FORMULATION AND EVALUATION OF DELAYED RELEASE PANTOPRAZOLE SODIUM ENTERIC COATED TABLETS

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MASTER OF PHARMACY

In

PHARMACEUTICS

By

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MAY 2012

CERTIFICATES

CERTIFICATE

This is to certify that the dissertation entitled "**FORMULATION AND EVALUATION OF DELAYED RELEASE PANTOPRAZOLE SODIUM ENTERIC COATED TABLETS "** is a bonafide and genuine research work carried out at Department of Pharmaceutics, K.K college of pharmacy by **M.I. AZARUDHIN, B.Pharm.,** during the year 2011-2012 under the supervision of **Prof. Dr. K. Senthilkumaran. M.Pharm., Ph.D.,** This dissertation is submitted in partial fulfillment of the requirements for the award of degree of Master of Pharmacy (Pharmaceutics), by the Tamilnadu Dr. M.G.R medical university ,Chennai-32.

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Dedicated to my Parents
&
Almighty

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LIST OF ABBREVIATIONS

BCS -Biopharmaceutical Classification System

IVIC -In-vitro In-vivo correlation

DDS -Drug Delivery System

EC -Enteric Coating

FDA	-Food &Drug Delivery System
GIT	-Gastro Intestinal Tract
PPI´S	-Proton Pump Inhibitor
IV	-Intravenous
AUC	-Area Under The Curve
HCL	-Hydrochloric Acid
MCC	- Micro crytaline cellulose
HPLC	-High Performance Liquid Chromatography
FTIR	-Fourier Transform Infrared Spectroscopy
U.V	-Ultra Violet Spectroscopy
NMT	-not more than
NLT	-not less than
API	-Active Pharmaceutical Ingredients
NCC	-No Characteristic Change
U.S.P	-Untied States Pharmacopoeia
Std	-Standard
Spl	-Sample
Q.S	-quantity sufficient
Fig	-Figure
SD	-Standard Deviation
RH	-Relative Humidity

NOMENCLATURE

RPM	-	Revolutions per minute
ppm	-	parts per million
mm	-	millimeter
#	-	mesh
g/ml	-	gram/ milliliter

sec	-	second
mg	-	milligram
cm	-	centimeter
µl	-	microlitres
w/w	-	weight by weight
v/v	-	volume by volume
%	-	Percentage
Min	-	minutes

1. INTRODUCTION

The treatment of acute diseases or a chronic illness has been mostly accomplished by delivery of drugs to patients using various pharmaceutical dosage forms including tablets, capsules, pills, suppositories, creams, ointments, liquids, aerosols, and injectables as drug carriers[1]. Drugs may be administered by variety of routes but oral administration is adopted wherever possible. There are many applications and large markets for non-oral products and the technologies that deliver them. However, if it is an applicable option, oral drug delivery will be selected in all but the most exceptional circumstances. It is safest, easiest, and most economical route of drug administration. Amongst drugs that are administered orally solid oral dosage forms i.e. tablets and capsules, represent the preferred class of products. Out of the two oral solid dosage forms, the tablets have number of advantages like tamper proof, low cost and speed of manufacturing (direct compression), ease of administration, patient compliance and flexibility in formulation etc.

1.1. Conventional Drug Therapy:

This requires periodic doses of therapeutic agents. These agents are formulated to produce maximum activity, stability and bioavailability. for most drugs, conventional methods of drug administration are effective, but some drugs are unstable or toxic and have narrow therapeutic index. some drugs posses solubility problem. conventional forms often cause problems to the patient, they maintain the therapeutic drug level for only short duration. this gives rise to sharp fluctuation of drug levels in plasma and tissue.

Disadvantages of conventional drug delivery system:

- In this system there is very less or no control over the release of the drug and effective concentration at the target site can be achieved by intermittent of excessive doses.
- The extent and rate of absortion of drug from conventional formulations may vary greatly, depending on the factors such as physio chemical properties of the drug presence of excipients ,various physiological factors such as the the presence or absence of food. pH of the gastro intestinal motility.[3]

- Care ful calculation necessary to prevent over dosing.

- The dosing pattern in conventional dosage forms results in constantly changing, unpredictable and often sub-therapeutic concentration, leading to marked side effects in some cases.

1.2. Modified Drug Delivery System: [4,5,6]

Modified release DDS include systems with pH–dependent, extended, delayed or pulsed drug release. sustained, extended or prolonged release drug delivery systems are terms used synonymously to describe this group of controlled drug delivery.

Classification:

The USP and NF has defined a modified release dosage forms as one in which the drug release characteristics of time course and location are chosen to accomplish therapeutic objectives not offered by conventional dosage forms.

Sustained Release: A sustained-release dosage form is designed to achieve a prolonged therapeutic effect by continuously releasing medication over an extended period of time after administration of a single dose. These systems try to mimic zero-order release by providing drug in a slow first-order fashion.

Controlled release: The term "Controlled release" has become associated with those systems from which therapeutic agents may be automatically delivered at predefined rates over a long period of time. These systems deliver drugs in a zero-order fashion.

Repeat Action: Alternative method of sustained release in which multiple doses of a drug are contained within a dosage form and each dose is released at a periodic interval.

Site-specific and receptor targeting: drug to the particular organ or tissue of the body. For receptor release, target is particular receptor for a drug within an organ or tissue.

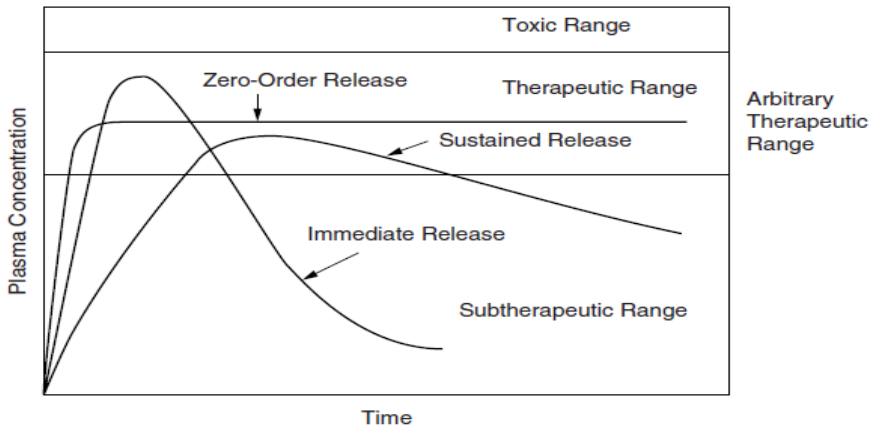

Fig.1 - Drug level versus time profile showing differences between zero-order controlled release; slow first-order sustained release, and release form a conventional tablet or capsule.

1.3. Delayed Release Systems

The design of such system involves release of drugs only at a site in the gastrointestinal tract. The drugs contained in such a system are those that are:

i) Destroyed in the stomach or by intestinal enzymes
ii) Known to cause gastric distress
iii) Absorbed from a specific intestinal site or
iv) Meant to exert local effect at a specific gastrointestinal site.

The two types of delayed release systems are:

- **Intestinal release systems:** A drug may be enteric coated for intestinal release for several known reasons such as to prevent gastric irritation, prevent destabilization in gastric pH etc.

- **Colonic release systems**: Drugs are poorly absorbed through colon but may be delivered to such a site for two reasons.

  a) Local action in the treatment of ulcerative colitis

  b) Systemic absorption of protein and peptide drugs

Advantage is taken of the fact that pH sensitive bioerodible polymers like polymethacrylates release the medicament only at the alkaline pH of colon or use of divinylbenzene cross-linked polymers that can be cleaved only by the azo reductase of colonic bacteria to release free drug for local effect or systemic absorption.

1.4. Delayed Release Solid oral Dosage Forms:

The correct selection and balance of excipients and processes in solid dosage formulations are designed either for improving the micrometric or macrometric proprerties of materials during manufacture and for providing a desired drug delivery system.[7] the most commonly used pharmaceutical delayed release solid dosage forms today include tablets, capsules, granules, pellets.

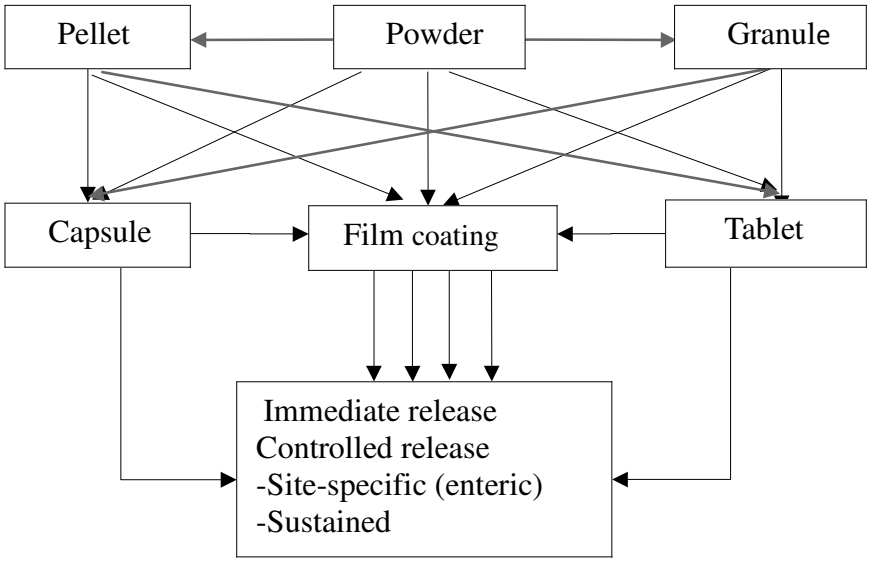

Fig .2 - RelationShip of Pharmaceutical Delayed Release Solid Dosage Forms

1.4.1. Classification of Delayed Release Solid Oral Dosage Forms:

Delayed release solid oral dosage forms are available either as single unit(non divided formulations–tablets, capsules) or as multiple unit (divide formulations-pellets, mini -tablets)forms.

1.4.1.1. Single unit dosage forms:

The single-unit dosage forms usually refer to diffusion controlled systems which include monolithic systems.where the diffusion of a drug through a matrix is the rate limiting step reservoir or multilayered matrix systems,[8] where the diffusion of the drug through polymer coating or layer of the system is the rate limiting step. However , generally, release of drugs will occur by a mixture of these two mechanisms.

1.4.1.2. Multi unit dosage forms: [9,10]

Types of multi unit dosage forms comprise :

- Granules
- Pellets
- Microparticles (microspheres ormicrocapsules) and Nano particles.
- Mini tablets and minidepots (dispersed and distributed through out the gastro intestinal tract when the capsule or tablet disintegrates).
- Multi unit tablets (divided at ingestion with out loss of the depot effect, as the sub unit act as a self contained depots).

1.4.1.3. Therapeutic Advantage of Multi units over single units:

When taken orally ,multi unit dosage forms

- Disperse freely in the gastro intestinal tract.
- Provides less risk of dose dumping.
- Reduces localized concentration of irritative drugs.
- Reduce risk of inter and intra patient variability.
- Improves safety and efficacy of a drug.
- Maximize drug absorption, reduce peak plasma fluctuations, minimize local irritation of the mucosa by certain irritant drugs and minimize potential side effects without appreciably lowering drug bioavailability.

1.5. Tablets: The Dominant Oral Dosage Form : [11,12]

Pharmaceutical tablets are the dominant dosage forms for drug delivery, occupying two third of the global market. Generally, they are formulated by compressing dry powder blends consisting of a number of components with different functionalities in a die. With advancement in technology and a rise in awareness towards modification in standard tablet to achieve better acceptability as well as bioavailability, newer and more efficient tablet dosage forms are being developed. The main intention behind formulation of different types of tablets are to create a delivery system that is relatively simple and inexpensive to manufacture, provide the dosage form that is convenient from patient's perspective and utilize an approach that is unlikely to add complexity during regulatory approval process.

1.5.1. Different Types of Tablets

- Tablets ingested orally:
    1. Compressed tablet
    2. Multiple compressed tablet
    3. Repeat action tablet
    4. Delayed release tablet
    5. Sugar coated tablet
    6. Film coated tablet

7. Chewable tablet

- Tablets used in oral cavity:
  1. Buccal tablet
  2. Sublingual tablet
  3. Troches or lozenges
  4. Dental cone

- Tablets administered by other route:
  1. Implantation tablet
  2. Vaginal tablet

- Tablets used to prepare solution:
  1. Effervescent tablet
  2. Dispensing tablet
  3. Hypodermic tablet
  4. Tablet triturates

1.5.2. Advantages:

- Dose precision and least content variability.
- Lightest and most compact of all dosage forms.
- They lend themselves to some special release profile products, such as enteric or delayed-release products.
- They are better suited to large-scale production than other unit oral forms.
- Their cost is lowest of all dosage forms.

1.5.3. Disadvantages:

- Some drugs resist compression into dense compacts, owing to their amorphous nature or flocculent, low-density character.

- Drug with poor wetting, slow dissolution properties, intermediate to large dosages, optimum absorption high in the gastrointestinal tract may be difficult or impossible to formulate and manufacture as a tablet.

- Drugs with bitter taste, odor or sensitive to oxygen or moisture may require encapsulation or entrapment prior to compression.

1.6 . Compression Machine Tooling [13]

The size and shape of a tablet as well as certain identification makings are determined by the compression machine tooling each tooling set consist of a die and upper and lower punches. The most common tools employed are referred as BB tooling and are 5.25 inches in length, and have a nominal barrel diameter of 0.75 inches and 1-inch head diameter's tooling is identical to BB type except that the lower punch is only 39/16 inches longed tooling is popular for large tablets, utilizing a 1- inch barrel diameter, 1.25- inch head diameter, and 5.25- inch length. the dies that are used with the above punches are either a 0.945 – inch outside diameter(OD) die capable of making a 7/16 – inch round tablet or 9/16-inch capsule shaped tablet.

Several types of steel are normally used in manufacturing of compression tooling. This steel differs in toughness, to withstand the cyclic compacting forces (ductility), and in wear resistance. The selection of the best steel for a specific application must be best on experience and an accumulated history of the product being tabletted. One should also consider the shape of the punch tip, whether or not debossing is to be employed on the tooling , the expected compression forces involved, and whether the materials to be processed are abrasive or corrosive.

The size, shape and contour of a tablet are almost unlimited within the given limits of the specified die size. Tooling can be made with certain other information to aid in producing visible unique tablet product Company names and symbol, trade names, dosage strength, or National Drug Code (NDC) numbers can be cut or engraved into a punch face, or the punches may be scored to produced uniquely embossed or engraved tablets. When the tip of the upper punch is not round, it must not rotate, or it will strike the edge of the die hole as it descents

for compression .To prevent this, a slot is curt longitudinally into the barrel of the punch, and a key is inserted. This key protrudes a short distance so that it engages a similar slot cut into the upper punch guides on the tablet press. Lower punches do not need keys because their tips remain within the die bore, which control the axial movement of the punch. Because keyed punches cannot rotate, wear is distributed unevenly, and punch life is shortened.

When a press is set up with keyed punches the upper punches are inserted first to determine the placement of the dies. Once the dies are properly aligned and seated, they are locked in

place, and the lower punches are inserted. The more curvature that is built into a tablet contour, the more difficult is to compress, especially if the tablet tends to laminate or cap. The engraving or embossing on a tablet must be designed to be legible, must not add to compression problems, and must fit on the tablet surface. Because of its hard steel structure tablet tooling may appear to be indestructible. During normal use, however, the punches and die become worn, and the cyclic application of stress can cause the steel to fatigue and break. The punch tips are especially delicate and susceptible to damage if the tips make contact with each other, the dies or the press turret upon insertion or removal of the tools from the tablet machine. To avoid tooling damage, compressive loads or pressure at the pressure rolls must be translated into a circulation of pressure at the punch tips. As tablet punch diameter decreases, less force is required to produce the same pressure at the punch face, since the face represents a smaller fraction of a unit area (square inch). The formula for area of a circle is πr2 where r is the radius of the circle. Given a flat punch face, the area of 22a ¼ - inch diameter punch would thus be 3.14*(1/8)2 or 3.14*1/64 or approximately 1/20 square-inch. If a 1-ton load is being applied by the pressure roll, this area is translated as 2000 pounds on 1/20 square inch, or 40,000.

1.7. Coating of tablets:

The application of coating is usually based on one or more of the following :

- To mask the taste,odor,or colour of the drug.
- To provide physical and chemical protection to the drug.
- To control the release of the drug.

- To protect the drug from the gastric environment of the stomach with an acid resistant coating.

- To incorporate another drug or formula adjuvant in the coating to avoid chemical incompatibility or to provide sequential drug release.

- To provide pharmaceutical elegance by use of special colour.

1.7.1. Types of coating:

1. Sugar coating
2. Film coating
3. Enteric coating
4. Extended release coating

1.7.2. Layers of coating in the formulation:

1. **Tablet core**
2. **Seal coating** acts as a inert intermediate layer between the core and outer layer(which are not compatible with one another).
3. **Enteric coating** acts as an outer layer which is resistant to gastric juice.

1.8. Enteric coatings:[14]

Enteric coatings are those which remain intact in the stomach, but will dissolve and release the contents once it reaches the small intestine. Their prime intension is to delay the release of drugs which are inactivated by the stomach contents or may cause nausea or bleeding by irritation of gastric mucosa.

The coatings that are used now a day to produce enteric effects are primarily mixed acid functionality and acid ester functionality, synthetic, or modified natural polymers. The most extensively used polymers are Cellulose acetate, poly vinyl acetate, pydroxy propyl methyl cellulose, Methacrylic acid copolymers. All these polymers have the common feature of containing the di carboxylic, pthalic acid in partially Esterified form

These polymers, being acid esters are insoluble in gastic media that have the pH of about 4. And then leave the stomach, and enter into the duodenum (pH 4-6) and further along the small intestine , where the pH is increase to a range of (pH 7-8).

The primary mechanism by which these polymers lose their integrity, is their by admitting the releasing drug to the intestinal fluid. in this ionization of the residual carboxyl groups on the chain and subsequent hydration.

1.8.1. Important reasons for enteric coating are as follows :

* To protect acid-liable drugs from the gastric fluid
* To protect gastric distress or nausea due to irritation from drug
* To deliver drugs intended for local action in the intestines
* To provide a delayed release component to repeat actions
* Protect the drugs from harmful effect of the gastric contents; some of the drugs are prone to be hydrolyzed in acid media (E.g., omeprazole, pantaprazole)

1.8.2. Ideal enteric coating materials should have the following properties:

* Resistance to gastric fluids
* Ready susceptibility to or permeability to intestinal fluids
* Compatibility with most coating solution components and the drug substrates
* The film should not change on aging
* Formation of continuous film
* Non-toxicity
* Low cost
* Ease of application

1.8.3. Enteric Coating Materials:

Enteric coatings polymers are selectively insoluble substances. They won't dissolve in the acidic juices of the stomach, but they will when they reach the higher pH of the small intestine. Most enteric coatings won't dissolve in solutions with a pH lower than 5.5.

Commonly-used enteric coating polymers:

* Methacrylic acid copolymers
* Cellulose acetate (and its succinate and phthalate version)
* Polymethacrylic acid/acrylic acid copolymer
* Hydroxypropyl methyl cellulose phthalate(HPMCP)
* Polyvinyl acetate phthalate (PVAP)
* Hydroxyethyl ethyl cellulose phthalate
* Cellulose acetate tetra hydro phthalate

The earliest enteric coatings utilized formalized gelatin , this was unreliable because of the polymerization of gelatin could not be accurately controlled. Another was shellac, disadvantage was polymerization with time, resulting in poor dissolution of the coating.

The most extensively used polymers are CAP, PVAP. The most recently used polymers are HPMCP, Methacrylic acid copolymers.

- **Cellulose Acetate Phthalate (CAP) :**
  Effective enteric coating, it only dissolves above pH 6 and may delay drug release longer than desired. it is permeable to moisture and simulated gastric fluid in comparison with other enteric polymers and it is susceptible to hydrolytic breakdown on storage.

- **Poly Vinyl Acetate Phthalate (PVAP) :**

  Less permeable to moisture and simulated gastric juice, it is more stable to hydrolysis on storage. Enteric dosage forms coated with PVAP disintegrates at pH 5

- **Hydroxy Propyl Methyl Cellulose Pthalate (HPMCP):**
  It is available in two grades HP50 and HP55.

HP55 solutions are more viscous than HP50.

HP50 disintegrates at pH5 and HP55 disintegrates at pH5.5.

