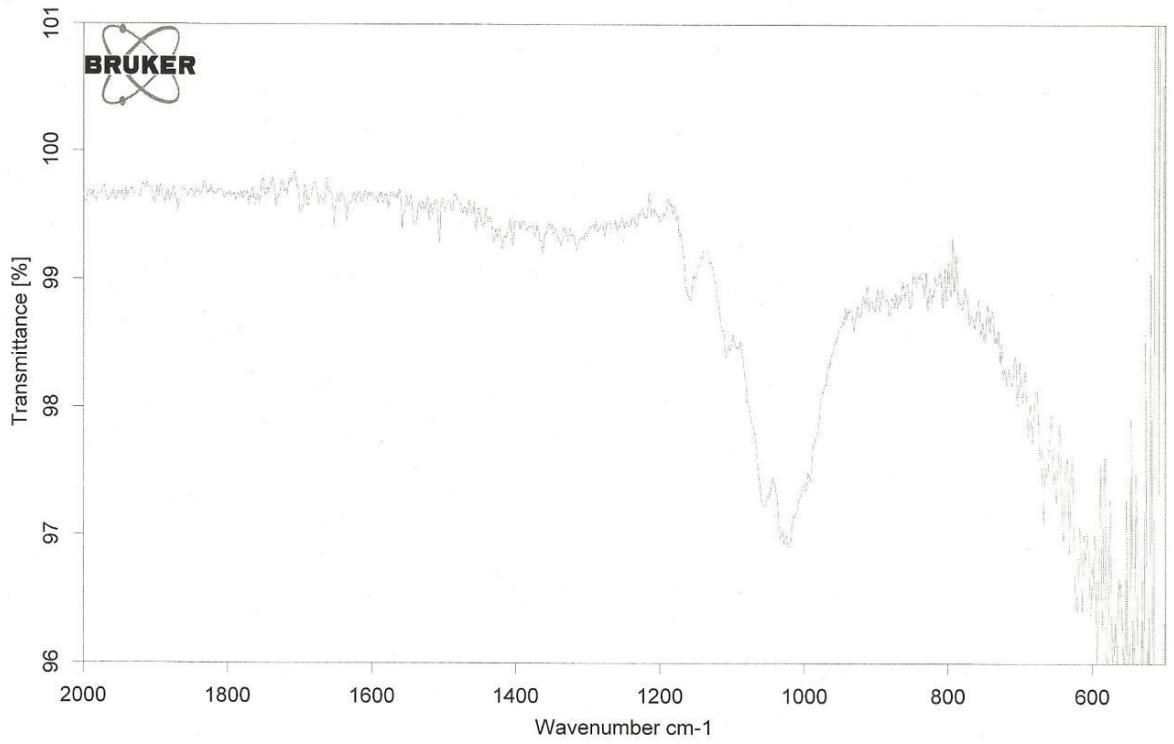


Figure 8. FTIR Spectrum of physical mixture of pantoprazole sodium with dicalcium phosphate