It has stability similar to that of PVAP and dissolves in the same pH range. The advantage is that it does not require Plasticizer.

- **Methacrylic acid copolymers :**[15]

Two grades are available A B and C which differs in the ratio of free carboxyl to ester groups therefore:

Type A - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio 1: 2: 0.2 and soluble in intestinal fluid from pH 6.

Type B - Poly (ethyl acrylate, methyl methacrylate, trimethylammonioethyl methacrylate chloride) has a ratio of 1:2:0.1 and soluble in intestinal fluid from pH 7.

Type C - Poly (methacrylic acid, ethyl acrylate) 1:1 and soluble in intestinal fluid from pH 5.5.

1.9. Disease Profile: [16]

Acid Related Disease: Thirty years ago, disorders associated with in appropriate levels of gastric acid were a major problem for which treatment option were is limited approaches to the control of gastric acid. there are number of condition that may intravenous acid suppression including gstric ulcer Gastro-esophageal reflux disease, Zollinger Ellison syndrome, Barett esophagus.

1.9.1. Physiology of Nocturnal secretion of Gastric acid :

The secretion of acid occurs at a continous basal level and increase after meals

1. Basal acid release is stimulated by food. when meal containing protein is Consumed, amino acid is released. which stimulates the release of gastrin by g –cells in the Lumen of antrum.
2. And which in turn stimulates the Paracrine Entero-chromaffin like cells called histaminocytes located in the oxyntic glands of the stomach to release histamine.

EC cells is in close proximity to the parietal cells by which it binds to specific receptors.

3. In response to various stimuli (signals) the parietal cell in the Fundus of Stomach Secrete HCL (Gastric acid).

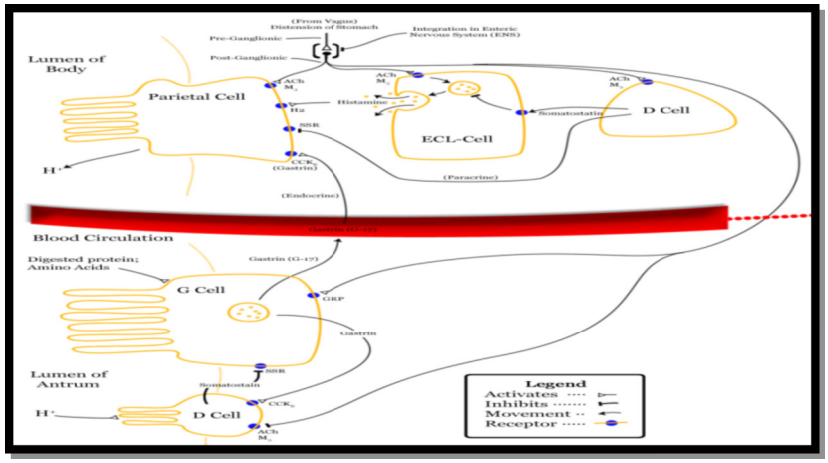

Fig .3 - Schemmatic representation of gastric acid secretion from the parietal cell present in the lining of the stomach

1.9.2. Concept Of Parietal Cell Mass

There are Normally about 10^9 parietal cell in the stomach (parietal cell mass) under maximal condition of stimulation. They secrete 20-25meq at low stimulation.the output is 2-3meq/hr. hence at low volume secretion rates the pH is higher, at higher rates the pH is lower. PCM varies with gender,age, body weight pathologies. Parietal cells secrete a fluid of constant composition (HCL) independent of rate, type or magnitude of stimulus, the volume of secretion is dependent on the number of parietal cells secreting

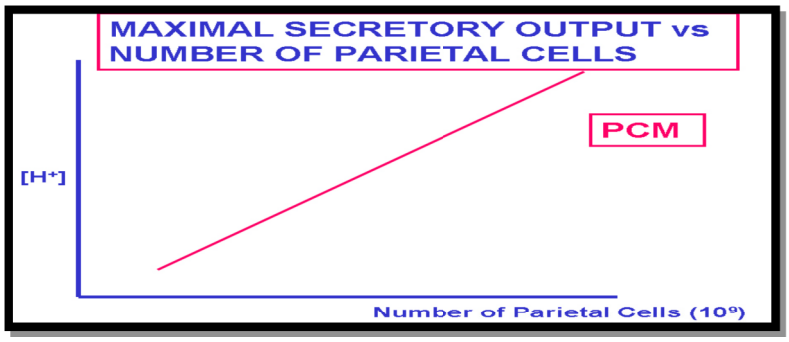

Fig .4 - Graph showing the maximum secretion of acid with increasing number of parietal cells

1.9.3. Peptic ulcer : [17]

Peptic ulcer disease refers to pain ful sores or ulcers in the lining of the stomach or the first part of the small intestine, the duodenum. Normally a thick layer of mucus protects the stomach lining from the effects of its digestive juices, but many things reduce this protective layer , allowing for ulcer to occur .

Classification

- **Type** 1**:** Ulcer along the body of the stomach , most often along the lesser at incisura angularis along the locus minoris resistentiae
- **Type2:** Ulcer in the body in the combination with duodenal ulcers. with acid secretion
- **Type 3:** In the pyloric channel with 3 cm of pylorus. associated with acid over secretion.
- **Type 4**: Proximal gastro esophageal ulcer .
- **Type 5:** can occur through out the stomach. Associated with chronic NSAID (such as aspirin).

Causes

- The major cause for peptic ulcer is due to helicobacter pylori, that colonizes the antral mucosa .
- The immune system is unable to clear the infection, despite the appearance of antibodies. Thus, the bacterium can cause a chronic active gastritis (type B) resulting in a defect in the regulation of gastrin production by the part of the stomach, and gastrin secretion can either be increased or decreased resulting in achlorhydria.
- Gastrin stimulates the the production of gastric acid by the parietal cells and the H pylori colonization responses to the increase gastrin, the increase in acid can contribute to the erosion of the mucosa and there fore ulcer formation occurs.

Symptoms

- Abdominal pain
- Bloating
- Hematemesis (vomiting of blood)
- Melana (foul smelling feces due to oxidized iron from haemoglobin).

Diagnosis

- Stomach pain is mainly the first signal of the peptic ulcer.
- Conducting endoscopy test or barium contrast x rays.
- Esophagogastroduodenoscopy (EGD), carried out for the patients with peptic ulcer suspected .

Treatment

- Younger patients with ulcer llike symptoms are often treated with antacids, H2 antagonists .
- H.pylori infection are treated with combination of two antibiotics clarithromycin, amoxicillin, metronidazole and one proton pump inhibitors
- Perforated peptic ulcer requires a surgical repair of the performation .
- Sucralfate has also been a successful for the treatment of peptic ulcer.

Table No: 1 – pH conditions of GIT (to match optimized value in biological fluid)

Region	pH (Fasted)	Resident time
Mouth	5.8-7.4	< 1 min
Esophagus	1-5	0.25-3 hrs
Stomach	1.5-3.5	1-5 hrs
Small intestine	5.5-7.8	3-4 hrs
Duodenum	2.4-6.8	> 5 hrs
Jejnum	6.0-7.0	1-2 hrs
Ileum	6.5	2-3 hr
Large intestines	6.2-7	< 8 - 30 hrs
Colon	8	15-48 hrs

1.9.3. Gastro Esophageal Reflux Disease[18]

Gastro esophageal reflux disease(GERD) is a condition in which the stomach contents (food or liquid) leaks backward from the stomach into the esophagus (the tube from the mouth to the stomach) this action can irritate the esophagus , causing heart burn .

Causes

- When you eat, food passes from the throat to the stomach through the esophagus once food is in the stomach , a ring of muscle fibers prevent food from moving. back ward into the esophagus . these muscle fibers are called the lower esophageal sphinter (LES).
- If the sphincter muscle does not close well, food , liquid , form stomach can leak back into the esophagus . this is called gastro esophagus reflux disease.

Risk Factors

- The risk factors for reflux include hiatal hernia (a condition in which a part of the stomach moves above the diaphragm, which is the muscle seperates the chest and abdominal cavities), pregnancy & Scleroderma
- Obesity ,cigrattes & possibly alcohol increase the chance of the GERD .

Symptoms

- Heart burn in the stomach (under the breast bone).
- Felling that food may be left trapped behind the breast bone.

Prevention

- To prevent heart burn, avoid following things such as smoke, alcohol, caffeine spicy or fatty foods tomatoes , carbonated beverages.
- Over use of NSAIDs should be avoided.

Diagnosis

If symptoms are severe one or more tests may help to diagnosis reflux.

- Continous esophageal reflux monitoring .
- Barium swallow test.
- Esophago gastro duodeno scopy is often used to identify the cause and examine the esophagus for damage

Treatment

- Ant acid can be used but the common side effects of ant acid includes diarrhea or constipation.
- Proton pump inhibitors :are the most potent acid inhibitors , omeprazole, pantoprazole rabeprazole ,esomeprazole.
- H2 antagonist: famotidine,cimetidine, ranitidine.
- Anti-h.pylori drugs :clarithromycin,amoxicillin.

1.9.4. Zollinger –Ellison Syndrome

Zollinger Ellison syndrome is a rare disorder, characterized byone or more tumours in the pancreas, duodenumor both. The tumour cause the stomach make to much acid, leading to peptic ulcer in the duodenum. The tumours are some times cancerous & spread to the other areas of the body .

Causes

Zollinger Ellison syndrome is caused by tumours called gastrinomas, which release the hormone gasrin. Normally , cells in the stomach produce and control gastrin so only the right amount is released . gasrin travels through the blood streams to signal other cells in the stomach to release gastric acid in the stomach and duodenum.The excess acid eventually causes sores called peptic ulcers. To form in the linig of the duodenum. Majority of gastrinomas . which appper sporadically. about 25% of gastrinomas cases are caused by by an inherited genetic disorder. Multiple endocrine neoplasia type 1(MEN 1).

Symptoms

- Burning abdominal pain
- Nausea and vomiting
- Weight loss
- Diarrhea

Diagnosis

- Measuring stomach acid and the amount of gastrin circulating in the blood.
- Conduting imaging tests to 100k for gastrinomas.
- Somatostatin receptor scintigraphy is used to find gastrinomas in the duodenum pancreas &other parts of the body SRS is used as a radio active compound called a radio tracer that when injected into the blood stream, selectively tumour cells.

- The labeled cells light up when scannrd with a device called gamma camer
- Angiography some timeused to find tumours in the pancreas.
- Computerized tomography scan takes hundred of cross sectional x- ray images in a few seconds a computer assembles the images to produce three dimensional views of internal organs.

Treatment

Proton pump inhibitors effectively reduces gastric acid secretion in the stomach and includes,

- Pantoprazole(protonix)
- Omeprazole(prilosec)
- Eesomeprazole(nexium)

Reducing stomach acid allows peptic ulcer to heal relives ZES symtoms,surgical removal of gastrinomas is the only cure for ZES. some gastrinomas behave like cancer and spread to the other Parts of the body , especially the liver and bones .

- **Classification of Acid suppressive Agents** [19]

  - **H-2 Receptor antagonist**– Cimetidine, Ranitidine, Famotidine**.**
  - **Protonpump inhibitors**– Omeprazole,Pantoprazole, Rabeprazole, Lansoprazole**.**
  - **Anticholinergics** – Pirenzepine, Oxyphenonium, Prophantheline**.**
  - **Prostaglandin analogue**– Misoprostol**.**

Table No: 2 - Mechanism of Action of Acid suppressive Agents [19]

Acid suppressive agents	Mechanism of action
Prostaglandin analogue	It inhibits the gastric secretion by opposing Camp generation in parietal cells and gastrin release from antral cells.
H-2 receptor antagonist	It performs by blocking the action of histamine on parietal cell in the stomach by this decreasing the production of gastric acid from the cell.
Proton pump inhibitor	PPIS acts by irreversibly blocking the enzyme system of the parietal cell by this it terminate the final stage in the gastric secretion.

1.10. Discovery

The Most potent inhibitor of gastric acid secretion is proton pump inhibitors, has revolutionalized the treatment of Acid related disorders, such as GERD, ZES, Idiopathic hyper secretion, stress related or drug induced erosive gastritis.

Omeprazole was the first drug in the class introduced in 1989, since then four other PPI´s has been introduced they are Lansoprazole (1995),Rabeprazole(1999),Pantoprazole (2000), And Esomeprazole(2001).

1.10.1. Mechanism of action of Proton pump inhibitors

The key action of the PPI´s is to decrease gasric acid and secretory volume. It acts by blocking the enzyme system responsible for active transport of acid into the gastrointestinal lumen, namely the hydrogen /potassium- adenosine triphosphate known as (Acid pump or Proton pump).an enzyme present in the gastric parietal cells this effect on the final step of the gastric acid formation there by reducing gastric acid output both during basal condition and simulated acid secretion, irrespective of stimulus.

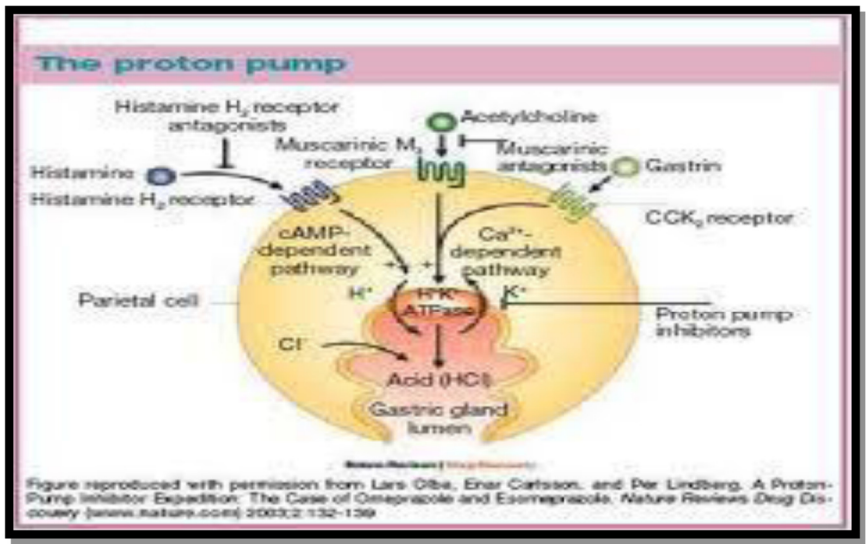

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Fig .5 - Mechanism of Action of PPI´s

1.10.2. Biopharmaceutical classification system [20]

According to the Biopharmaceutical classification system (BCS), drug substances are classified as follows:

- Class I - High permeability, High solubility.
- Class II - High permeability, Low solubility.
- Class III - Low permeability, High solubility.
- Class IV - Low permeability, Low solubility.

Class I drugs are likely to exhibit few bio availability problems.

Class II drugs are prone to dissolution rate- limited absorption.

Class III drugs are likely to exhibit permeation rate-limited absorption.

Class IV drugs may be present serious obstacles to oral bio availability, and some may be best formulated in a solubilized form such as a liquid filled or semi solid-filled capsule.

Pantoprazole belongs to class III drugs of the BCS, characterized by high solubility and low permeability.

Table No: 3 –Pharmacokinetics of Delayed Release Proton-Pump Inhibitors

S.No	Parameters	Pantoprazole	Omeprazole	Esomeprazole
1	Absolute Bioavailabilty (%)	77	40	64-90
2	Time to peak plasma Level (h)	2-4	0.5-3.5	1.5
3	Plasma half- life (h)	1.0	0.5-1.0	0-1.5
4	Plasma protein binding (%)	97	95	97
5	Hepatic metabolism	Yes	Yes	Yes

2. AIM & OBJECTIVES

The aim of the present study was to develop a pharmaceutically equivalent, stable, cost effective and quality improved formulation of Pantoprazole Sodium enteric coated tablets.

To achieve these goal various prototype formulation trails were taken and evaluated with various quality control such as dissolution, assay. the formula was finalized by comparing the in vitro dissolution profile with that of the marketed tablet.

Objectives:

- To formulate and evaluate delayed release tablets of Pantoprazole sodium.
- To determine the best fit dissolution profile for the formulated dosage form.
- To study the release profile of the dosage form and to compare their drug release profile with the innovator product.
- To study the stability of formulated dosage form and compare with the specifications.

3. PLAN OF WORK

1. Literature survey.
2. Preformulation studies
- Evaluation of API.
- Drug-Excipients Compatibility Studies.

3. Selection of excipients based on Drug excipients compatibility data.
4. Preparation of granules of Pantoprazole sodium by Wet granulation method.

5. Evaluation of pre compression studies for the final blend of all formulations.
- Bulkdensity, Tap density.
- Compressibility index, Hausner´s ratio.
- Angle of Repose, Moisture Content.

6. To perform Coating of Compressed tablet.
- Seal coating.
- Enteric coating.

7. Evaluation of post-compression parameters

- Hardness, Thickness,Weight variation .
- Dissolution study, Disintegration test.
- Drug content (Assay).

8. Selection of bioequivalent formulation by comparing *invitro* dissolution profile of formulated batches with that of innovator product – Determination of **f1** ,$\mathbf{f_2}$ factor.

9. To perform Stability studies for final optimized formulation.

4. LITERATURE REVIEW

- **Kishore Babu , N. Bhanu Teja, B. Ramakrishna et al.,**[21] Designed and developed gastro resistant drug delivery system for pantoprazole. Pantoprazole is an acid labile drug, whichcan be degraded in the stomach. Therefore, the drug should be targeted to intestine; tobypass the stomach the gastro resistant double walled microspheric drug delivery systemwas adopted. The formulations were developed consisting of double wall. The primary wallcomposed of muco adhesive polymer HPMC and a release controlling polymer sod.Alginate. The second wall coating the primary microspheres was composed of eudragit RS100. Eudragit RS 100 provides sustained drug release upto 14hrs with the influence of pH 7.4buffer. The effect of polymer concentration on the particle size, shape drug entrapmentefficiency, muco adhesive property, and release study of core microspheres were evaluated.

- **Santosh Kumar Jindal et al.,**[22] Formulated and evaluated oral drug delivery device for insulin and to protect the sensitive drug from digestive enzymes and proteolytic degradation in stomach and upper part of gastro intestinal tract (GIT). So, for this purpose insulin enteric microspheres (EMS) were prepared using Hydroxy propyl methyl cellulose acetate succinate as enteric polymer,. In-vitro drug release studies determined that almost no drug was released in HCl (pH 1.2) for 2 hours and then maximum amount of drug was released within 70 minutes in Phosphate buffer (pH 7.4). In-vivo studies on male wistar rats confirmed a remarkable decrease in blood glucose level after 2 hours of administration of insulin EMS.

- **Rajesh z. mujoriya et al.,**[23] Formulated and evaluated pantoprazole sodium enteric coated pellets.Before going to develop the formulation a detail product literature review was carried out to know about the MUPS and type of dosage form available in market. The present study was focused to formulate delayed release capsule by MUPS Technique.Average pellets size was determined by sieve analysis and found to be (ASTM sieve no. 12-16). Sieve analysis was the essential step before coating. Because uniform sized pellets undergo effective coating. The result indicates a effective enteric coating and delay the drug release, with 32% acryl ezee solution, is

possible. The formulation developed can further be worked on. For identifying a best formulation for delayed release pellets of pantoprazole sodium.

- **Juliana Siqueira Chaves et al.,**[24] Formulate and evaluated the spray-dried extract of feverfew and further designing and standardizing enteric coated tablets. In this work, the spray-dried extract of feverfew was evaluated for its parthenolide, santin and total flavonoid content, parthenolide solubility, particle size, tap density, hygroscopicity, angle of repose and moisture content. Tablets containing the spray-dried extract were tested for their average weight, friability, hardness, and disintegration time. The total flavonoid and parthenolide contents in the spray-dried extract were 1.31 % and 0.76% w/w, respectively. The spray-dried extract presented consistent pharmacotechnical properties and allowed its tableting by direct compression. Tablet properties were in accordance with the proposed specifications. The procedures described herein can be used to prepare and evaluate pre-formulations of feverfew with adequate properties for the development of a high-quality phytomedicine.
- **Ajit Patil , John Disouza et al.,**[25] Formulated and evaluated enteric coated tablets for azithromycin dihydrate to reduce th Gastrointestinal tract side effects.Three formulations of Core tablets were prepared and one whoshows rapid disintegration (below three minutes) was selected for enteric coating . Enteric coat was employed by usingdifferent polymers such as HPMC-55, Eudragit, Ethyl cellulose in different ratios Combination of HPMC-55 and ethylcellulose (10:1.5) exibited better dissolution ,disintegration, hardness and friability properties .This study concluded thatenteric coated tablets of azithromycin dihydrate can be prepared by using combination of polymers studied and we can reduce the GI tract side effects.

- **Sanjay R.et al.,**[26] Developed and evaluated the enteric coated tablets of Rabeprazole sodium by using Methacrylic acidcopolymer (Colorcoat EC4S) and to optimize coating process parameters which implicate more significant effects on tablet coating process. The different batches of uncoated tablets were prepared by both wet granulation and direct compression method. Batch B6 of uncoated tablets preparedby direct compression method shown good results of evaluation parameters compared to other batches. Results of the preliminary trials indicated that process parameters individually affected the quality of coated tablets. At this point of time it was seen that spray rate, inlet air temperature and hence to study the combined effect of this factors on the coating process, 33 full factorial design was applied.

Comparative study of dissolution profile of final batch with market preparations was conducted and it was concluded that final formulation F shown good similarity with market products. The results of the accelerated stability of final formulation F for 3months revealed that storage conditions were not found any significant changes in final formulation F. The photoinstability of the rabeprazolesodium showed by the photostabilty studies indicated that special care to avoid exposure of the drug to the light effects must be taken during themanufacture and storage of the pharmaceutical preparations.

- **Banerjee T, Muruganantham et al.,** [27] Designed and developed novel sustained-release (SR) Muco adhesive tablet formulations of naproxen sodium a non-steroidal anti inflammatory drug. Pantoprazole Sodium is added to the naproxen to overcome the side effect such as ulcer and bleeding. Sustained release tablets Naproxen formulated by using polymers such as sodium alginate, gelatin and carbopol 934P. A combination of hydrophilic polymers was used in the ratio of 1:1:1 to1:1:5 along withusual tablet additives like lactose and MCC. The compressed Mucoadhesive tablets were evaluated for various parameters like hardness, friability, weight variation, drug content uniformity which shows the drug content was uniform in all the formulations of thetablets prepared. IR studies indicated that the drug is compatible withthe polymers and stability studies also performed were no appreciable difference was observed. The in-vitro release of Naproxen and Pantoprazole were studied by using the buffer solutionof pH 1.2. The in-vitro release of drug showed that tablets (batch F9)of combined S: G: C is 1:1:5 containing tablets (96%) at the end of10thhour and was found to release the drug.

- **Damodharan , Manimaran V et al.,**[28] Developed and evaluated small intestine targeting tablets of doxycycline hydrochloride by wet granulation method and enteric coating of tablets (conventional standard coating technique).This drug is universal antibiotic and can be targeted to the specific site of absorption by enteric coating using pH dependant polymers.Polymers like Eudragit and HPMC Phthalate are selected where dissolution is above pH 6 and pH 6.4 respectively.Preformulation studies like angle of repose, bulk density, tapped density, porosity, Carr's index, Hausner's ratio wereperformed. Six batches (F1 to F6) were formulated and evaluated for hardness, friability, weight variation, drugcontent, disintegration and in-vitro

dissolution. Among the six batches, batch F4 was showing 94% drug release and was considered to be best formulation.

- **Anroop B Nair, Rachna Kumria1et al.,**[29] Formulated and evaluated enteric coated tablets for Esomeprazole magnesium trihydrate. Different core tablets were preparedand formulation (F-1) was selected for further enteric coating, based on the disintegrationtime. Seal coating was applied to achieve 3% weight gain using opadry®. Entericcoating was carried out using different polymers like Eudragit L-30 D-55, hydroxy propylmethylcellulose phthalate, cellulose acetate phthalate and Acryl-EZE® to achieve 5% weight gain. Disintegration studies showed that the formulations failed in 0.1 NHCl 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.Stability studies indicate that the prepared formulations were stable for a period ofthree months. This study concluded that enteric coated tablets of esomeprazole canbe prepared using any of the enteric coating polymer studied using a minimal weight gain of 8%.

- **Hemanta Kumar Sharma, Siba Prasad et al.,**[30] Designed and formulated the Pantoprazole loaded microbeads by ionotropic gelation technique using sodium alginate and natural Mucoadhesive substance from the fruit of Dillenia indica followed by a coating with Eudragit L100-55. The microspheres have been characterized in terms of theirmorphology, particle size, encapsulation efficiency, swelling ratio, mucoadhesivity and ability of stabilizingPantoprazole in acidic media. Different formulation variables like polymer-polymer ratio, drug-polymer ratio and coating concentration were considered. Almost spherical microbeads were obtained with sufficient swelling,Mucoadhesive property and acid resistance. Dissolution study was followed at phosphate buffer (pH 7.4) for 8 hr.

- **Rabia Bushra1,Muhammad Harris Shoaib et al.,**[31] Developed and investigated the 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 super disintegrant. Formulating this enteric coated tablets could increase patient compliance by decreasing adverse drug reactions (ADR_S) associated with Ibuprofen therapy.

- **Chanchal Kumar Mishra, Anil Goyal,et al**.,[32] Investigated the Pantoprazole and its enteric coating polymer concentration for stable coating in acid media which is an orally administered benzimidazole anti-ulcer drugs. To achieve this goal, 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 unstability 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 unfavourable 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. Delayed release products are typically enteric coated or colon targeted system. Formulation can be evaluated by Acid resistant test and *In vitro* drug release test. Delayed release dosage form has an enteric polymeric coating with characteristic pH-dependant solubility (or stability) to prevent release of the active ingredient in the stomach at low acidic pH (i.e. 1-3). Once the delayed release product leaves the stomach, the enteric coating dissolves subsequent *in-vivo* drugs release and then generally follow the same course as for an immediate release product. Applied different parameters of enteric coated tablets evaluation and IR spectral analysis of

Pantoprazole that justified the enteric coating polymer concentration for stable coating in acid media in stomach.

- **Rupesh S. Kamble**, **Archana et al.,**[33] formulated and evaluated Enteric Coated Dosage Form using Ketorolac Tromethamine. Reduction of side effects while prolonging its action by using controlledrelease of oral dosage forms is highly desirable. In the present study direct compression method is used for the preparation of fabricated batches and EudragitL100 is used as coating polymer for enteric coating. In vitro release profiles of batches F1-F4 shows that KetorolacTro methamine 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 f 85.21%, 95.52%, 93.50%, 97.24% respectively in 12 hours. In vitro release profile ofbatches F9-F12 shows that Ketorolac Tromethamine in ratio 1:3 with Guar gum, Xanthan Gum, Ethylcellulose and Sodium alginate gives release of 89.50%, 98.25%, 95.22%, 100.27% respectively in 12hours. 2 andthen showed higher increase in phosphate buffer of pH 6.0 up to 12 hours. All these batches follow near zero order kinetic. This indicates that the Guar Gum, Xanthan Gum and Ethyl cellulose and Sodium alginate at minimum concentration is not only able to sustain but also control the drug release.
- **Rajeshwar Arya, Vijay juyal et al**.,[34] Investigated and developed a gastro resistant drug delivery system for pantoprazole. Pantoprazole is an acid labile drug, which can be degraded in the stomach. 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. Theprimary wall composed of mucoadhesive polymer sod. CMC and a release controlling polymer sod. alginate. The second wall coating the primary microspheres was composed of eudragit S-100.The effect of polymer concentration on the particle size, shape drug entrapment efficiency,mucoadhesive property, release study of core microspheres were evaluated.

- **Rahman A et al.,**[35] Developed and evaluated multiparticulate formulation of sodium para amino salicylate for oral administration was developed by extrusion spheronization technique. micro crystalline cellulose was used as filler in

concentration of 14.4%W/W. pellets were coted with eudrajit L30 D55 using fluid bed processor. Different weight gains of acrylic polymer were applied onto the pellets and evaluated for invitro dissolution behavior in 0.1 N HCL for 2 hours and then media was changed to phosphate buffer p^H 6.8. a 60%w/w coating level of Eudrajit L30 D55 has produced the most acceptable results against the gastric attack. 3% seal coat of HPMC E5 was applied in order to protect the drug from migration into the eudrajit coat and flim coat was applied in order to prevent aggregation of pellets in the dissolution media.morphological characteristic of developed pellets were also investigated by scanning electron microscopy and found to be smooth and spherical. Developed system was found to be suitable for the delivery of sod PAS into intestinal region.

- **Subramaniam Kannan, Rangasamy Manivannan et al.,**[36] Formulated and evaluated the enteric coated aspirin tablets.The delayed release tablet is intended to release the drug after some delay or after tablet pass GI tract. The enteric coating is common example of this tablet. All enteric coated tablets are delayed release tablet but all delayed release tablet are not enteric coated tablets.1 Aspirin delayed release tablet is used to increase bioavailability and to reduce risk of hospitalization for heart failure, coronary thrombosis deliver drug at a near constant rate for 24hr. 2,10 Keeping these factors in view it is aimed to formulate, evaluate and stabilize Aspirin (75mg) DR tablet to provide a controlled and predictable release of Aspirin and which is used in the treatment of Coronary Thrombosis (heart disease)13, 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. Aspirin anti-platelet compounds which suppress or inhibit the cyclooxygenase enzyme which is responsible for the formation of thromboxane A2, thus block the formation of thromboxane A2. Thromboxane A2 is a activator of platelet aggregation.3,12 Hence our present study was performed on these formulations as aspirin delayed release tablet.

- **US Patent2003/5,997,903**: [37] It discloses an orally administable medicament in tablet/pellet form that is resistant to gastric juice which consist of a core of active compound admixed with binder , a filler , basic physiologically tolerated in organic compound , an inert water soluble intermediate layer surrounding the core , an outer layer which is resistant to gastric juice.

- **Prathima srinivas et al.,**[38] Formulated and evaluated duloxetine hydrochloride delayed release enteric coated pellets in capsules. Since Duloxetine hydrochloride degrades in the acidic environment, it is important to by pass the acidic pH of the stomach. Protection of drug from acidic environment is done by coating the drug with enteric polymers by using suspension layering technique in Fluidized bedprocessor (FBP) with different enteric polymers like PVAP (Poly vinyl Acetate phthalate),Kollicoat MAE 30 DP, Eudragit L30 D55 (Methacrylic acid copolymer) and HPMCP (Hydroxy propyl methyl cellulose phthalate). Eudragit L30 D55 is a good enteric material. Based onthe vendor data and details, drug release shows after pH6.5 buffer, where as marketed preparation release starts at pH 5.5 buffer. So Eudragit was not taken for further trails. The prepared pellets were studied for their Invitro release studies and were analyzed by using HPLC technique. The released kinetics was analyzed using the zero-order model, first-order model and Higuchi's square root equation. FT-IR (Infrared spectroscopy) and DSC(Differential Scanning Calorimetry) studies were performed to know the compatibility of the drug with various excipients and SEM (Scanning Electron Microscopy) analysis performed to know the particle size and morphology of the pellet. The results depicted that HPMCP gave a good dissolution profile and process suitability compared to Eudragit L30 D55,Kollicoat MAE 30DP and PVAP and hence optimized based on the similarity factor (f2value).

- **Raju, Padmavathy et al.,**[39] Investigated and developed enteric coated tablets of prednisolone and to reduce the side effects of anti inflammatory drugs in G.I.T. by developing conventional tablets of prednisolone by wet granulation technique and the prepared prednisolone based tablets were coated with different ratios of pectin and ethyl cellulose as enteric coating material by spraying organic system. The enteric coated tablets of prednisolone were subjected to an *in vitro* drug release study in the presence and absence of pectinolytic enzyme using simulated colonic fluid of pH 6.0

as the dissolution medium.. Colon drug delivery is advantageous in the treatment of colonic disease, where oral deliveries of drugs are unstable or susceptible to enzymatic degradation in upper GI tract. In this study, coated tablets which were resistant to gastric and small intestinal pH conditions but dissolving in colonic pH conditions were fabricated., D batch results matched with our theoretical profile.

- **Putta rajesh kumar et al**., [40] Designed and evaluated the directly compressible esomeprazole magnesium trihydrate enteric coated tablets were prepared to deliver drug in upper git, different tablets were prepared with super disintegrants like Ac-Di-Sol, crospovidone ,sodium starch glycolate and diluents like pharmatose DCL1, mannogem EZ, tablets were enteric coated using Acryl-EZE. The tablets were evaluated for hardness,disintegration time and invitro drug release. The powder bed showed good rheological properties and enteric coated tablets showed acid uptake value <5 indicates significant protection of of acid labile drug. The compressional parameters were with in the limits,the drug content in all formulation was found to be uniform and consistent.invitro dissolution studies indicated there is no drug loss during gastric phase.the tablets wth pharmatose which could be due to swelling of the super disintegrant. Stability studies indicated that the prepared formulation were stable for a perid of four months of all formulations showed comparable dissolution profiles with similarity factor more than fifty $p< 0.05$. orom the above findings it can conclude that an esomeprazole magnesium trihydrate enteric coated could developed to deliver the drug into peoximal small intestine.

- **De macknkeey et al.,**[41] Studied the Plasma and urine concentrations of 5-ASA and its N-acetyl metabolite 5-AcASA were measured over 48 h in 12 young healthy male subjects, who received three doses of threet imes enteric coated 500 mg 5-ASAtablets at 7 h interval, on two occasions 14 days a part.on one occasion the doses were given after standard meals; on the other occasion, they were given 1 h before meals. Administration of the tablets after meals delayed systemic drug absorption but did not affect the extent of absorption. There was a sharp rise in the plasma concentrations of 5-ASA and 5-AcASA in the early morning of the 1st dose

  Independent of when the tablets were taken with respect to the meals.. Thus, diurnal effects may be more important than prandial effects in the evaluation of the kinetics of 5-ASA and its metabolites after per oral administration of enteric coated tablets.

- **Sumit Chakraborty, Sibaji Sarkar et al.,**[42] Formulated and evaluated the pantoprazole sodium enteric coated tablets .This compound inhibits gastric acid formation and there by it is very efficient for the treatment of gastric and duodenum ulcers. 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, , light and especially to substances containing an acidic group. Pantoprazole which is an acid labile drug it degrade on the stomach pH , can be coatedwith a substance that will only dissolve in the small intestine. For 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.

5. MATERIALS AND INSTRUMENTS

5.1. List of Materials used:

Table No - 4

S.No	Name of Ingredients	Category	Manufacturer/Suppliers
	Tablet core		
1	Pantoprazole sodium	Drug	Vasudha pharma ltd, india
2	Mannitol	Filler	Roquette-france
3	Cros povidone	Dis integrant	Blagden Specialty Chemicals
4	Sodium carbonate	Alkalizing agent	S D fine chemical
5	Povidone	Binder	Blagden Speciality Chemicals
6	Magnesium stearate	Lubricant	Kant Healthcare
7	MCC (avicel p^H112)	Filler	Fmc biopolymer –USA
8	Aerosoil	Glident	Wacker Chemical Corp
9	Purified water	Vechicle	Fourrts india ,chennai
	Seal coating		
10	HPMC 15 cps	Film former	Dow chemicals
11	Propylene glycol	Plasticizer	Fisher Scientific UK Ltd
12	Titanium dioxide	Opaquant	Kronos ltd
13	Purified water	Vechicle	Fourrts india ,Chennai
	Enteric coating		
14	Eudrajit-L30 D-55	Enteric coating flim former	Degussa international
15	Diethyl phthalate	Plasticizer	Vopak USA Inc
16	Titanium dioxide	Opaquant	Kronos ltd
17	Purified talc	Anti tacking agent	Vijaya minerals
18	Triethyl citrate	Plasticizer	Morflex
19	Ferric oxide	Colouring agent	Colorcon asia limited
20	Purified water	Vechicle	Fourrts india, Chennai

5.2. List of Equipments/Instruments:

Table No- 5

S.No.	Name of the Equipment	Manufacturer
1.	8 station compression machine	Accura, Ahmedabad
2.	Electromagnetic sieve shaker	EMS 8.
3.	Friability test apparatus (ET-2)	Electrolab, India.
4.	Bulk density apparatus	Campbell electronics, Thermonick.
5.	Fluid bed processor	Paam Glatt.
6.	Hardness tester	Monsanto.
7.	Disintegration test apparatus (ED-2L)	Electrolab, India.
8.	Dissolution apparatus (Disso 2000)	Lab India.
9.	UV-Visible spectrophotometer (UV-1601)	Schimadzu-corporation, Japan.
10.	pH meter (Digital 7007)	Lab india.
11.	IR Moisture balance	OHAVS moisture balance
12.	Electronic weighing balance (AR 2140)	Adventurer Mettler Toleda.
13.	Digital Vernier Caliper	Mitutoyo Corp., Japan.
14.	FT-IR spectrophotometer (FTIR 8300)	Perkin elmer,
15.	Hot air oven	Pathak electrical works.
16.	Stability chamber	Thermolab.
17.	HPLC with PDA/Binary system	Schimadzu Corp., Japan.

6. DRUG AND EXCIPIENTS PROFILE

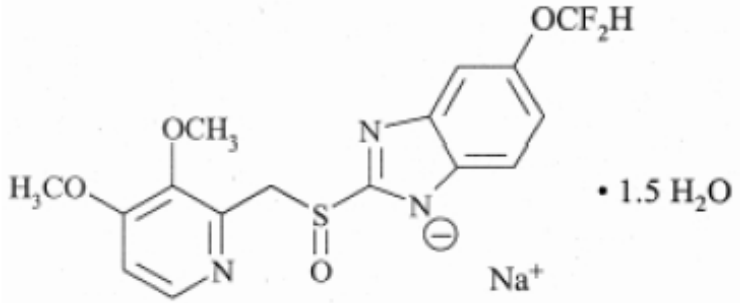
6.1. Drug profile: [43,44,45,46,47]

Drug name : **Pantoprazole sodium sesquihydrate**

Molecular formula : $C_{16}\ H_{14}\ F_2\ N_3\ Na\ O_4\ S_X\ 1.5\ H_2O$

Molecular weight : 432.4 g/ml

Structural formula :



Chemical Name :

Sodium 5-(difluoromethoxy)-2-(3,4-dimethoxy-2-pyridinyl)methyl)sulfinyl]-1H-Benimidazole Sesquihydrate.

Description : A white to off-white crystalline powder, and is racemic.

Dosage :

- Gastric ulcer: 40 mg once daily for 8 weeks.
- Gastro esophageal reflux disease:10, 20, or 40mg once daily for 8 weeks.
- Zolinger –Ellison Syndrome: 40 mg twice daily, may require dosage upto 240 mg daily for more than 2 years.

Half Life : 1 hour, because of binding extend to 24 hours approximately.

Solubility : Freely soluble in water; slightly soluble in chloroform and practically in soluble in n-hexane.

Wave length **:** 288 nm (pH 6.8 phosphate buffer); 305 nm (HCL)

Standard **:** Assay : Pantoprazole sodium delayed release tablets contain an amount of pantoprazole equivalent to not less than 90% and not more than 110 % of the labelled amount of pantoprazole.

Dissolution : Not less than 75% of labeled amount of pantoprazole in 45mins.

BCS classification **:** Class III (Solubility – High; Permeability – Low)

Therapeutic Category : Proton pump inhibitor.

Route Of Administration : Oral, I.V

Mechanism of Action:

Pantoprazole is a substituted benzimidazole compound which inhibits the secretion of gastric acid in the stomach by specific action on the proton pump in the parietal cells. Pantoprazole is converted to its active form in the acidic channel of the parietal cells where it binds covalently with Cysteine 813 in the luminal loop between transmembrane domains 5 and 6 on the alpha sub unit of the adenosine triphosphatase enzyme at the parietal cell this effect leads to inhibition of both basal and stimulated gastric acid secretion,irrespective of the stimulus. the because of drug irreversible binding to the H+K+ATPase results in a duration of Anti Secretory effect that persists longer than 24 hours for all the doses tested.

Advantage of Pantoprazole over other Proton pump inhibitors:

- Good solubility and very high solution stability allowed it to become the first marketed proton pump inhibitior for intravenous use in critical care patients.
- Drug –Drug interaction of Pantoprazole is very less compare to other proton pump inhibitors

PHARMACOKINETICS:

Absorption & Bioavailability :

- Pantoprazole sodium is a acid labile drug so it is prepared as enteric coated tablet, and it is well absorbed in the gastrointestinal tract after oral administration.
- The absolute bioavailability of of Pantoprazole sodium is 77%. The absorption of pantoprazole is rapid ,with a Cmax of 2.5 µg/ml that occurs approximately 2.5 hours (tmax). After administration of a single or multiple oral 40mg doses of Pantoprazole.
- The total area under curve(AUC) is 4.8 µg/ml. the Pantoprazole is well absorbed; it undergoes little first pass metabolism.