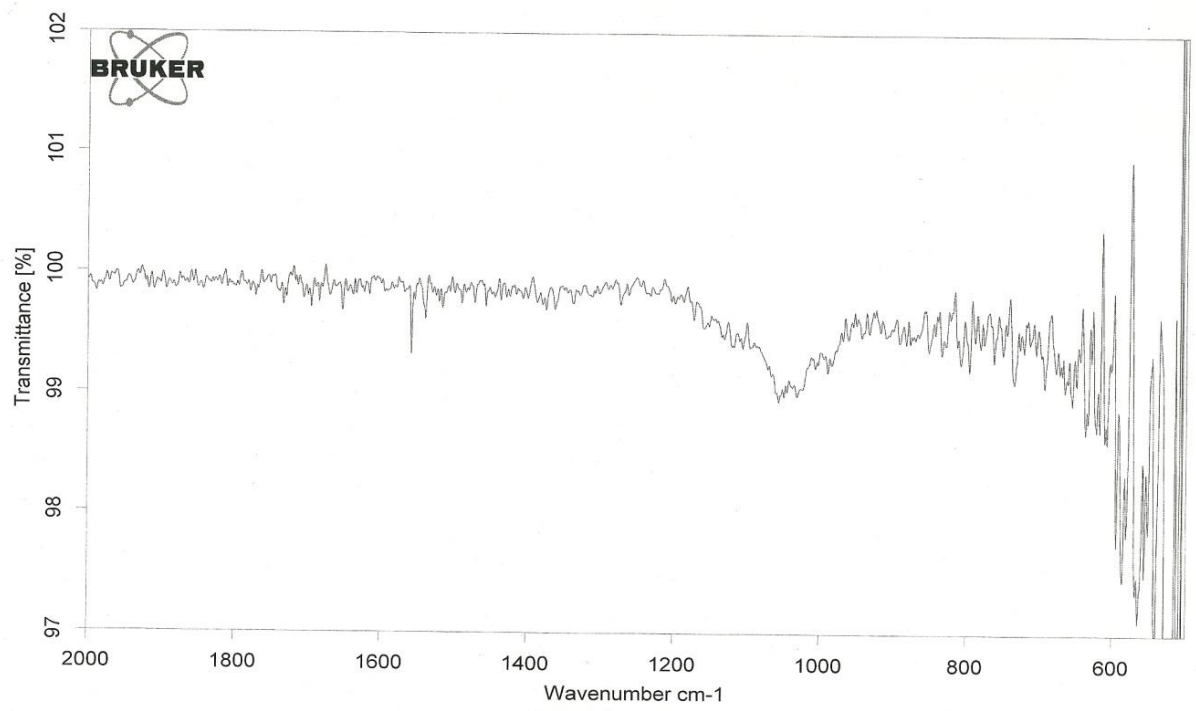
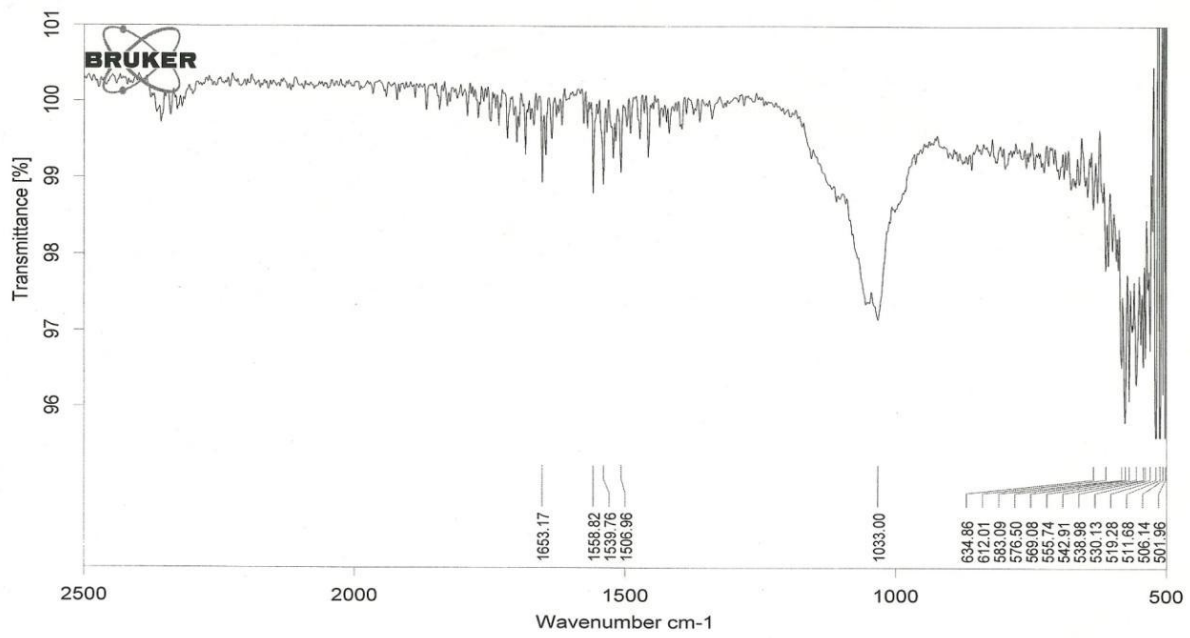


Figure 9. FTIR Spectrum of physical mixture of pantoprazole sodium with Dicalcium phosphate and mannitol



The standard band frequency of the pantoprazol sodium is show in the Table 7.

Table 7. Standard band frequency of Pantoprazole Sodium

Wave number in cm^{-1}	**Characteristic**
1900	C=H
1650 - 1580	N-H bending
1600 - 1400	Aromatic C=C stretching
1400 - 1000	C-N bending
1373	C-F
1049	S=O

The spectra obtained from the physical mixture show that all the principle peaks are at or around the requisite wave number of pure drug. Thus it may be inferred that there was no chemical interaction between drug and polymer and the purity and integrity of drug was maintained in the physical mixtures.

7.2. Evaluations

7.2.1.Precompression parameters

The prepared pantoprazole powder blend for tabletting was prepared by direct compression method. The prepared pantoprazole powder blend were evaluated angle of repose, bulk density, tapped density, Hausner's ratio and compressibility index as given on **Table 8.**

The bulk densities of the granules were found to be in the range of 0.306 ± 0.03 to 0.384. ± 0.04 gm/mL, while the tapped densities were ranged between 0.313 ± 0.04 to 0.429 ± 0.05 gm/mL. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility (5.74 ± 0.13 to 10.48 ± 0.20%) signify good flowability. The angle of repose of all formulation was less than 30 º (25.79 ± 0.24 to 29.52 ± 0.14) also indicate the good flowability of the prepared granules.

7.2.2 Formulation studies

7.2.2.1. Preparation of of pantoprazole sodium tablets

The pantoprazole sodium sesquihydrate tablets were prepared by direct compression method A total of nine formulations (F1-F9) by using a rotary tablet compression machine (8 mm diameter, Riddhi 10 stn mini tablet press RDB4-10, Rimek, Ahmedabad, India). Compositions of the pantoprazole sodium sesquihydrate tablets are shown in **Table 3.**

Table 8 Pre compression parameters of pantoprazole sodium

Formulation Code	Parameter				
	Bulk density (gm/mL) *	**Tapped density (gm/mL) ***	**Carr's Index (%)***	**Hausner's ratio***	**Angle of repose (Ɵ)***
F1	0.357±0.03	0.384±0.05	7.03±0.09	1.075±0.04	28.31±0.26
F2	0.312±0.04	0.335±0.02	6.86±0.15	1.073±0.05	27.20±0.14
F3	0.306±0.03	0.326±0.03	6.13±0.12	1.065±0.02	29.13±0.34
F4	0.312±0.03	0.334±0.06	6.58±0.14	1.070±0.06	26.13±0.26
F5	0.306±0.03	0.334±0.05	8.38±0.17	1.091±0.08	26.78±0.18
F6	0.384±0.04	0.429±0.05	10.48±0.20	1.117±0.07	25.79±0.24
F7	0.358±0.05	0.385±0.04	7.01±0.13	1.075±0.03	29.52±0.14
F8	0.286±0.05	0.313±0.04	8.62±0.07	1.094±0.03	26.95 ±0.15
F9	0.348±0.08	0.328±0.05	5.74±0.13	1.06±0.08	26.13±0.26

***Mean ± SD n=3

7.2.2.2. Post compression parameters of pantoprazole sodium core tablet

The pantoprazole tablets were prepared by direct compression method and were evaluated for their hardness, weight variation, content uniformity, friability and *in vitro* drug release **(Table 9).**

Hardness has to be controlled to ensure that the product is firm enough to withand handling without breaking or crumbling and not so hard that the disintegration time is unduly prolonged. The average hardness of the tablets to be in range was found within 4.93 ± 0.15 to 6.20 ± 0.35 Kg / cm2. Friability value which also affected by the hardness value of tablets should be in the range 1% limits, which is the usual friability range of tablets. The friability of the prepared tablets was found less than 1% w/w. The drug content uniformity of

pantoprazole sodium present in tablets formulation ranged from 96.28 ± 0.15to 100.34 ± 0.13%. The average weight found 198 ± 0.15 to 206 ± 0.24 mg. Disintegration time varied between 11.48 ± 0.15 to 5.38 ± 0.23, hence all shows favorable result.