Distribution:

- Apparent volume of distribution of Pantoprazole is approximately 11.0-23.6 Litres, distributing mainly in extracellular fluid.
- The serum protein binding of Pantoprazole is about 98%, primarily to Albumin.

Metabolism:

Pantoprazole is extensively metabolished in the liver through the Cytochrome p450 system. Pantoprazole is independent of the route of administration (i.v or oral). the main metabolic is demethylation, by Cytochrome p2c19, with subsequent sulfation There is no evidence that any of the pantoprazole metabolites have significant of pharmacological activity. Cytochrome 2c19 displays a known genetic polymorphism due to its deficiency In sub population (3% of caucasions and African –American and 17-23% Asians).

Elimination

After a single oral or i.v dose of 14 C – labeled Pantoprazole to healthy, normal metabolizer volunteers, approximately 71% of the dose was excreted in the urine with 18% excreted in the feces through bililary excretion. There is no excretion of unchanged pantoprazole.

Table No: 6 - Pharmacokinetic parameters of Pantoprazole.

Parameters	Data
C max	2.5µg/ml
t max	2.5 hours
AUC	4.8 µg-hr/ml
Bioavailability	77%
Biological half life	1.0 hours
Volume of distribution	11.0-23.6 L

Special population

Geriatic:

Only slight to moderate in Pantoprazole auc 43% and cmax26% were found in elderly volunteers 64-67% yrs of age. After repeated oral administration, compared with younger subjects no dosage adjustment is recommended based on age.

Gender:

There is a modest increase in Pantoprazole AUC and Cmax in women compared to men. however weight normalized clearance values are similar in women and men.no adjustment is needed based on gender.

Renal Impairment;

In patients with severe renal impairment , Pharmacokinetic parameters for pantoprazole were similar tothose of healthy subjects. no dosage adjustment is necessary in patients with renal impairment .

Hepatic Impairment:

In patients with mild to severe hepatic impairment, maximum Pantoprazole conceentration increase only slightly relative to healthy subjects. although serum half lifes increase to 7-9hrs and AUC values increase by 5-7 folds in hepatic impaired patients, these increase were no greater than those observed in slow cyp2cyp19 metabolizer.

These pharmacokinetic changes in hepatic impareid patients results in minimal drug accumulation following once daily multiple dose administration. no dosage adjustment. doses higher than 40mg was not studied in hepatically impaired patients.

Method of administration

Pantoprazole 40 mg tablets should not be Split, chewed or crushed, and should be swallowed whole with water either before or during breakfast.

Duodenal ulcer

The recommended dosage is 40 mg pantoprazole daily (1 Pantoprazole Generics 40 mg gastro-resistant tablet). Duodenal ulcers generally heal within two weeks. If a two-week period of treatment is not sufficient, healing will be achieved in almost all cases within a further two weeks. Consideration should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents.

Gastric ulcer and moderate and severe reflux oesophagitis

The recommended dosage is 40 mg Pantoprazole daily (1 Pantoprazole Generics 40 mg gastro-resistant tablet). A four-week period is usually required for the treatment of gastric ulcers and refluxoesophagitis. If this is not sufficient, healing will usually be achieved within a further four weeks.

Eradication of Helicobacter pylori (*H. pylori*)

The recommended dose is 40 mg pantoprazole 2 times daily (1 Pantoprazole Generics 40 mg gastroresistant tablet 2 times daily) in combination with one of the following three combinations:

a) amoxicillin 1 g twice daily + clarithromycin 500 mg twice daily

b) clarithromycin 250–500 mg twice daily + metronidazole 400–500 mg twice daily

c) amoxicillin 1 g twice daily + metronidazole 400–500 mg twice daily

The second Pantoprazole tablet should be taken before the evening meal. Combination therapy should be administered for 7 days in most cases but sometimes up to 14 days.

Consideration should be given to official local guidance (e.g. national recommendations) regarding bacterial resistance and the appropriate use and prescription of antibacterial agents.

Zollinger-Ellison-Syndrome and other hypersecretory conditions

In the treatment of Zollinger-Ellison syndrome and other hypersecretory conditions, the initial dose is 80mg daily (2 Pantoprazole Generics 40 mg gastro-resistant tablets). There after, the dosage can be increased or decreased, as needed using measurements of gastric acid secretion to guide. With doses above 80 mg daily, the dose should be divided and given twice daily. A temporary increase of the dosage above 160 mg Pantoprazole is possible but should not be applied longer than required foradequate acid control. Treatment duration in Zollinger-Ellison-Syndrome and other pathological hypersecretory conditions is not limited and should be adapted according to clinical needs.In patients with Zollinger-Ellison Syndrome and other pathological hypersecretory conditions requiring long-term treatment, Pantoprazole, as all acid-blocking medicines, may reduce the absorption of vitamin B1 (cyanocobalamin) due to achlorhydria. This should be considered if respective clinical symptoms are observed.

Elderly

A daily dose of 40 mg pantoprazole should not be exceeded except in eradication treatment of H.pylori, where elderly patients should receive the standard pantoprazole dose (2 × 40 mg/day) during one-week treatment.

Patients with renal impairment

The daily dose of 40 mg Pantoprazole should not be exceeded in patients with impaired renal function.For this reason, H. pylori triple therapy is not appropriate in these patients.

Patients with hepatic impairment

Patients with severe hepatic impairment should be given 40 mg of Pantoprazole every other day. In these patients, hepatic enzyme levels should be monitored during the treatment. If hepatic enzyme levels become elevated, treatment with Pantoprazole should be discontinued. For this reason, H. pylori triple therapy is not appropriate in these patients.

Children

There is no information on the use of pantoprazole in children. Therefore pantoprazole tablets should not be used in children.

Drug –Drug Interactions

Pantoprazole is metabolized mainly by cyps 3a4,2ds,and 2c9. Invivo drug-drug interactions studies with cyp2c19.substrates.Nifidepine, diclofenac,and theophyline in healthy subjects. The pharmacokinetics of Pantoprazole were not significantly altered. Invivo studies also suggest that pantoprazole does not significantly affect the kinetics of the other drugs cisapride, theophyline, diazepham, phenytoin, warfarin, carbamazepine, clarithromycin, oral contraceptives metabolized by these iso enzymes cyps2c19, 3a4,2c9, 2ds, and 1a2 there pantopazole doesnot affect the pharmacokinetic of other drugs metabolized by these iso enzymes.

Interference with Antiretroviral Therapy

Concomitant use of atazanavir or nelfinavir with proton pump inhibitors is not recommended. Coadministration of atazanavir or nelfinavir with proton pump inhibitors is expected to substantially decrease atazanavir or nelfinavir plasma concentrations and may result in a loss of therapeutic effect and development of drug resistance.

Coumarin Anticoagulants

There have been postmarketing reports of increased INR and prothrombin time in patients receiving proton pump inhibitors, including Pantoprazole sodium delayed-release tablets, and warfarin concomitantly. Increases in INR and prothrombin time may lead to abnormal bleeding and even death. Patients treated with proton pump inhibitors and warfarin concomitantly should be monitored for increases in INR and prothrombin time.

Drugs for Which Gastric pH Can Affect Bioavailability

Pantoprazole causes long-lasting inhibition of gastric acid secretion. Therefore, pantoprazole may interfere with absorption of drugs where gastric pH is an important determinant of their bioavailability (e.g., ketoconazole, ampicillin esters, and iron salts). Possible delayed proton pump inhibitor absorption and decreased bioavailability by the use of sucralfate. Administer proton pump inhibitor at least before 30 mins.

Adverse Effects

The most common side effects with Pantoprazole sodium in adults include:

- Headache
- Diarrhea
- Nausea
- Stomach pain
- Vomiting
- Gas
- Dizziness
- Pain in your joints

The most common side effects with Pantoprazole sodium in children include:

- Upper respiratory infection
- Headache
- Fever
- Diarrhea
- Vomiting
- Rash
- Stomach pain

People who are taking multiple daily doses of proton pump inhibitor medicines for a long period of time may have an increased risk of fractures of the hip, wrist or spine.

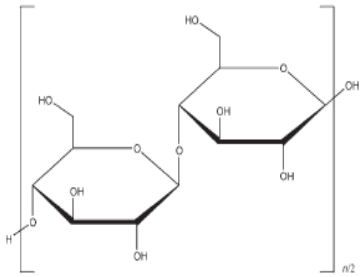
6.1. Excipient Profile: [48]

6.1.1. Microcrystalline Cellulose

- Synonyms:

  Avicel PH, celex, cellulose gel, hellulosum microcrystallinum, Emcocel, Fibrocel, Pharmacel, Vivapur.

- Structural formula:



- Empirical formula:

  $(C_6H_{10}O_5)_n$, where n =220.

- Molecular weight: Approx. 36000

- Description:

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

- Functional category:

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

- Typical properties:

  - ✓ pH – 5.0 to 7.5
  - ✓ Density – 1.512 to 1.668 g/cm^3
  - ✓ Angle of repose – 34.4˚

- Solubility:

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

- Pharmaceutical applications:

Use	Concentration (%)
Adsorbent	20-90
Antiadherent	5-20
Capsule binder/diluents	20-90
Tablet disintegrant	5-15
Tablet binder/diluents	20-90

- Incompatibilities: Incompatible with strong oxidizing agents.
- Safety: Microcrystalline cellulose is widely used in oral pharmaceutical formulations and food products and is generally regarded as a relatively nontoxic and nonirritant material.

Microcrystalline cellulose is not absorbed systemically following oral administration and thus has little toxic potential. Consumption of large quantities of cellulose may have a laxative effect, although this is unlikely to be a problem when cellulose is used as an excipient in pharmaceutical formulations.

Deliberate abuse of formulations containing cellulose, either by inhalation or by injection, has resulted in the formation of cellulose granulomas.

6.1.2. Mannitol

- Synonyms : cordycepic acid ,pearlitol
- Chemical name : D-mannitol
- Emprical formula : $C_6 H_{14} O_6$
- Molecular weight : 182.17
- Description :

  It is a hexa hydric alcohol related to mannose,mannitol occurs as a white odourless, crystalline powder, it has a sweet taste, approximately as sweet as glucose and half as sweet as sucrose

- Typical properties :

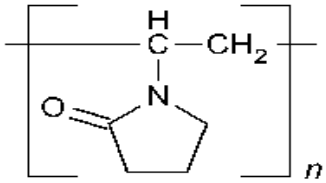
  - ✓ Density (bulk): 0.430 g/cm3 for powder;
    0.7 g/cm3 for granules.
  - ✓ Density (tapped): 0.734 g/cm3 for powder;
    0.8 g/cm3 for granules.
  - ✓ Density(true) : 1.514 g/cm3

- Solubility : Freely soluble in alkalis, water ,insoluble with ether.
- Storage : Mannitol is stable in the dry state and in aqueos solutions, the bulk material should be stored in a well closed container, in a dry place.
- Application : It is primarily used as a diluents (10-90 %)
- Incompatibilities : Mannitol is in compatible with xylitol infusion and may form a complexes with some metals such as aluminium, copper , and iron. reducing sugars impurities in mannitol have been implicated in the oxidative degradation of a peptide in a lyophilized formation.

6.1.4. Povidone

- Synonyms : Kollidon, Poly [1-(2-oxo-1-pyrrolidinyl) ethylene], polyvidone, polyvinylpyrrolidone,povidonum, Povipharm, PVP, 1- vinyl-2-pyrrolidinone

- Chemical structure :



- Molecular Weight : 2500–3000000

- Description :

Povidone occurs as a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder.

- Solubility :

Freely soluble in acids, chloroform, ethanol (95%), ketones, methanol and water. Practically insoluble in ether, hydrocarbon and mineral oil.

- Functional Category :

Disintegrant, dissolution enhancer, suspending agent and tablet binder.

- Applications :

  - ✓ In tableting, povidone solutions are used as binders in wet-granulation processes.
  - ✓ It is used as a solubilizer in oral and parenteral formulations.
  - ✓ Povidone solutions may also be used as coating agents or as binders
  - ✓ The solubility of a number of poorly soluble active drugs may be increased by mixing with povidone.

6.1.5. Crospovidone

- Synonyms : Kollidon cl; polyplasdone XL.

- Chemical name : 1-ethenyl-2-pyrrolidinone homopolymer

- Empirical formula : $(C_6H_9NO)_n$

- Molecular weight : ≥ 1000000

- Description :

  Cros povidone is a white to creamy white , finely divided ,free flowing , practically taste less , odourless , hygroscopic powder

- Typical Properties:

  - ✓ Acidity/alkalinity: pH = 5.0–8.0 (1% w/v aqueous slurry)
  - ✓ Moisture content: maximum moisture sorption is approximately60%.
  - ✓ Particle size distribution: less than 400 mm for PolyplasdoneXL; less than 74 mm for Polyplasdone XL-10. Approximately50% greater than 50 mm and maximum of 3%greater than 250 mm in size for Kollidon CL. Minimum of 90% of particles are below 15 mm for Kollidon CL-M.
  - ✓ Density : 1.22 g /cm2
  - ✓ Solubility : practically insoluble in water and common organic solvents

- Functional category : Tablet disintegrant

- Storage : Cros povidone is stable .however , since it is hygroscopic it should be stored in a cool , dry place.

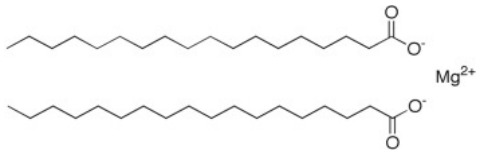
- Application :

  - ✓ Cros povidone is a water insoluble tablet dis integrant used at 2-5% concentration.
  - ✓ It is rapidly exhibits high capillary activity and pronounced hydration capacity with little tendency to form gels.

6.1.6. Magnesium Stearate

- Synonyms: Dibasic magnesium stearate, magnesium distearate, Synpro 90.

- Chemical structure:



- Empirical formula: $C_{36}H_{70}MgO_4$
- Molecular weight: 591.24
- Structural formula: $[CH_3(CH_2)_{16}COO]_2Mg$
- Description:
  A very fine, light white, precipitated or milled, impalatable powder of low bulk density, with a faint odour of stearic acid and a characteristic taste. The powder is greasy to touch and readily adheres to the skin.
- Functional category: Tablet and capsule lubricant.
- Solubility: Practically insoluble in ethanol, ethanol (95%), ether and water; slightly soluble in warm benzene and warm ethanol (95%).
- Typical properties:
  - ✓ True density – 1.092 g/cm^3
  - ✓ Flowability – Poor flowing, cohesive powder
  - ✓ Melting point – 117 to 150˚c
  - ✓ Loss on drying - ≤ 6.0%
- Pharmaceutical Applications:

  Magnesium stearate is widely used in cosmetics, foods, and pharmaceutical formulations. It is primarily used as lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.
- Safety: Oral consumption of large quantities may result in some laxative effect or mucosal irritation.
- Incompatibilities:

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

6.1.7. Colloidal Silicon Dioxide

- Synonyms: Avicel,cellulose gel,aerosol, fumed silica
- Emprical formula: SIO_2
- Molecular weight: 60.08
- D*escription*:

  Colloial silicon dioxide is a sub microscopic fumed silica with a particle size of about 15 nm. It is a light , loose , bluish white coloured , odour less,taste less, non gritty amorphous powder.

- Solubility: Pratically insoluble in prganic solvent , water and acids, except HF, in Soluble in hot solution of alkali hydroxide
- Typical Properties :
  - ✓ Density (bulk): 0.029–0.042 g/cm3
  - ✓ Flowability: 35.52% (Carr compressibility index)
  - ✓ Moisture content: ≤ 0.25% as per USP Nf 23
  - ✓ Particle size distribution: 7–16 nm
  - ✓ Refractive index: 1.46
  - ✓ Specific gravity: 2.2
- Functionl category :
  Adsorbent , anticaking agent ,glident, suspending agent , tablet disintegrant, viscosity increasing agent .
- Storage :
  Cso is a hygrosopic , but absorbs large quantities of water with out liquefying. It is stored in well closed container.
- Application : It is primarily used as an glident in tablet formulation,and it is used as thxotrophic and suspending agent in gels and semisolid preparation, it also used as tablet disintegrants, additionally it is used as dispersing agent for liquids.

6.1.8. Polymethacrylates(Eudrajit L 30 D 55) [48,49]

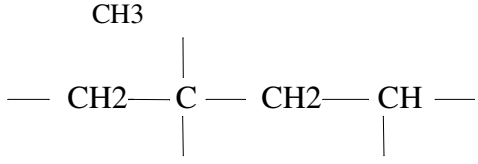
- Synonyms :

  Acryl-EZE; Acryl-EZE MP; Eastacryl 30D; Eudragit; Kollicoat MAE 30 D; Kollicoat MAE 30 DP; .Eudrajit L30 D55.

- Chemical Name :

  Poly (methacrylic acid, ethyl acrylate) 1 : 1 aqueous dispersion

- Molecular Weight : 250 000
- Structural formula :



- Description :

Eudragit L-30 D-55, is an aqueous dispersion of an anionic copolymer based on methacrylic acid and ethyl acrylate. The copolymer corresponds to USPNF 23 methacrylic acid copolymer,Type C. The ratio of free-carboxyl groups to ester groups is 1 : 1. Films prepared from the copolymers dissolve above pH5.5, forming salts with alkalis, thus affording coatings that are insoluble in gastric media but soluble in the small intestine. Milky-white liquid of low viscosity with a faint characteristic odour.

- Functional Category : Film former; tablet binder; tablet diluent Release retardant.
- Solubility: The dispersion is miscible with water in any proportion, the milky-white appearance being retained.A clear or slightly cloudy, viscous solution is obtained by

mixing 1 part Eudrajit L 30 D-55 with 5 parts acetone. The same results are obtained by mixing with ethanol or isopropyl alcohol; initially,the polymer is precipitated, but then dissolves again in the excess organic solvent.A clear or slightly cloudy liquid is obtained by mixing 1 part Eudrajit L 30 D-55 with 2 parts 1 N sodium hydroxide.

- Typical Properties ;
  - ✓ Acid value: 300–330
  - ✓ True density : 1.062–1.072 g/cm3
  - ✓ Viscosity : 415 mPas
  - ✓ pH **:** 2.1 - 3.0
  - ✓ Relative density **:** 1.062 - 1.072

- Pharmaceutical application :

Eudragit L 30 D-55 is used as an enteric coating film former solid-dosageforms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

- Stability and Storage Conditions **:**

Dispersions are sensitive to extreme temperatures and phase separation occurs below 8C. Dispersions should therefore be stored at temperatures between 5 and 258^{0}C and are stable for at least 18 months after shipping from the manufacturer's warehouse if stored in a tightly closed container at the above conditions.

- Safety :

Polymethacrylate copolymers are widely used as film-coatingmaterials in oral pharmaceutical formulations. They are alsoused in topical formulations and are generally regarded as nontoxic and non irritant materials. A daily intake of 2mg /kg body weight of Eudragit (equivalent to approximately 150mg for an average adult) maybe regarded as safe in humans.

- Application :

Eudragit L 30 D-55 is used as an enteric coating film former for solid-dosage forms. The coating is resistant to gastric juice but dissolves readily at above pH 5.5.

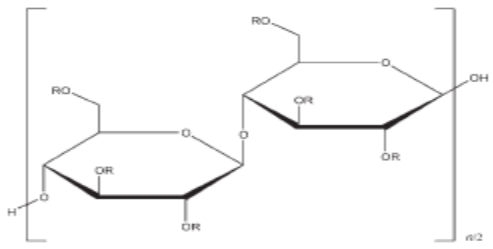
6.1.9. Hydroxypropyl methylcellulose

- Non-proprietary names: Hypromellose (BP, JP, PhEur, USP)

- Synonyms:

Benecel MHPC E464; Hydroxypropyl methylcellulose HPMC; Hypromellosum; Methocel; Methylcellulose propylene glycol ether; Metolose; Pharmacoat; Tylose MO.

- Structural formula:



where R is H, CH_3, or $CH_3CH(OH)CH_2$

- Molecular weight:

Approx. 10000 to 1500000.

- Description:

Hypromellose is an odourless and tasteless, white or creamy-white fibrous or granular powder.

- Functional category:

Bioadhesive material; coating agent; controlled-release agent; dispersing agent; dissolution enhancer; emulsifying agent; emulsion stabilizer; extended-release agent; film-forming agent; foaming agent; granulation aid; modified-release agent; mucoadhesive; solubilising agent; stabilizing agent, suspending agent; sustained-release agent; tablet binder; thickening agent; viscosity-increasing agent.