Table 9 . Post compression parameters of pantoprazole sodium core tablets

Formulation Code	Parameter				
	Hardness (Kg/cm^2)*	**Friability (%)***	**Weight variation (mg) ***	**Drug content (%)***	**Disintegration time(min) ***
F1	5.80 ± 0.12	0.69 ± 0.015	199 ± 0.12	96.28 ± 0.15	10.6± 0.62
F2	5.56 ± 0.24	0.51 ± 0.017	206 ± 0.24	97.62 ± 0.27	8.26± 0.56
F3	5.83 ± 0.08	0.48 ± 0.014	201 ± 0.17	99.51 ± 0.36	5.38± 0.23
F4	4.93 ± 0.15	0.64 ± 0.015	208 ± 0.20	98.17 ± 0.16	11.48± 0.15
F5	5.73 ± 0.25	0.71 ± 0.016	203 ± 0.16	98.92 ± 0.42	9.32± 0.18
F6	5.12 ± 0.34	0.68 ± 0.026	206 ± 0.14	100.34 ± 0.13	6.13± 0.25
F7	5.66 ± 0.17	0.54 ± 0.026	199 ± 0.22	98.50 ± 0.48	10.54± 0.43
F8	6.20 ± 0.35	0.49 ± 0.025	204 ± 0.18	98.41 ± 0.34	9.12± 0.71
F9	5.60 ± 0.24	0.42 ± 0.018	198 ± 0.15	99.08 ± 0.35	6.02± 0.21

***** Mean ± SD, n=3

7.2.2.3. Physicochemical evaluation of coating films

Physicochemical evaluation of cellulose acetate phthalate, Eudragit L100 and were studied for different parameters such as film thickness, film weight and film solubility. The enteric polymer cellulose acetate phthalate, Eudragit L100 were found to be completely soluble in pH6.8 and insoluble in pH1.2 (**Table 10).**

7.2.2.4. Physicochemical evaluation of pantoprazole sodium enteric coated tablets

The tablets which shows most satisfactory result in disintegration, and drug content parameters(F3 and F9) coated by dip coating method. The results of physicochemical evaluation of prepared coated tablets are shown in **Table 11**. The weight variation was found to be between 0.211 ± 0.024 % to 214 ± 0.021 mg. The drug content was found to be between 93.47 ± 0.23% to 98.45 ± 0.12%. The hardness was found to be from 5.2 ± 0.11 to 6.5 ± 0.15 Kg / cm2.

Table 10 Physicochemical evaluation of different polymer coating films

Polymer	Parameter		
	Film solubility		Film thickness (mm) *
	pH 1.2	pH 6.8	
CAP	Insoluble	Soluble	0.21 ± 0.07
Eudragit L 100	Insoluble	Soluble	0.24 ± 0.08

***Mean±SD, *n* = 3

Table 11. Physicochemical evaluation parameters of enteric coated tablets

Polymer	Batch Code	Parameter		
		Weight Variation (mg) *	Hardness Kg/cm^2*	Drug content (%)*
CAP	C1F3	211 ± 0.035	6.5 ± 0.15	96.75 ± 0.14
	C2F3	214 ± 0.016	5.9 ± 0.24	93.65 ± 0.35
	C1F9	212 ± 0.006	5.4 ± 0.09	94.45 ± 0.26
	C2F9	210 ± 0.024	6.3 ± 0.14	98.54 ± 0.12
Eudragit L 100	E1F3	214 ± 0.021	5.5 ± 0.16	93.47 ± 0.23
	E2F3	213 ± 0.012	6.0 ± 0.06	94.56 ± 0.14
	E1F9	215 ± 0.015	6.5 ± 0.31	98.27 ± 0.45
	E2F9	211 ± 0.024	5.7 ± 0.20	96.35 ± 0.12