- Solubility:

Soluble in cold water; practically insoluble in hot water, chloroform, ethanol (95%), and ether; but soluble in mixtures of ethanol and dichloromethane and mixtures of methanol and dichloromethane and mixtures of water and alcohol.

- Typical properties:

  - ✓ pH (for a 2%w/w aqueous solution) – 5.0 to 8.0
  - ✓ Melting point – browns at 190-200˚c; chars at 225-230˚c.
  - ✓ Glass transition temperature – 170-180˚c.
  - ✓ Specific gravity – 1.26
  - ✓ Loss on drying - ≤5.0%
  - ✓ Nominal viscosities (mPa s) - 3 - 100000 (2%w/w solution at 20ºC

- Pharmaceutical applications:

Solid oral dosage forms	i) As tablet binder in either wet or dry granulations (2-5%w/w). ii) High viscosity grades as matrix formers for sustained drug release (10-80%w/w). iii) Depending on viscosity grade, concentrations of 2-20%w/w are used for film-forming solutions to coat tablets. iv) Lower viscosity grade – aqueous film coating.

	v) Higher viscosity grade – Nonaqueous coating.
Liquid oral dosage forms	As suspending or thickening agents at concentrations of 0.25 o 5.0%.
Ophthalmic preparations	Thickening agent to vehicles for eye drops and artificial tear solutions (0.45 to 1.0%).
Nasal preparations	At a concentration of 0.1%.
Topical preparations	As an emulsifier, suspending agent and stabilizing agent in topical gels and ointments.

6.2.0. Propylene glycol

- Synonyms : Dihydroxypropane, 2-hydroxypropanol, methyl ethylene glycol, methyl glycol, propane-1,2-diol.

- Chemical name : 1,2-Propanediol
  Empirical formula : $C_3H_8O_2$
- Molecular weight : 76.09

- Description : Propylene glycol is a clear, colorless, viscous, practically odorless liquid with a sweet, slightly acrid taste resembling that of glycerin.

- Typical properties:

  - ✓ Boiling point:
  - ✓ Density: 1.038 g/cm3 at 20^0C
  - ✓ Melting point: -59^0C
  - ✓

- Solubility :
  miscible with acetone, chloroform, ethanol (95%),glycerin, and water; soluble at 1 in 6 parts of ether;Not miscible with light mineral oil or fixed oils, but will Dissolve some essential oils.

- Functional Category **:** Antimicrobial preservative; disinfectant; humectant solvent; stabilizer for vitamins. Plasticizer**.**

- Applications :

  - ✓ Propylene glycol has become widely used as a solvent.
  - ✓ preservative in a variety of parenteral and non parenteral pharmaceutical formulations.
  - ✓ As an antiseptic it is similar to ethanol, and against molds it is similar to glycerin and only slightly less effective than ethanol.

6.2.1. Triethyl Citrate

- Synonyms: Citric acid, ethyl ester; Citroflex 2; Citrofol AI; E1505;Hydagen CAT; TEC.
- Empirical Formula : $C_{12}H_2O_7$

- Molecular Weight : 276.29

- Chemical Name: 2-Hydroxy-1,2,3-propanetricarboxylic acid, triethyl ester.
- Description : Triethyl citrate is a clear, odorless, practically colorless, Oily liquid.
- Functional Category: Plasticizer.

- Typical Properties:
  - ✓ Acid value: 0.02
  - ✓ Boiling point: 2888C (decomposes)
  - ✓ Flash point: 1558C
  - ✓ Viscosity (dynamic): 35.2 mPa s (35.2 cP) at 258C

- Solubility: soluble 1 in 125 of peanut oil, 1 in 15 of water.Miscible with ethanol (95%), acetone, and propan-2-ol.

- Applications:

  - ✓ Used to plasticize polymers in formulated pharmaceutical coatings.The

coating applications include capsules, tablets, beads, and granules for taste masking, immediate release, sustained release, and enteric formulations.

- ✓ Triethyl citrate is also used as a direct food additive for flavoring, for solvency, and as a surface active agent.

6.2.2. Titanium dioxide

- Synonyms : Anatase titanium dioxide; brookite titanium dioxide; color
- Empirical Formula : TiO_2
- Molecular Weight: 79.88

- Description :

White, amorphous, odorless, and tasteless non hygroscopic powder. Although the average particle size of titanium dioxide powder is less than 1 mm, commercial titanium dioxide generally occurs as aggregated particles of approximately100 mm diameter.

- Typical Properties :

  - ✓ Density (bulk): 0.4–0.62 g/cm3
  - ✓ Density (tapped): 0.625–0.830 g/cm
  - ✓ Density (true):3.8–4.1 g/cm3
  - ✓ Melting point: 18558C
  - ✓ Moisture content: 0.44%
  - ✓ Refractive index: 2.55

- Solubility:

Practically insoluble in dilute sulfuric acid, hydrochloricacid, nitric acid, organic solvents, and water. Solublein hydrofluoric acid and hot concentrated sulfuric acid. Solubility depends on previous heat treatment; prolongedheating produces a less-soluble material.

- Functional Category : Coating agent, Opacifier, Pigment.

- Applications:

- ✓ Titanium dioxide is widely used in confectionery, cosmetics and foods, in the plastics industry, and in topical and oral pharmaceutical formulations as white pigment.
- ✓ Titanium dioxide is used as a white pigment in film-coating suspensions, sugar-coated tablets, and gelatin capsules.

6.2.2. Diethyl phthalate

- Synonyms : DEP; ethyl benzene-1,2-dicarboxylate; ethyl phthalate; Kodaflex DEP; phthalic acid diethyl ester.

- Chemical Name : 1,2-Benzenedicarboxylic acid, diethyl ester .

- Empirical Formula : $C_{12}H1_4O_4$

- Molecular Weight : 222.24

- Description :

  Diethyl phthalate is a clear, colorless, oily liquid. It is practically odorless,with a Very slight aromatic odor and a bitter, disagreeable taste.

- Typical Properties :

  - ✓ Boiling point: 2958C
  - ✓ Flash point: 1608C (open cup)
  - ✓ Melting point: 408C
  - ✓ Refractive index: 25 = 1.501
  - ✓ Specific gravity: 1.120 at 258C

- Solubility: Miscible with ethanol (95%), ether, and many other organic solvents practically insoluble in water.

- Functional Category : Film-former; plasticizer; solvent.

- Applications :

  - ✓ Diethyl phthalate is used as a plasticizer for film coatings tablets, beads, and granules at concentrations of 10–30% by weight of polymer.
  - ✓ Diethyl phthalate is also used as an alcohol denaturant.

7. METHODOLOGY

7.1. Preformulation studies:

Preformulation is usually defined as the science of investigation of Physio-Chemical properties of a drug substance alone and when combined with excipients. Since tablets and capsules account for approximately 70% of pharmaceutical preparations, it is important to undertake an investigation into the solid-state properties of candidate drugs during preformulation.

The basic purpose of the Preformulation activity is to provide a rational basis for the formulation approaches, to minimize the chances of success in formulating an acceptable product and to ultimately provide a basis for optimizing drug product quality and performance. The first step in any formulation activity is careful consideration of a complete physicochemical profile of the active ingredients available, prior to initiating a formulation development activity.[50]

7.1.1. Evaluation of API

The Evaluation of Pantoprazole sodium was done according to USP. Following are some of the important parameters evaluated during preformulation studies and results are tabulated in ***Table No: 17 to 19.***

- **Raw material analysis of Pantoprazole sodium:** [51]

- **Appearance:** white to off white crystaline powder.
- **Solubility studies** :
  Pantoprazole sodium is classified under class III according to BCS i.e; highly soluble but low permeable. Solubility studies were conducted at all pH ranges from 1 to 12. The solubility of API was determined by dissolving the highest unit dose of the drug in 250 mL of like water, acetone, chloroform, n-hexane Highest dose of the drug i.e., 45.1mg was dissolved in 250 mL of medium and was kept untouched for 12 hrs. Later the insoluble drug was filtered off and the solution was analysed by HPLC technique to find out the solubility.

- **Assay of Pantoprazole sodium : (HPLC METHOD)**

Preparation of Buffer solution : Dissolved 1.74 g of dibasic potassium phosphate in 1000 ml of water and adjusted with a solution of phosphoric acid to a pH of 7.0.

Diluent: Prepared a mixture of acetonitrile and 0.001 N sodium hydroxide solution (50:50).
Mobile phase: A filtered and degassed mixture of buffer solution and acetonitrile.

Preparation of Standard solution :

45.1 mg of Pantoprazole sodium RS was weighed accurately and then transferred into 100 ml volumetric flask. To this 50 ml of 0.001 N sodium hydroxide was added Then it was shaken and sonicated for 5 mins to dissolve the content. and make up the volume with diluent. from this 3.4 ml was pipette out and transferred to 50 ml volumetric flask. and make up the volume with diluent.

Preparation of Sample solution:

45.1 mg of Pantoprazole sodium was weighed accurately and then transferred into 100 ml volumetric flask**.** To this 60 ml of 0.001 N sodium hydroxide was added Then it was shaken and sonicated for 10 mins to dissolve the content. and make up the volume with diluent.

Chromatographic Condition

- Apparatus : HPLC
- Coloumn : (4.0mm X 25cm) coloumn, that contains 5-µm packing L1
- Flow rate : 1ml/min
- Coloumn temp : 40^0 C
- Wave length : 290 nm
- Inj volume : 20µl

Procedure:

20 µl of filtered portion of the standard preparation (five injections and sample preparation were separately injected into the chromatographic system. The chromatograms was

recorded and the responses were measured for the major peaks. Then calculated the percentage of impurities in the portion of pantoprazole sodium by using the following expression.

Evaluation of system suitability:

The coloumn efficiency as determined for the Pantoprazole peak from the standard preparation is not less than 2000 theoretical plates and the tailing factor for the same peak is not more than 2.0. the The percentage relative standard deviation for five replicate injections is not more than 5.0%. The reporting level for impurities is 0.05%.

7.1.2. Drug-Excipient compatibility studies : [52]

In the tablet dosage form the drug is in intimate contact with one or more excipients; the latter could affect the stability of the drug. Knowledge of drug- excipient interactions is therefore very useful to the formulator in selecting appropriate excipients. This information may be present for known drugs. For new drugs or new excipients, the preformulation scientist must generate the needed information.

- **Physical studies:**

Active ingredient was mixed well with all excipients in binary ratio and small portion of this mixed powder was placed in a 2 ml of cleaned and dried vial (USP Type I). This vial was kept for observation in stability chamber at 40ºC ± 2ºC/ 75 ± 5% RH. Physical observation has been carried out visually at the initial stage and after 30 days exposure to the stated conditions. The results were tabulated in ***Table No:20.***

- **FT-IR studies :**

Physical compatibility studies were assured by FT-IR studies. The crude drug sample, drug-excipient mixtures of the formulation were chosen for the study. The FT-IR spectra's of the above samples were studied after a period of 30 days from preparation of the mixtures, to facilitate prompt detection of incompatibility. The spectra's were obtained by preparing Potassium bromide pellets under dry condition by using pellet press.The spectra of the crude drug sample and that of the drug-excipient mixtures were compared to check the incompatibility problems. The FT-IR spectra's were shown in ***Fig. 6 to Fig 13.***

TableNo:7- Protocol For Drug-Excipient Compatibility Studies

S.No	Drug and excipients	Ratio
1	Drug alone	-
2	Drug + Mannitol	1:2
3	Drug + Crospovidone	2:1
4	Drug + Povidone + Sodium carbonate	5:1:1
5	Drug + MCC pH112	2:1
6	Drug + Aerosil	10:1
7	Drug + Magnesium Stearate	10:1

7.2. Formulation of Pantoprazole sodium delayed release tablet :

- **Conversion Factor Calculation**:

Molecular weight of Pantoprazole sodium sesquihydrate = 432.37

Molecular weight of Pantoprazole = 383.37

Conversion factor = 432.37 / 383.37 = 1.127

40mg Pantoprazole per tablet is the required label claim.

Thus, amount of Pantoprazole Sodium Sesquihydrate equivalent to 40 mg of Pantoprazole = 40*1.127 = 45.11mg.

- **Selection of Process** :

Micrometric Studies has been carried out for the Pantoprazole sodium. based on the results it was concluded that the drug is not suitable for direct compression method due to fine particle size and poor flow characteristics. So, the Delayed release tablet of Pantoprazole sodium was

prepared by wet granulation technique. All tablet ingredients was accurately weighed as mentioned in ***Table No:8.*** The Average weight of each core tablet was set to 150 mg in all trails taken.

Table No: 8 - Formulation Trials

Formula for Preparation of Pantoprazole Sodium Core Tablet

S.No	Ingredient (mg)	Formulation code				
		F1	**F2**	**F3**	**F4**	**F5**
	Core Formulation					
1	Pantoprazole sodium sesquihydrate	45.11	45.11	45.11	45.11	45.11
2	Mannitol	90.59	70.00	70.00	65.00	63.00
3	Crospovidone	8.00	8.00	8.00	13.00	15.00
4	Sodium carbonate	1.60	1.60	1.60	1.60	1.60
5	Povidone	3.20	3.20	3.20	3.20	3.20
6	Purified water	Q.S	Q.S	Q.S	Q.S	Q.S
7	MCC pH 112	-	20.44	20.44	20.44	20.44
8	Aerosil	-	0.15	0.15	0.15	0.15
9	Magnesium stearate	1.50	1.50	1.50	1.50	1.50
Total weight (mg)		**150**	**150**	**150**	**150**	**150**

7.3. Coating Formula:

3% seal coating has been given for all the three formulation F_3,F_4,F_5 To prevent direct interaction between pantoprazole sodium and Eudrajit Polymer.

Table No: 9 - Composition of Ingredient For Seal Coating

S.No	Ingredient	Quantity(gm)
1	HPMC 15 cps	10
2	Titanium oxide	7.0
3	Propylene glycol	1.0
4	Purified water	Q.S

7.3.1. Preparation of seal coating solution:

Weighed accurately a required quantity of HPMC 15 cps and soaked in water for 30 mins, and stirred until it swells. Mean while titanium dioxide was Triturated in a motar and added to the solution and stirred. followed by propylene glycol to the solution and stirred**.** Finally the volume were make up to required quantity with purified water**.** Filtered the above solution with #100 mesh.

7.3.2. Weight Built up calculation for Seal coating: [3%]

150 x 3 % (3gm ⟶ 100 ml) 0.03 = 4.5 mg

150 + 4.5 = 154.5 mg

The weight of seal coated tablet **= 154.5 mg.**

Table No:10 - Composition of Ingredient For Enteric Coating

12% seal coating has been given for all the three formulation F_3,F_4,F_5 to protect the drug from acidic environment.

S.No	Ingredient	Quantity (gm)		
		F3	**F4**	**F5**
1	Eudrajit L30 D55	92.00	92.00	92.00
2	Diethyl Phthalate	14.40	14.40	-
3	Titanium dioxide	16.60	16.60	16.60
4	Triethyl citrate	-	-	14.40
5	Purified Talc	23.00	23.00	23.00
6	Ferric oxide	2.00	2.00	2.00
7	Purified water	Q.S	Q.S	Q.S

7.3.4. Preparation of Enteric Coating solution:

A required quantity of Methacrylic acid copolymer dispersion, was weighed accurately and stirred until it swells. Mean while plasticizer, titanium dioxide, purified talc and ferric oxide were triturated separately in a motar. and added to the solution and stirred. Finally the volume were make up to required quantity with purified water**.** Filtered the above solution with #100 mesh.

7.3.5. Weight Built up calculation for enteric coating : [12 %]

154.5 x 12% (12 gm 100ml) 0.12 =18.54 mg

154.5 + 18.54 = 173.04 mg

⟶

The weight of enteric coated tablet = **173.04mg.**

Table No:11 - Operation Condition For Seal and Enteric Coating Process

Specifications	Range	
	Seal coating	**Enteric coating**
Pan diameter	12”	12”
Speed of pan revolution	8-10 rpm	10-12 rpm
Distance of spray gun	5-6”	5-6”
Spray nozzle diameter	1.2 mm	1.2 mm
Spray rate	2.5-3 ml /min	1.5 -2.0 ml /min
Dry air temperature	50 ± 5/ 30 mins	50 ± 5^0C / 30 mins
Coating time	2 hours	4 hours
Bed temperature	30-40^{0}C	30-40^{0}C

7.4.

TRIAL I

Accurately weighed the specified quantity of ingredients – Pantoprazole sodium, Mannitol, Crospovidone. and the above materials were Sifted through #30 mesh and placed in a separate polythene bag and they are used as dry mix .

Preparation of Binder solution :

Purified water was taken in a SS Vessel. To this Povidone was added and Stirred to get a clear solution. Sodium carbonate was added into the solution and kept under stirring condition and used as binder solution.

[Notification : Na_2co_3 monohydrate is added with povidone, because povidone is in Acidic pH when it is added as binder solution , the drug which is unstable in the gastric condition (Acidic pH) will be degraded. So to avoid that Sodium carbonate is added to

maintain in Alkaline pH.

The sifted materials were mixed for 5 mins in a poly bag before granulating and transferred to a vessel and granulated with required quantity of binder solution by kneading method and the granules were dried in hot air oven at 50^0C. then semi dried granules were passed through sieve No. 20, and continued the drying till the moisture content of granules is less than 1.0 %. Then after obtaining the optimum moist content, granules were removed from the oven. and the the size of granules were reduced to get uniform particle size. and the above granules were mixed with Crospovidone. and sifted through #60 mesh for 5 mins, in a polybag. Finally lubricated with required quantity of magnesium stearate after sifting it through # 60mesh for 5 min. and the lubricated granules was then compressed into tablets with an average weight of 150 mg using 8.00 mm punches.

TRIAL I I

Same as procedure of trial 1. but in this formulation the concentration of Mannitol was decreased to 70 mg/unit. MCC pH 112 was included as diluent in the Extra granular portion of the formulation, because of its less moisture content. Aerosil was also included to improve the flow property of the granules. Further trial has been taken as scale up of trail 2.

TRIAL I I I

In trail 3 the core tablets were coated with seal coating solution with an average weight built up of 3%. these seal coated tablets were further coated with enteric coating solution with an average weight built up of 8, 10,12%.

TRIAL IV

In trial 4 the concentration of Mannitol is further decreased to 65mg/unit and increasing the Crospovidone concentration to 13mg/unit.

TRIAL V

In trail 5 the concentration of Mannitol is still decreased to 63mg/unit and increasing the Crospovidone concentration to 15mg/unit. diethyl phthalate was replaced with triethyl citrate in the enteric coating part, to give better flexibility to the polymer.

7.5. Evaluation of Precompression Parameters:

The characteristics of a tablet that make it a popular dosage form, e.g. compactness, physical stability, rapid production capability, chemical stability and efficacy are in general dictated primarily by the qualities of the granulation from which it is made. Basically stated, materials intended for compaction into a tablet must possess two characteristics: Fluidity and Compressibility.[53] To a great extent these properties are required by the compression machine design. Thus good flow properties are a prerequisite for the successful manufacture of tablets. It is a property of all powders to resist the differential movement between particles when subjected to external stresses. This resistance is due to the cohesive forces between the particles. Tablets require the flow of the correct weight of material into a specific volume, the behaviour of the material under pressure is important; and the wetting of the powder is also critical for granulation and subsequent disintegration and dissolution of the dosage form.

7.5.1. Bulk density:

Bulk density is a characteristic of a powder rather than individual particles and is given by the mass, M, of the powder occupying a known volume, V_o. It is expressed in g/ml. An accurately weighed quantity of granules was transferred into a 50 ml measuring cylinder with the aid of the funnel. The unsettled apparent volume, to the nearest graduated unit occupied by the granules was measured. Bulk density was determined using the formula [54],

$$\rho_{bulk} = m/V_o$$

Where,

ρ_{bulk} = Bulk density;

m = Mass of the blend

V_o = Untapped Volume

7.5.2. Tapped density:

Tapped density is achieved by mechanically tapping a measuring cylinder containing a powder sample. After observing the initial volume, the cylinder is mechanically tapped, and volume readings are taken until little further volume change is observed.[54] The measuring cylinder containing a weighed quantity of granules (after measurement of bulk density) was subjected to 500 taps in tapped density tester (Electro Lab USP II). The tapped density was calculated by using the formula,

$$\rho_t = m/V_t$$

where, ρ_t = Tapped density; m = Mass of the granules and V_t = Final tapped volume.