*****Mean±SD, *n* = 3

7.2.2.5. *In vitro* drug release studies of enteric coated tablets

The *in vitro* release of pantoprazole sodium from the prepared tablets was studied in ph 1.2 for 2 h and in phosphate buffer pH 6.8 for 1 h. *In vitro* dissolution studies were performed using USP Type II rotating paddle dissolution apparatus (Electrolab TDT-08L, India) by using 1.2 N HCl and phosphate buffer (pH 6.8) as a dissolution medium. Formulation which shows most satisfactory result is C2F9, where drug release started after 2 hrs, and released maximum 99.72 by 3 hrs. Remaining were respectively, released started and reached maximum, CIF3-90 min and 96.42 in 3 hrs, C2F3-2 hrs and 94.59 in 195 min, E1F3-90 min and 98.15 in 165 min, E2F3-105 min and 97.54 in 3 hrs, C1F9-90 min and 99.79 in 165 min, EIF9-90 min and 97.97 in 165 min, E2F9-2 hrs and 97.39 in 3 hrs. The cumulative percentage releases of pantoprazole sodium from the tablets were shown in **Table 12-19 and Figure 11-12.**

Table 12. *In vitro* drug release of pantoprazole sodium (C1F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg /mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.024	0.6469	5.822	0	0	5.822	14.62±0.52
120	0.06	1.6172	14.555	0.0064	0.0064	14.561	36.58±0.40
135	0.091	2.3884	21.496	0.0161	0.0226	21.518	54.05±0.90
150	0.121	3.1758	28.582	0.0238	0.0465	28.629	71.91±0.39
165	0.142	3.7270	33.543	0.0317	0.0782	33.621	84.46±0.17
180	0.162	4.2519	38.267	0.0372	0.1155	38.383	96.42±0.40

***** Mean±SD, $n = 3$

Table 13. *In vitro* drug release of pantoprazole sodium (C2F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0
135	0.019	0.4986	4.488	0	0	4.488	11.27 ±0.90
150	0.082	2.1522	19.370	0.0049	0.0049	19.375	48.67±0.27
165	0.122	3.2021	28.818	0.0215	0.0265	28.845	72.46±0.18
180	0.149	3.9107	35.196	0.0320	0.0585	35.255	88.56±0.42
195	0.159	4.1732	37.559	0.0391	0.0976	37.656	94.59±0.70

***** Mean±SD, $n = 3$

Table 14. *In vitro* drug release of pantoprazole sodium (E1F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.041	1.1051	9.946	0	0	9.946	24.98±0.34
120	0.071	1.9137	17.223	0.0110	0.0110	17.234	43.29±0.62
135	0.116	3.0446	27.401	0.0191	0.0301	27.431	68.91±0.72
150	0.137	3.5958	32.362	0.0304	0.0606	32.422	81.44±0.58
165	0.165	4.3307	38.976	0.0359	0.0965	39.072	98.15±0.40

***** Mean±SD, $n = 3$

Table 15. *In vitro* drug release of pantoprazole sodium (E2F3)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0.02	0.5390	4.851	0	0	4.851	12.18+0.82
135	0.07	1.8372	16.535	0.0053	0.0053	16.540	41.55±0.66
150	0.116	3.0446	27.401	0.0183	0.0237	27.425	68.89+0.72
165	0.142	3.7270	33.543	0.0304	0.0542	33.597	84.39+0.48
180	0.164	4.3044	38.740	0.0372	0.0914	38.831	97.54±0.70

***** Mean±SD, $n = 3$

Table 16. *In vitro* drug release of pantoprazole sodium (C1F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.04	1.0781	9.703	0	0	9.703	24.48±0.18
120	0.079	2.1293	19.164	0.0107	0.0107	19.175	48.38±0.67
135	0.121	3.1758	28.582	0.0212	0.0320	28.614	72.20±0.58
150	0.15	3.9370	35.433	0.0317	0.0638	35.496	89.56±0.42
165	0.167	4.3832	39.448	0.0393	0.1032	39.552	99.79±0.70