7.5.3. Carr's compressibility index:

Compressibility index are a measure of the tendency for arch formation and the ease with which the arches will fail.[55] ***Table No: 12*** shows the relationship between compressibility index and flowability. It is calculated by using the formula[56],

$$CI = \rho_t - \rho_{bulk} / \rho_t \times 100$$

where, CI = Compressibility index; ρ_{bulk} = Bulk density and ρ_t = Tapped density.

Table No - 12

Compressibility index (%)	Flow characters
< 10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

7.5.4. Hausner's ratio:

Hausner found that the ratio ρ_t / ρ_{bulk} was related to interparticle friction and, as such could be used to predict powder flow properties. He showed that powders with low interparticle friction, such as coarse spheres, had ratios of approximately 1.2; whereas more cohesive, less free flowing powders such as flakes have values greater than 1.6.[57] ***Table No: 13*** shows the flow characters and corresponding Hausner's ratio. It is calculated using the formula[58],

$$\textbf{Hausner's Ratio} = \rho_t / \rho_{bulk}$$

where,

ρ_{bulk} = Bulk density and ρ_t = Tapped density.

Table No- 13

Flow characters	Hausner's ratio
Excellent	1.0– 1.11
Good	1.12 – 1.18
Fair	1.19 – 1.25
Passable	1.26 – 1.34
Poor	1.35 – 1.45
Very poor	1.46 – 1.59
Very, Very poor	>1.60

7.5.5. Angle of repose:

Angle of Repose (θ) is the maximum angle between the surface of a pile of powder and horizontal plane. It is usually determined by fixed funnel method and is the measure the flowability of powder/granules**.** The angle is a measure of the cohesiveness of the powder, as it represents the point at which the interparticle attraction exceeds the gravitational pull on a particle. [59] shows the flow properties and corresponding angle of repose.

Procedure

Weighed quantity of granules was passed through a funnel kept at a height of 2 cm for the base. The powder is passed till it forms heap and touches the tip of the funnel. The height of the heap formed and radius of the base of the heap was measured. Angle of repose was calculated by using the formula [60],

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

where, θ = Angle of repose;

h = height of the heap of pile and r = radius of base of pile.

Table No -14

Flow properties	**Angle of repose (degree)**
Excellent	25-30
Good	31-35
Fair – aid not needed	36-40
Passable – may hang up	41-45
Poor,must agitate	46-55
Very poor	56-65
Very, very poor	>66

7.5.6. Moisture content:

A known quantity of granules say 3gm was weighed on the sample pan of the IR moisture balance. The sample was dried until anhydrous at 60˚c by the use of IR radiation. The percentage of moisture content of the granulation can be determined as the end point display when all the moisture in the sample has been removed by the radiation.

7.6. Evaluation of post-compression parameters:

7.6.1. Hardness:

Tablets require a certain amount of strength or hardness to withstand mechanical shocks of handling in manufacture, packaging, and shipping. Tablet hardness has been defined as, the force required to break a tablet in a diametric compression test. [60] Tablet hardness of all the formulations was measured using a Monsanto hardness tester.

7.6.2. Thickness:

Tablet thickness is an important parameter to be controlled to facilitate packaging. Tablet thickness, at constant compressive load, varies with changes in die fill, with particle size distribution and packing of the particle mix being compressed; whereas at constant die fill, thickness varies with variations in compressive load. Tablet thickness must be controlled within a ±5% variation of a standard value. Any variation within a particular lot should not be apparent to the unaided eye of the consumer. [61] Thickness of all the formulations was measured using a digital vernier tandar.

7.6.3. Friability:

Friability is a measure of the resistance of the tablet to abrasion. Tablets are generally subjected to a standardized level of abrasion for a given time and the friability is expressed as a %weight loss. The measure is useful to determine the ability of the tablet to withstand abrasion during handling, coating, packing and transport. The laboratory friability tester is known as the Roche friabilator. This device subjects the tablets to the combined effects of

abrasion and shock by utilizing a plastic chamber that rotates at 25 rpm, dropping the tablets form a height of 6 inches with each revolution. [62]

Twenty tablets were weighed accurately and placed in the friabilator and was operated for 100 revolutions or 4 minutes. The tablets were then de dusted and weighed. The weight loss of 0.5 to 1% is considered as acceptable limits for conventional uncoated tablets. The weight loss was calculated using the formula[62] .

Friability, F (%) = (Weight loss/Initial weight)*100

The friability of the all the formulations was determined as per the above procedure.

7.6.4. Weight Variation Test:

Twenty tablets were selected randomly and weighed individually. Calculate average weight and compare the individual tablet weight to the average. Not more than two of the individual weights deviate from the average weight by more than the percentage shown in and none deviate by more than twice the percentage. [63]

Table No - 15

Average weight of Tablets (mg)	Max. Percentage deviation (%)
130 or less	10
130 – 324	7.5
324 or more	5

7.6.5. Disintegration test:

Tablet disintegration study was performed for delayed release enteric coated tablets of pantoprazole sodium. Disintegration time was determined using USP tablet disintegration tester the study was conducted at 37ºC±2˚C for 2 hours in 800 ml 0.1N Hcl (pH 1.2), then the medium was with 800 ml of pH 6.8 phosphate buffer and tested for disintegration for 60 mins.

7.6.6. Preparation of Standard curve for Pantoprazole sodium in 0.1N Hcl :

Pantoprazole sodium was scanned from wave length 210nm-360 nm in UV-Visible Spectrophotometer. it was found that maximum absorption of the drug (4µg/ml) was found in **λmax** 305 nm is given in ***Table No:25*****.**

45.1 mg of Pantoprazole sodium were accurately weighed and transferred to 100 ml standard flask, dissolved first in 0.1N sodium hydroxide, using 10% of the final volume & the volume was make up with pH 6.8 phosphate buffer. From this primary stock solution pipetted out 1ml and transferred to 100 ml standard flask and made up the volume with 0.1N Hcl (pH 1.2) medium. this is secondary stock solution, from this various concentration of drug (0, 1, 2, 3, 4, 5 µg/ml) were pipetted out separately into 10 ml standard flask and make up to required volume using 0.1N Hcl. Their individual absorbance was readed using UV-Visible Spectrophotometer. The Standard curve was prepared by plotting various concentrations against respective absorbance .

7.6.7. Preparation of Standard curve for Pantoprazole sodium in pH 6.8 phosphate buffer :

Pantoprazole sodium was scanned from wave length 210nm-360 nm in UV-Visible Spectrophotometer. it was found that maximum absorption of the drug (23µg/ml) was found in **λmax** 288 nm is given in ***Table No:26*****.**

45.1 mg of Pantoprazole sodium were accurately weighed and dissolved first in 0.1N sodium hydroxide, using 10% of the final volume, and the volume make up with pH 6.8 phosphate buffer. From this 10 ml was pipetted out and transferred into 100 ml volumetric flask and make up to required volume using pH 6.8 phophate buffer, this is secondary stock solution, from this various concentration of drug (0, 5, 10, 15, 20, 25, 30µg/ml) were pipetted out separately into 10 ml standard flask and make up to required volume using pH 6.8 phophate

buffer. Their individual absorbance was readed using UV-Visible Spectrophotometer. The Standard curve was prepared by plotting various concentrations against respective absorbance .

7.6.8. *In vitro* dissolution study:

Dissolution media preparation:

- **Preparation of 0.1N Hcl -** 8.5 ml of concentrated Hcl was added to 1000 ml of purified water and the pH was found to be 1.2.

- **Preparation of pH 6.8 phosphate buffer-** Dissolved 6.8 g of potassium Dihydrogen phosphate in Purified water. And the volume was make upto1000 ml with purified water and adjusted the pH by using 0.1 N sodium hydroxide solution.

Standard Preparation for Acid stage: Accurately weighed and transferred 45.1 mg of Pantoprazole sodium in 100 ml standard flask, dissolved first in 0.1 N sodium hydroxide, using 10% of the final volume & the volume was make up with pH 6.8 phosphate buffer . From this primary stock solution pipetted out 1ml and transferred to 100 ml standard flask and made up the volume with 0.1N Hcl (pH 1.2) medium.

Standard preparation for Buffer stage: Accurately weighed and transfer 45.1 mg of Pantoprazole sodium reference standard in to 100 ml volumetric flask, dissolve first in 0.1N sodium hydroxide, using 10% of the final volume, then dilute to required volume with pH 6.8 phosphate buffer this is primary stock solution. From this 10 ml was pipette out into 100 ml volumetric flask and made upto required volume using pH 6.8 phophate buffer this is secondary stock solution, from this 5 ml was pipette out into 10 ml volumetric flask and made up to required volume with pH 6.8 phophate buffer.

Test procedure: Drug release study was carried out using USP dissolution rate test Apparatus-II. And the study was conducted at 37˚C ± 0.5˚C 100rpm for 2 hrs in 1000 ml 0.1N Hcl of pH 1.2, and the sample was withdrawn after 2 hr. Then the dissolution medium was replaced with 1000 ml of pH 6.8 phophate buffer and the dissolution was carried out upto 45 mins. An Aliquots of the dissolution medium was withdrawn at the 5, 10, 15, 20, 30, 45 mins time points filtered. 5 ml of the filtrate from each bowl was separately diluted to 10 ml each with dissolution medium. the samples were analyzed with UV-VIS Spectrophotometer

at 305nm for 0.1N Hcl and 288 nm for pH 6.8 phosphate buffer. The percentage of drug released at each time point was calculated by mentioned formula.

7.6.9. Assay of Enteric coated tablets of Pantoprazole sodium[64] : (HPLC)

Preparation of Buffer solution: Dissolved 3.85 g of ammonium acetate and 1.1 g of tetrabutylammonium hydrogen sulfate in 1 L of water, and adjusted with ammonium hydroxide solution diluted 1 : 1 with water to a pH of 7.9.

Diluent: A mixture of 0.02 N sodium hydroxide and acetonitrile (1 : 1) was prepared**.**

Mobile phase: A filtered and degassed mixture of buffer solution and acetonitrile (65 : 35) was prepared .

Preparation of standard solution :

45.1 mg of Pantoprazole sodium RS was weighed accurately and then transferred into 200 ml volumetric flask 60 ml of 0.02 N sodium hydroxide was added Then it was shaken and sonicated for 5 mins to dissolve the content. Add about 2 ml of acetonitrile and made up the volume with 0.02 N sodium hydroxide to Filtered a portion of this solution through 0.45micron membrane filter. The filtrate was collected after discarding the first few ml of the filtrate.

Preparation of sample solution:

20 tablets were weighed and powdered, A quantity of powdered tablet equivalent to about 174 mg of Pantoprazole sodium was transferred to 200 ml and diluents was added to about 60 ml, and the flask was shaked mechanically for about 60 mins, and the volume was make up with 0.02 N sodium hydroxide and acetonitrile (1:1) Then the solution was filtered through 0.45 micron membrane filter. The filtrate was collected in HPLC vial after discarding the first 10ml of the filtrate.

Chromatographic Condition

- Apparatus : HPLC
- Coloumn : (4.0mm X 25cm) coloumn, that contains 5-µm packing L1
- Flow rate : 1ml/min
- Coloumn temp: Ambient
- Wave length : 290 nm
- Inj volume : 20µl
- Detector : Photodiode array

Procedure:

20 µl of filtered portion of the standard preparation (five injections and sample preparation were separately injected into the chromatographic system. The chromatograms was recorded and the responses were measured for the major peaks. The content of Pantoprazole per tablet was calculated using the following expression.

Evaluation of system suitability:

The coloumn efficiency as determined for the Pantoprazole peak from the standard preparation is not less than 2000 theoretical plates and the tailing factor for the same peak is not more than 2.0. The percentage relative standard deviation for five replicate injections of standard preparation not more than 2.0.

7.7. Comparative dissolution profile study: [65]

In recent years, FDA has placed more emphasis on a dissolution profile comparison in the area of post-approval changes and biowaivers. Under appropriate test conditions, a dissolution profile can characterize the product more precisely than a single point dissolution test. A dissolution profile comparison between pre-change and post-change products for SUPAC related changes, or with different strengths, helps assure similarity in product performance and signals bio inequivalence. Comparison of therapeutic performances of two medicinal products containing the same active substance is a critical means of assessing the possibility of alternative using between the innovator and any essentially similar medicinal product. Dissolution profiles of two products can be considered similar by virtue of

- Overall profile similarity, and

- Similarity at every dissolution sample time point.

A simple model independent approach uses a difference factor (f_1) and a similarityfactor (f_2) to compare the dissolution profiles. The difference factor calculates the percentage

difference between the two curves at each time point and is measurement of the relative error between the two curves:

$$f_1 = \{[\sum_{t=1}^{n} | R_t - T_t |]/[\sum_{t=1}^{n} R_t]\} \bullet 100$$

where, n is the number of time points, R_t is the dissolution value of the reference batch at time t and T_t is the dissolution value of the test batch at time t.

The similarity factor f_2 is a logarithmic reciprocal square root transformation of the sum of squared error and is a measurement of the similarity in the percent dissolution between the two curves.

$$f_2 = 50 \bullet \log \{[1+(1/n)\sum_{t=1}^{n} (R_t - T_t)^2]^{-0.5} \bullet 100\}$$

General procedure*:*

i. Determine the dissolution profile of two products (6 units each) of the test and reference products.

ii. Using the mean dissolution values from both the curves at each time interval, calculate the difference factor (f_1) and similarity factor (f_2) using the above equations.

iii. For curves to be considered similar, f_1 values should be close to 0, and f_2 values should be close to 100. Generally, f_1 values upto 15 (0-15) and f_2 values greater than 50 (50-100) ensures sameness or equivalence of the two curves.

The comparative dissolution study was performed to determine the similarity of dissolution profiles for delayed release layer; between the innovator product (PROTONIX) and the optimized formulation **F_5.** The results are tabulated in ***Table No: 28.***

7.8. Stability studies:

Stability of a drug has been defined as the ability of a particular formulation, in a specific container, to remain within its physical, chemical, therapeutics and toxicological specifications. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light, and to establish a retest for the drug substance or a shelf life for the drug product and recommended storage conditions. The ICH guideline recommends the following storage conditions for stability studies:

Table No - 16

S.No.	Study	Storage Condition
1.	Long term	25°C±2°C / 60%RH±5%RH
2.	Intermediate	30°C±2°C / 65%RH±5%RH
3.	Accelerated	40°C±2°C / 75%RH±5%RH

As per ICH guidelines, the samples for stability analysis must be exposed to an environment of 40˚C± 2˚C / 75% RH±5% RH for a period of 3 months. As per the standard protocol the samples must be analysed at 0, 1, 2, and 3 months time points. Accelerated stability studies were performed for the final Enteric coated tablets. The tablets were blister packed and 5 pouches were placed into the stability chamber. The samples were analyzed at 0, 1, 2 and 3 months time points.

Test Performed:

i. Test for physical parameters (description, hardness, thickness, friability).

ii. Assay.

iii. *In vitro* Dissolution Study.

The results of the stability studies are tabulated in ***Table No: 29& 30.*** The data was analyzed for any significant change in the values from the initial data.

8. RESULTS & DISCUSSION

8.1. Preformulation Studies:

8.1.1. Evaluation of API

Table No- 17

S. No	Test	Limit	Observation
1	Appearance	White to off white crystalline powder	Complies
2	Infra red spectra	Sample IR spectrum should comply with standard IR spectrum	Sample IR spectrum complies with standard IR spectrum
3	Heavy metals	NMT 20 ppm	Complies
4	Test for Sodium	It gives reaction of sodium by producing whiteprecipitate	Complies
5	Total impurity	NMT 0.50 %	0.23%
6	Water content (by KF %w/w)	5.9-6.9 %	6.69%
7	Assay	99.0-101.0%	99.64%

Table No :18 - Solubility Studies

S.No	Solvent	Quantity dissolved at 25^0c (mg/ml)
1	water	1023
2	Acetone	270
3	Chloroform	0.022
4	Di chloro methane	0.018
5	n- hexane	0.001

Table No :19 - Micrometric Properties of API

API	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose* (Degree)	Moisture content (%)
Pantoprazole sodium	0.358±0.003	0.507±0.004	29.45±0.48	1.41±0.009	39.61±0.26	0.67%

Inference :

- The Bulk density of the powder was found to be 0.358gm/ml.
- The Tapped density of the powder was found to be 0.507gm/ml.
- The Compressibility Index was found to be 29.45 indicating poor flow properties.
- The Hausner's ratio was found to be 1.41 and the value was indicating poor flow properties.
- The Angle of repose was obtained as 39.61°, indicating poor flow of powder drug.

Based on the above results it was concluded that the drug is not suitable for direct compression method due to fine particle size and poor flow characteristics.

8.1.2. Drug-Excipient compatibility studies

a) Physical studies:

Table No : 20 - Drug-Excipient Compatibility Study

S.No	Composition details	Initial	Storage condition / duration (40^0C / 75%RH) / 30days	Comments
1	API (Pantoprazole sodium)	White to off white crystalline powder	NCC	Compatible
2	API+Mannitol	Off White crystalline Powder	NCC	Compatible
3	API + Crospovidone	Off White crystalline Powder	NCC	Compatible
4	API + Povidone + Sodium carbonate	Off White crystalline Powder	NCC	Compatible
5	API + Microcrystaline cellulose (avicel pH112)	Off White crystalline Powder	NCC	Compatible
7	API + Aerosil	Off White crystalline Powder	NCC	Compatible
8	AP I + Magnesium Stearate	Off White crystalline Powder	NCC	Compatible

NCC- No Characteristic Change

b) FT-IR studies

The FT-IR spectra of the crude drug samples and the drug-excipient mixtures are as shown below.

Fig.6 - FT-IR spectra of Pantoprazole Sodium pure drug

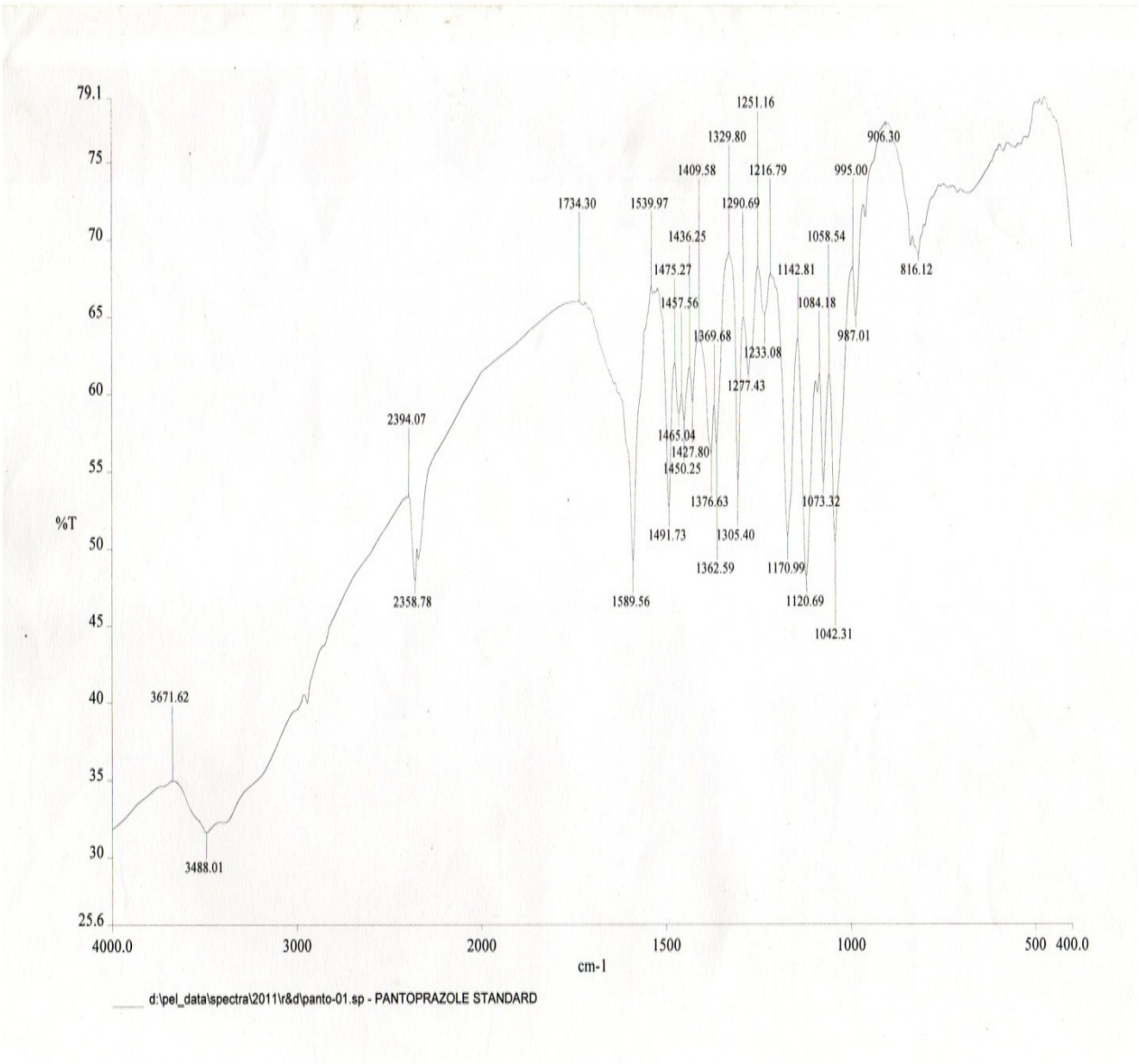


Fig. 7- FT-IR Spectra of Pantoprazole Sodium + Mannitol

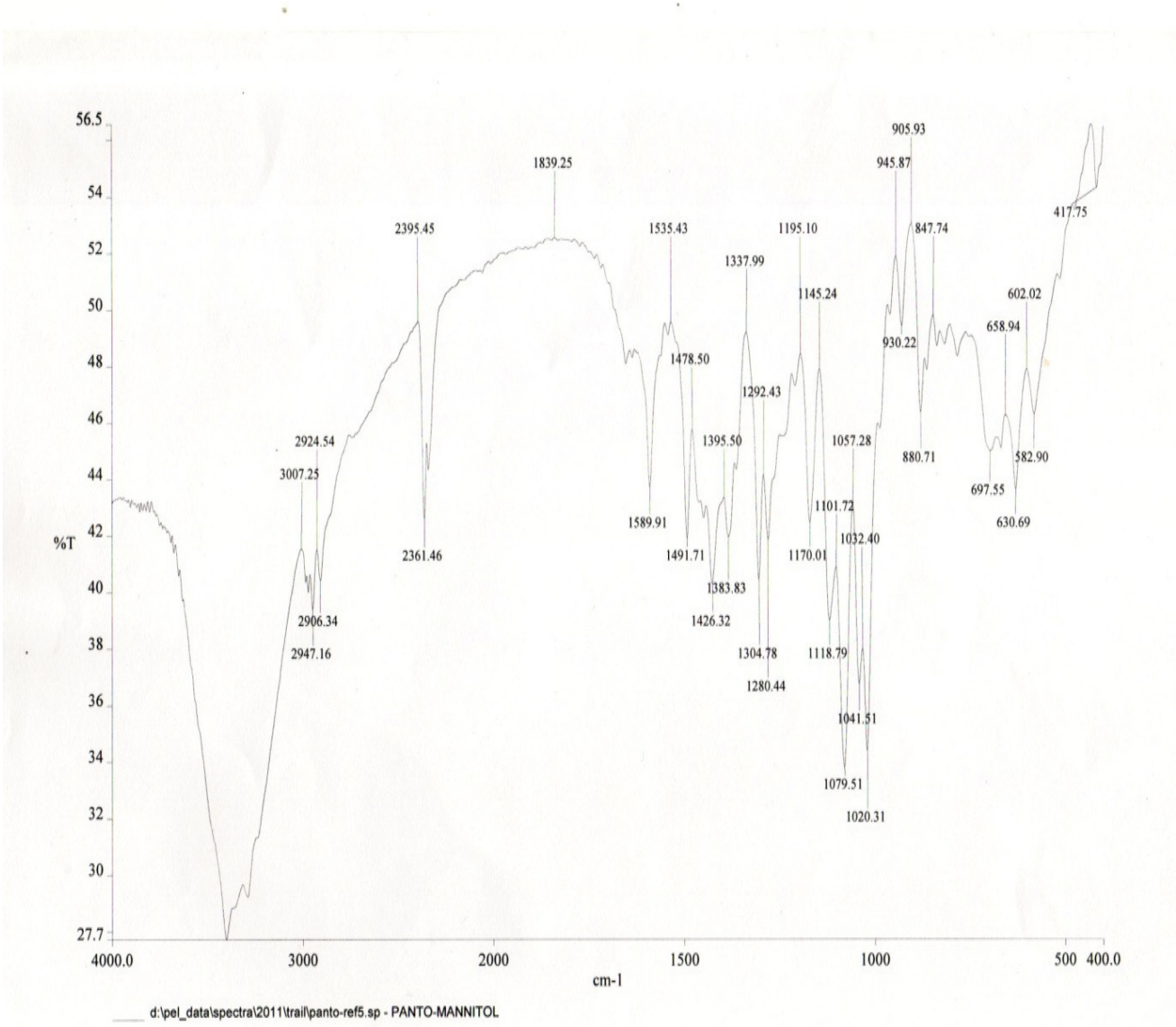


Fig .8 - FT-IR Spectra oF Pantoprazole Sodium + Povidone +Sodium Carbonate

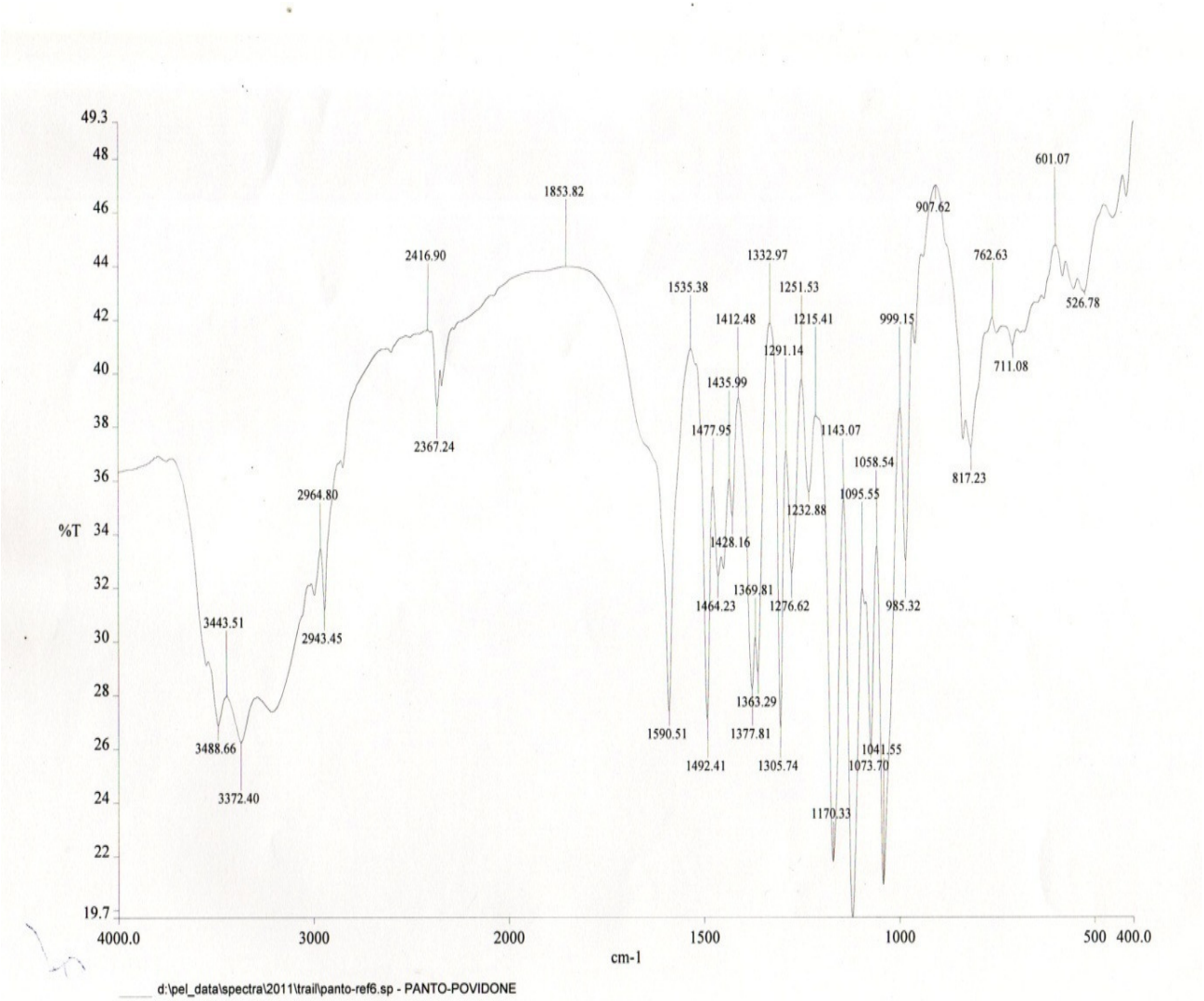


Fig.9 - FT-IR Spectra of Pantoprazole Sodium + Crospovidone

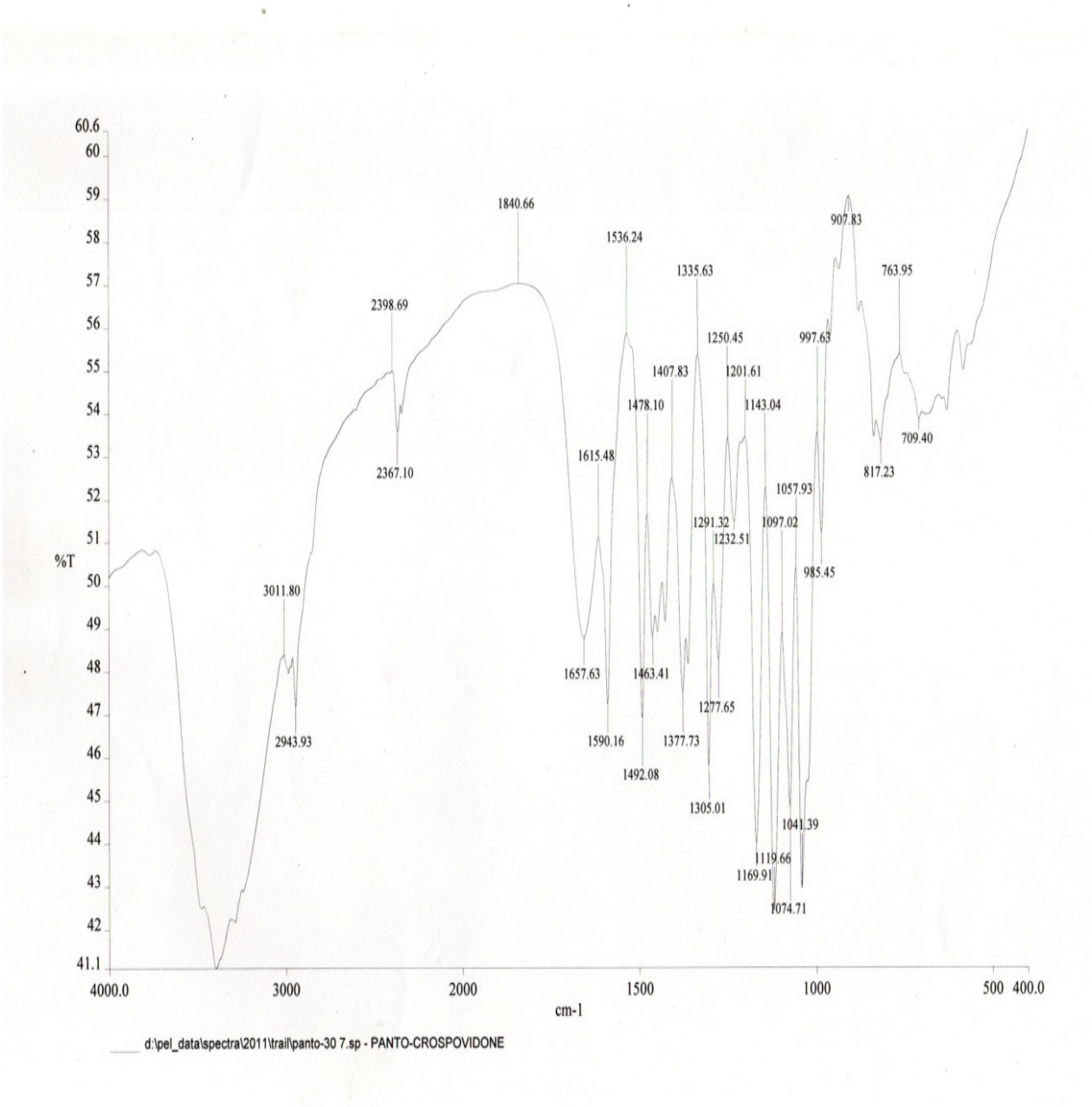


Fig.10- FT-IR Spectra of Pantoprazole Sodium + MCC pH 112

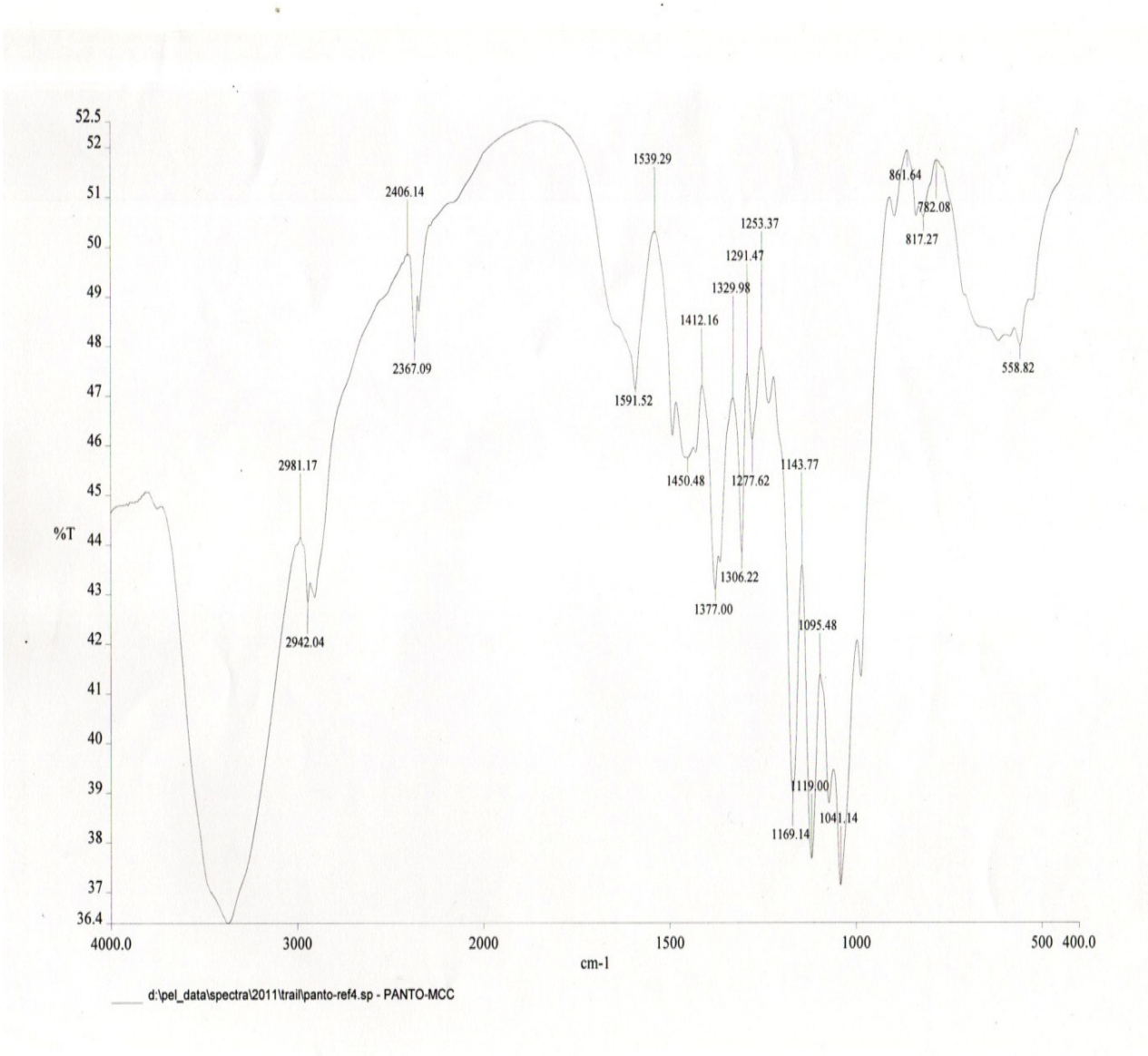


Fig .12- FT-IR Spectra of Pantoprazole Sodium + Aerosil

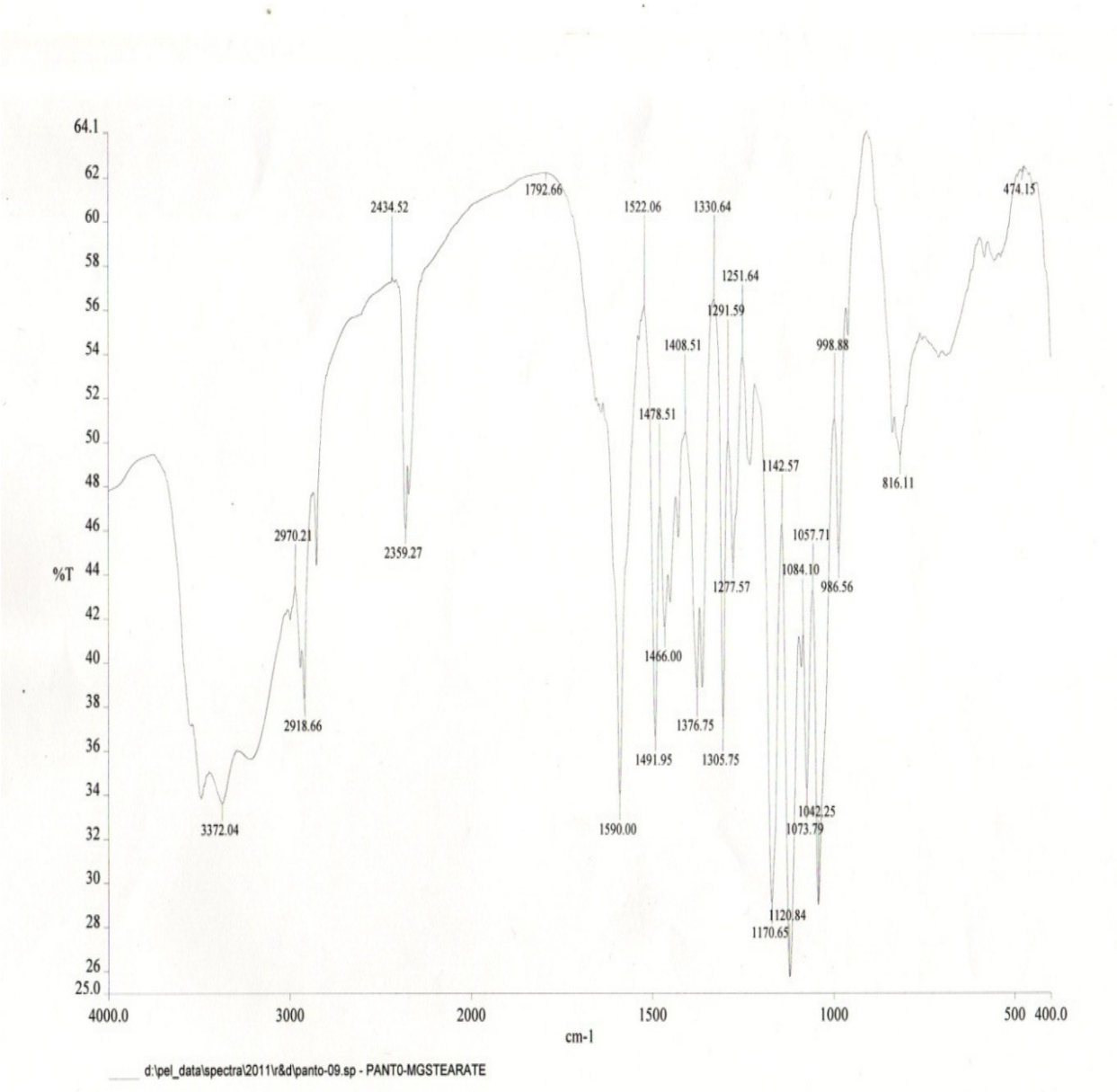
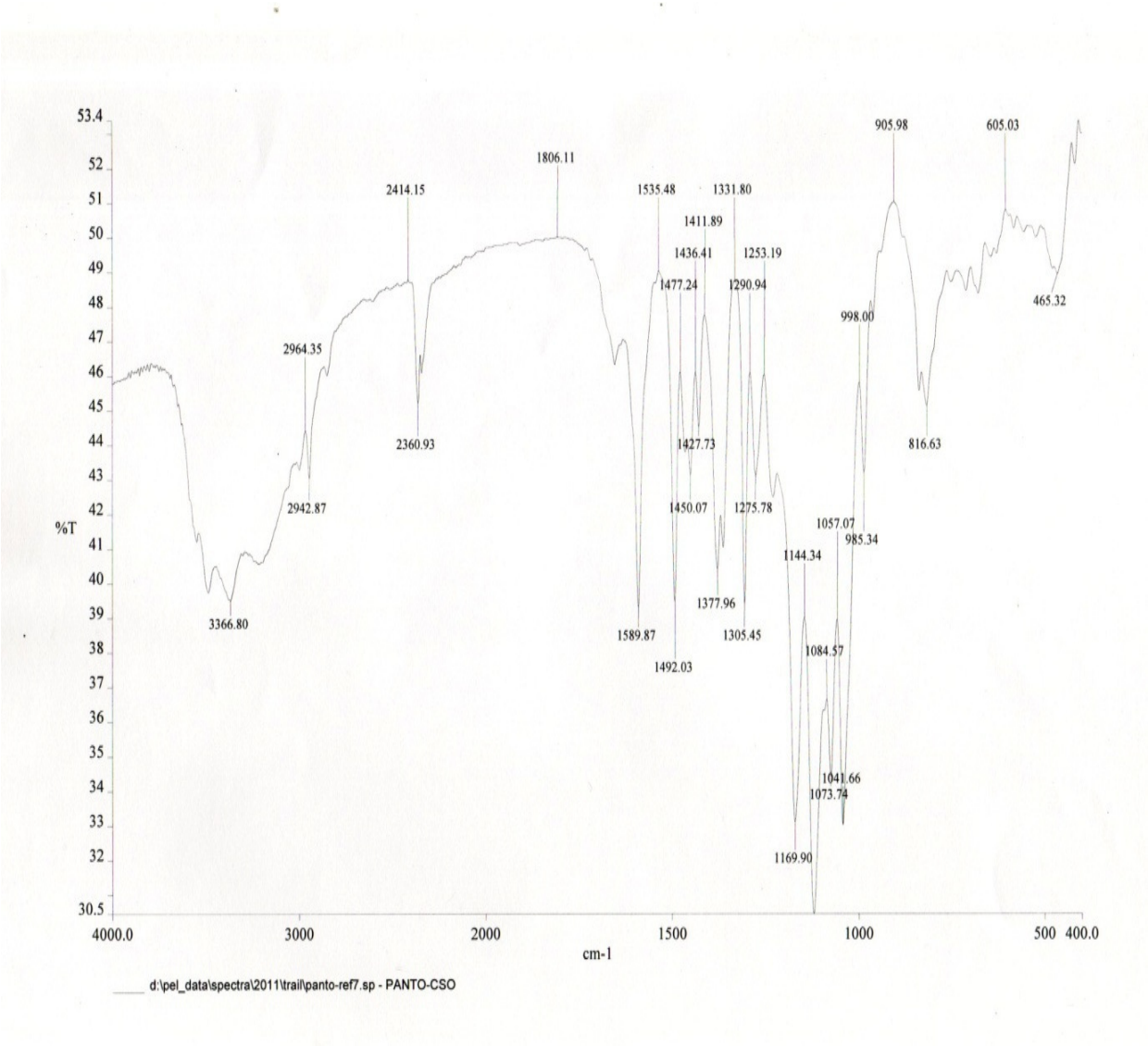