***** Mean±SD, $n = 3$

Table 17. *In vitro* drug release of pantoprazole sodium (C2F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0	0	0	0	0	0	0
135	0.054	1.417	12.755	0	0	12.755	32.18±0.34
150	0.098	2.572	23.149	0.0141	0.0141	23.163	58.44±0.58
165	0.139	3.648	32.834	0.0257	0.0398	32.874	82.94±0.18
180	0.167	0.038	0.043	39.448	0.0364	0.076	99.72±0.46

***** Mean±SD, $n = 3$

Table 18. *In vitro* drug release of pantoprazole sodium (E1F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0.03	0.8086	7.277	0	0	7.277	18.36±0.42
120	0.063	1.6981	15.283	0.0080	0.0080	15.291	38.58±0.22
135	0.104	2.7296	24.566	0.0169	0.0250	24.592	62.05±0.58
150	0.15	3.9370	35.433	0.0272	0.0523	35.485	89.53±0.39
165	0.164	4.3044	38.740	0.0393	0.0917	38.831	97.97±0.48

***** Mean±SD, $n = 3$

Table 19. *In vitro* drug release of pantoprazole sodium (E2F9)

Time (min)	Absorbance	Conc. (µg/mL)	Conc. in 900 mL (mg / mL)	Loss	Cumulative loss	Cumulative drug released	Cumulative percentage drug released *
0	0	0	0	0	0	0	0
15	0	0	0	0	0	0	0
30	0	0	0	0	0	0	0
45	0	0	0	0	0	0	0
60	0	0	0	0	0	0	0
75	0	0	0	0	0	0	0
90	0	0	0	0	0	0	0
105	0	0	0	0	0	0	0
120	0.027	0.7277	6.549	0	0	6.549	16.52±0.16
135	0.071	1.8635	16.771	0.0072	0.0072	16.778	42.33±0.35
150	0.118	3.0971	27.874	0.0186	0.0259	27.899	70.39±0.63
165	0.149	3.9107	35.196	0.0309	0.0568	35.253	88.95±0.44
180	0.163	0.0381	0.042	38.503	0.0391	0.095	97.39±0.61

***** Mean±SD, *n* = 3

Figure 11. *In vitro* drug release of pantoprazole sodium (C1F3 to E2F3)

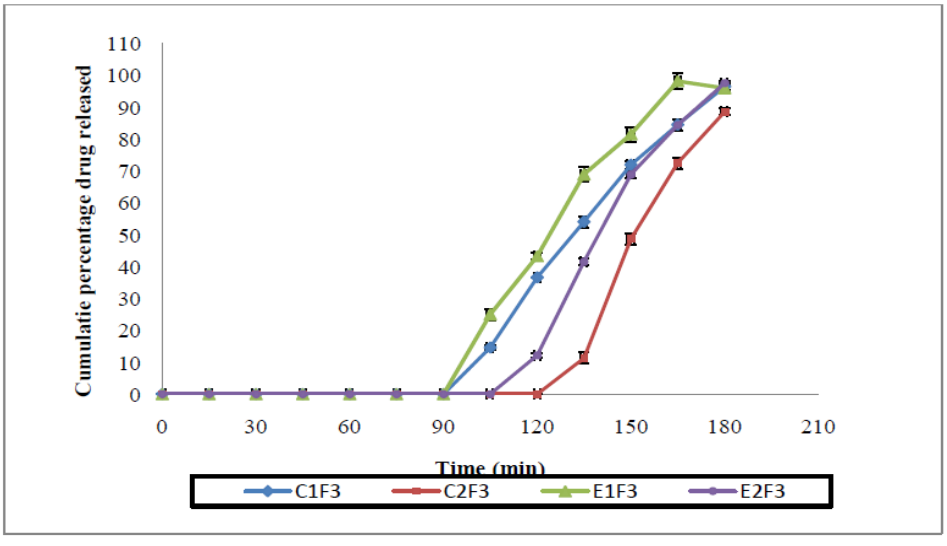
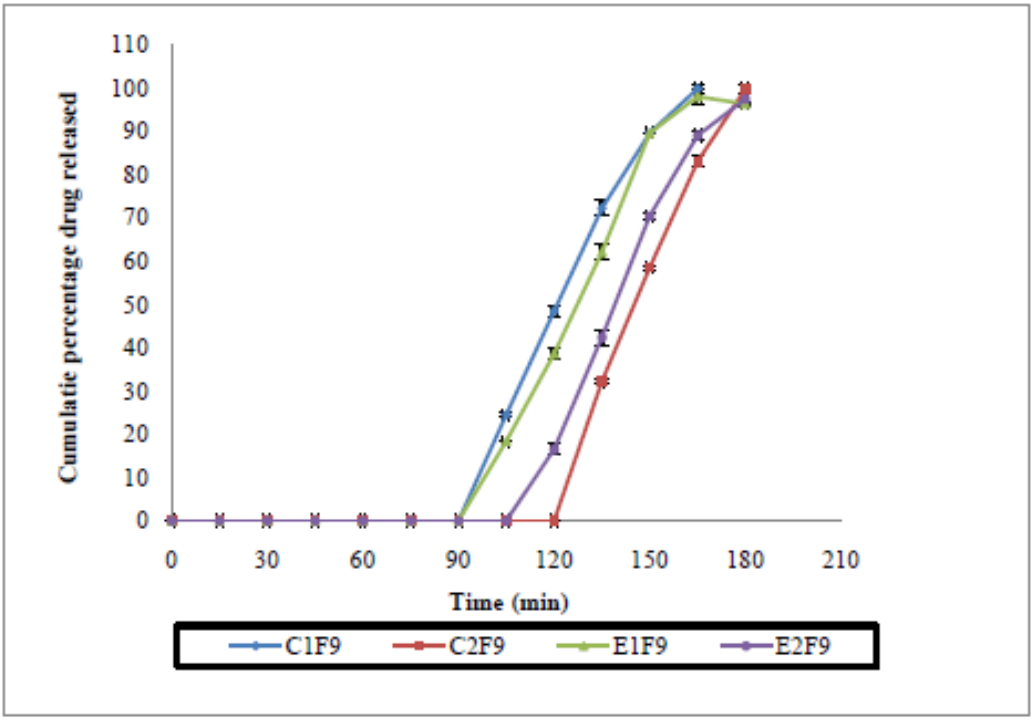


Figure 12. *In vitro* drug release of pantoprazole sodium (C1F9 to E2F9)



7.2.2.6. Stability studies

Stability of a drug in a dosage form at different environmental conditions is important as it determines the expiry date of that particular formulation. Changes in the physical appearance, color, odor, taste or texture of the formulation indicate the drug instability. Among the three enteric coated Formulation, Formulation C2F9 was selected for stability studies based on the physicochemical characterization of coating films and release characteristics.

The stability studies were carried out at 40 ± 2 °C with 75 ± 5%% RH which shown in **Table 20**. There were no significant changes in their physical appearance, average weight of tablets and hardness. It was observed that the initial drug content and the drug contents of the samples analyzed after 1,2,3 month of storage were similar. The release profile also not showed any significant changes indicating that there were no significant changes in the physical

as well as chemical characteristics of the formulation. Hence, it can be concluded from the results that the developed tablets were stable and retain their pharmaceutical properties over a period of 3 month.

Table 20.Stability studies of cellulose acetate phthalate coated tablet formulation C2F9

Evaluation parameters	Observation in month			
	Initial	**1st month**	**2nd month**	**3rd month**
Physical Appearance	white color tablets	No change	No change	No change
Hardness (Kg / cm^2) *	6.3 ± 0.14	6.2 ± 0.56	6.2 ± 0.64	6.2 ± 0.26
Drug Content (%)*	98.54 ± 0.12	98.36 ± 0.52	98.16 ± 0.36	98.07 ± 0.28

***Mean ± SD, n=3

8. SUMMARY & CONCLUSION

SUMMARY

The aim of the present study was to formulate and evaluate of enteric coated pantoprazole sodium sesquihydrate tablets by using manotol, dicalcium phosphate, microcrystalline cellulose, crossrmelose sodium, magnesium starate and talc.

FT-IR study was carried out to check any possible interactions between the drug and the excipients manotol, dicalcium phosphate, microcrystalline cellulose, crosscarmelose sodium,

Pantoprazole sodium sesquihydrate were prepared by direct compression method using different concentration of, Avicel PH (MCC) as filler, mannitol and dicalcium phosphate as diluents, croscarmellose sodium as disintegrating agents, magnesium stearate and talc was used as a glidant and lubricant respectively. The granules were evaluated for the precompression parameters like angle of repose, bulk density, tapped density and compressibility index. The flow characteristics of the granules were assessed by determining their angle of repose and Carr's Index. The values of compressibility index and angle of repose signify good flowability of the granules for all the batches. This shows that the granules had smooth flow properties ensuring homogenous filling of the die cavity during the compression (punching) of tablets.

Coating has been done for the selected formulation from the proposed formulation 1-9. Coating materials like CAP and Eudragit L100 with the difference concentration.

The *in vitro* dissolution studies were carried out for compressed and coated tablets using USP dissolution apparatus type II. The cumulative percentage of drug release from the tablets varied and depends on the type of polymer used and its concentration.

Formulation 3 and formulation 9 was selected for the coating. CAP and Eudragit L 100 was used for the coating polimer. In this present study coating material was used with 6 and 8 percentage on the above mentioned formulation.

The stability study indicated that the prepared formulation was stable retained their pharmaceutical properties at room temperature and 40°C/75% RH over a period of 1 month. The coated tablets did not release the drug in hostile acidic environment (pH 1.2) due to protective polymer coating and released the drug in the intestinal environment (pH 6.8).

Formulation 9, coated with 8% CAP was found to be best formulation, based on release time of the drug in the intestine.

CONCLUSION

An attempt was made in this research work to formulate an oral enteric coating pantoprazole sodium tablet and evaluate it. An ulcer is the disease caused by an imbalance between aggressive and defensive factors. Ulcer sarecrater-like sores which form in the lining of the stomach, just below the stomach at the beginning of the small intestine in the duodenum.Pantoprazole is a substituted benzimidazole derivative that targets gastric acid proton pumps, the final common pathway for gastric acid secretion. The drug covalently binding to the proton pumps, causing prolonged inhibition of gastric acid secretion.The stability of pantoprazole is depending on pH and it rapidly degrades in acid medium of the stomach,but stable in alkaline conditions. Therefore, pantoprazole should be delivered into the intestine. Hence, an attempt was made to formulate an enteric coated drug delivery system for pantoprazole by using various enteric coating polymers.

From the reproducible results obtained from the executed experiments it can be concluded that CAP and Eudragit L 100 can be used as enteric coated polymer. Both the polymer can protect the drug from the acid environment that is in gastric pH and release the drug when it’s reached in intestinal pH.

In this present research work, both the polymer have been used as an enteric coating polymer, with the best formulation. CAP and EudragitL100 have been used 6% and 8% with the best formulation. From the dissolution studies it was observed that, the enteric coated both polymer was intact for 2 hours in pH 1.2 buffer. The formulation which is said to the best formulation is C2F9, which is formulation no. 9 and coated with 8% CAP.

Therefore thestudyprovedthat the pantoprazole enteric coated tablets can be used for ulcer and GERD disease.

Hence, formulation of pantoprazole as an enteric coated tablet may solve the stability problem of drug in the stomach and release the drug in the intestine. After satisfied pre-compression and post compression result the of core tablets, tablets were coated with suitable coating material to develop the dosage form which is to overcome the drug degradation by the gastric enzymes as well as the acidic environment of the stomach.

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