Fig .13- FT-IR Spectra of Pantoprazole Sodium +Magnesium Stearate



Inference: The results of the physical compatibility studies confirmed that there is no characteristic change was observed.

Chemical compatibility was studied with FT-IR.The FT-IR spectrum of Pantoprazole sodium with excipients resembles almost with the spectra of authentic sample of Pantoprazole sodium, that shows the drug and excipients used in formulation were compatible with each other. based on the above proof, further formulations of Pantoprazole sodium with combination of excipients were done.

8.2. Formulation Trials Explanation

TRIAL I

In trial 1 die wall friction was observed to the tablets. in trial 1 the concentration of Mannitol taken was 90.59 mg/unit.

Conclusion:

In further trial the concentration of Mannitol was decreased to 70 mg/unit. MCC pH 112 was included as diluent in the Extra granular portion of the formulation, because of its less moisture content. Aerosil was also included to improve the flow property of the granules.

TRIAL I I

In trial 2 No defect was found during compression . and the core tablets were evaluated for post compression parameters. and were submitted for analysis. All the parameters were found satisfactory for the core tablet. coating was not given for the core tablets because of small scale batch. Further trial has been taken as scale up of trail 2.

TRIAL I I I

In trail 3 the tablets were compressed. And the core tablets were evaluated, all the parameters were found satisfactory. Core tablets were coated with 3 %w/w of seal coating solution with an average weight built up of 3%.these seal coated tablets were further coated with enteric

coating solution with an average weight built up of 8%. Disintegration test was performed for coated tablets, softening & colur change were observed on the tablets in the Acid medium. further weight gain from 8% to10% w/w. and D.T was performed, still softening of tablets were observed in the acid media. further weight built up from 10% to12% w/w showed no sign of softening of the tablets in the acid media during 2 Hours of the study period.

Remarks

Dissolution were Performed, *in-vitro* drug release was not complies with the USP limits.

Conclusion:

So, further trial was taken by increasing the concentration of Crospovidone, to make the tablets disintegrate rapidly.

TRIAL IV

In trial 4 based on the above conclusion, the concentration of Mannitol is further decreased to 65mg/unit and increasing the Crospovidone concentration to 13mg/unit.

Initial dissolution test were performed for the tablets, Coating layer around the tablet showed sticking tendency to the bottom of the bowls, because of that reason the drug was not able to release completely from the tablet and drug release were found to be 68% at the end of 45 min. which was not complies with the USP limits.

TRIAL V

In trail 5 based on the above conclusion, the concentration of Mannitol is still decreased to 63mg/unit and increasing the Crospovidone concentration to 15mg/unit. diethyl phthalate is replaced by triethyl citrate in the enteric coating part, to give better flexibility to the polymer.

Dissolution test was performed and the acid release was found to be 1.6% at the end of 2 hrs. which showed excellent physical resistance to the acid medium compared to other formulations. Altering the media to basic (pH 6.8 phosphate buffer) and the *in-vitro* drug release was found to be 104% at the end of 45 min. which met the criteria outlined in this study. And the tablets were kept for stability studies & they are analysed periodicaly.

Table No 21 - Evaluation of Pre compression Parameters For Granules

Formulation Code	Bulk Density* (g/ml)	Tapped Density* (g/ml)	Compressibility Index (%)*	Hausner's Ratio*	Angle of Repose* (Degree)	Moisture content (%)
F1	0.569±0.002	0.678±0.003	16.08±0.053	1.19±0.005	33.16±0.585	0.63%
F2	0.575±0.003	0.675±0.004	12.16±0.122	1.17±0.002	27.84±0.537	1.00%
F3	0.576±0.003	0.681±0.002	15.79±0.33	1.18±0.005	27.45±0.622	0.85%
F4	0.579±0.001	0.656±0.005	11.73±0.0499	1.26±0.005	26.27±0.448	1.05%
F5	0.574±0.001	0.648±0.001	11.29±0.125	1.12±0.001	24.51±0.333	0.88%

***All the values are mean ±SD, n=3**

Inference: The result of flow properties of prepared granules of various formulations of Pantoprazole Sodium is given in ***TableNo: 21***. Flow properties of the granules, resistance to particle movement can be judged from the bulk density, tapped density, compressibility index, Hausner's ratio and angle of repose. This measurement gives qualitative and quantitative assessment of internal cohesive and frictional force under low levels of external loading as might be applied in mixing and tabletting. The bulk density was found within the range of 0.569 to 0.579 g/ml. The tapped density was found within the range of 0.64 to 0.68 g/cc. using the density data, Hausner's ratio and Compressibility index was calculated. The Hausner's ratio was found within the ranges of 1.12 to 1.19 which indicates better flowability. The Compressibility index was found within the ranges of 11.29 to 16.08, explaining good flow properties. The angle of repose was found using fixed funnel method, which is within the ranges of 24.51 to31.16, indicating better flow properties.

Table No: 22 - Evaluation of Post-compression Parameters For Un Coated Tablets

Formulation Code	Average Weight (mg)	Thickness (mm)*	Friability (%)*	Hardness* (Kg/Cm^2)	Disintegration Time # (Sec)
F1	151.30±1.12	2.75±0.03	0.048±0.001	4.5±0.12	1min50sec ±0.011
F2	151.34±0.67	3.12 ± 0.01	0.046±0.001	5.5±0.17	2min46sec ±0.056
F3	151.84±0.87	3.09±0.03	0.046±0.002	5.3±0.25	2 min7 Sec ±0.018
F4	150.64±1.23	3.34±0.02	0.046±0.002	5.4±0.24	2 min40 Sec ±0.057
F5	151.78±1.18	3.36±0.01	0.036±0.002	5.6±0.16	2 min38 Sec ±0.021

***All the values are mean ±SD, n=3**

#All the values are mean ±SD, n=6

Table No: 23 - Evaluation of Post-compression Parameters for Enteric Coated Tablet

Formulation Code	Average Weight (mg)	Thickness (mm)*	Hardness* (Kg/Cm^2)	Disintegration Time #	Drug Content (%)*
F3	173.42±1.65	3.39 ± 0.03	6.2± 0.11	128 min 7 sec ±0.05	101.37± 0.77
F4	171.0±1.56	3.45 ± 0.02	6.4± 0.12	126min13sec ±0.08	100.86±0.658
F5	172.36±1.32	3.68 ± 0.01	6.7± 0.11	125min63sec ±0.03	103.47±0.605

***All the values are mean ±SD, n=3**

#All the values are mean ±SD, n=6

Inference :

- All the tablets hardness were found to be in the range of 2-8 kg/cm2 in all the formulations indicating good mechanical strength.
- In all the formulations the friability value is less than 1 % giving an indication that tablets formulated are mechanically stable during handling & transporting.
- The thickness values were found to be with in the limits This may be due to the adjustments of upper and lower punch during compression process.
- The percentage weight variation was with in the USP limits.
- The disintegration of different formulations complies with the pharmacopeia specifications.
- The drug content was known by performing assay and it was found to be 90-110% and it was with in the limits .

8.3. Innovator Product Characterization :

Table No- 24

Brand Name	Protonix	
Label Claim	Each protonix delayed release tablets contains 45.1 mg of pantoprazole sodium sesquihydrate equivalent to 40mg of pantoprazole .	
Manufacturer	Wyeth pharmaceuticals inc., Philadelphia	
Physical Parameters	Description	40mg yellow, oval biconvex shaped tablets plain on one side and imprinted with Protonix (brown ink) on other side.
	Thickness	4.5 mm
Packaging details	30 tablet in blister strips	
Storage	Store at room temperature between 59-86^{0}F (15-30^{0}C)	
Shelf life	3 years	
In active ingredient	Calcium stearate, Crospovidone, ferric oxide, hypromellose, mannitol, methacrylic acid copolymer, polysorbate 80, povidone, propylene glycol, sodium carbonate, titanium dioxide, and triethyl citrate.	

Table No :25 - Standard curve for Pantoprazole sodium in 0.1N Hcl

Concentration (mcg/ml)	Absorbance at 305nm
0	0
1	0.041
2	0.078
3	0.116
4	0.153
5	0.189

Fig.14 – Calibration curve for Pantoprazole Sodium in 0.1N HCl (pH 1.2)

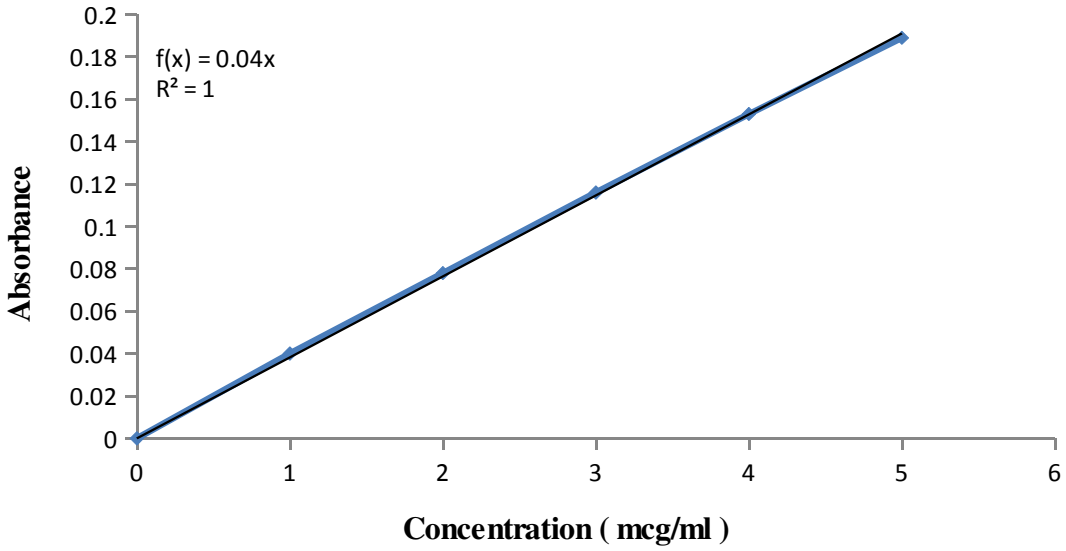
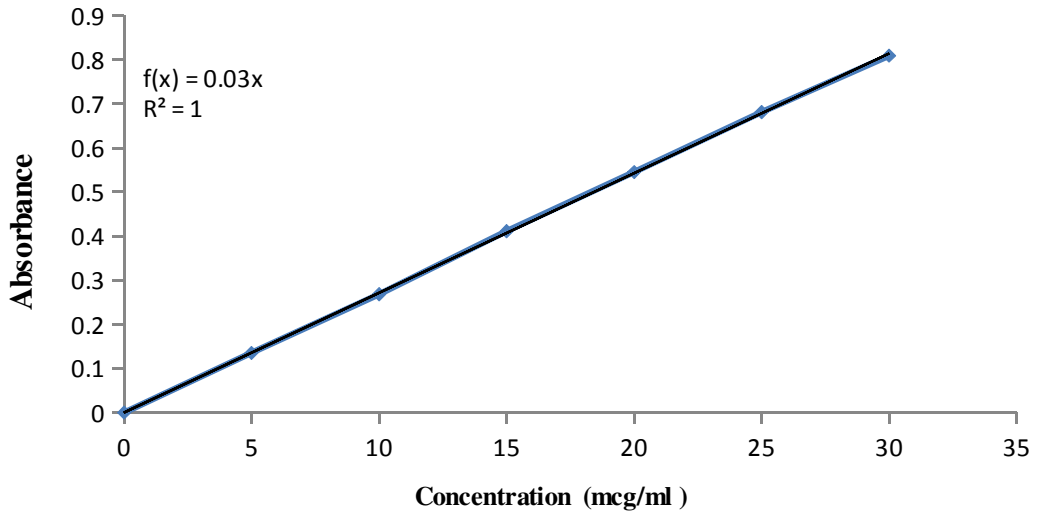


Table No :26 - Standard curve for Pantoprazole sodium in pH 6.8 Phosphate buffer

Concentration (mcg/ml)	Absorbance at 288nm
0	0
5	0.135
10	0.268
15	0.411
20	0.545
25	0.681
30	0.809

Fig.14 – Calibration curve for Pantoprazole Sodium in pH 6.8 Phosphate buffer



TableNo : 27 - *In-Vitro* Dissolution Profile of Enteric Coated Tablets :

Dissolution Media	**Sampling time**	**Cumulative% drug release in different trials**		
		F3	**F4**	**F5**
Simulated gastric fluid (0.1 HCL)	2 Hrs	2.57±0.534	2.08±0.483	1.6±0.501
Simulated Intestinal Fluid ($6.8p^H$ Phosphate buffer)	5 Min	4.89±0.474	2.44±0.554	4.34±0.333
	10 Min	7.55±0.319	5.10 ±0.319	9.77±0.672
	15 Min	38.79±0.486	29.03±0.338	40.37±0.589
	20 Min	41.38±0.665	72.6±0.366	75.28±0.383
	30 Min	52.91±0.653	64.97±0.662	87.19±0.226
	45 Min	63.60±0.597	68.32 ±0.658	104.53±0.550

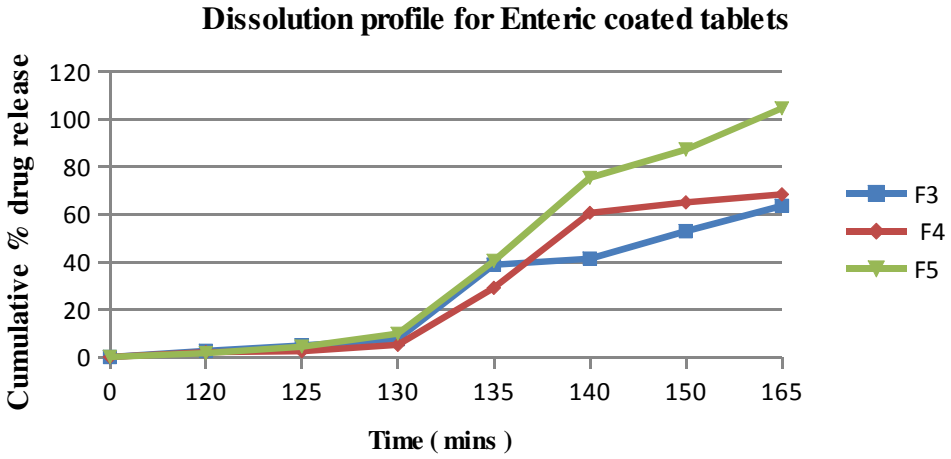
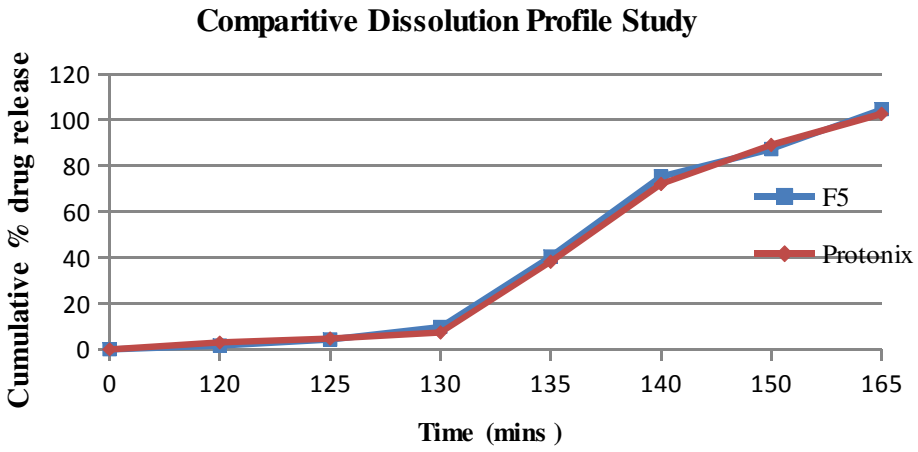


Table No :28 – Comparative Dissolution Profile Study with the Innovator Product

Dissolution Media	Sampling time	Cumulative % Drug Release		f1	f2
		F5	Protonix		
Simulated Gastric fluid		1.59	2.17	4.2	81.7
Simulated intestinal fluid (6.8 PH Phosphate buffer)	5 Min	4.34	4.67		
	10 Min	9.77	7.31		
	15 Min	40.37	38.11		
	20 Min	75.28	71.98		
	30 Min	87.19	88.95		

	45 Min	104.53	102.55		

Fig. 16



Inference: The f_2 value of 81.7 indicates that the two products are similar in *in vitro* performance.

8.4. Stability Studies

Accelerated stability studies were carried out at 40˚C/75% RH for about 3 months in stability chamber for formulation F5.

Table No - 29

Parameters	40˚C ± 2˚C / 75% RH ± 5% RH			
	Initial	1st month	2nd smonth	3rd month
Description	*	*	*	*

Average weight (mg)	172.36±1.32	172.38±1.14	172.42±1.67	172.43±1.37
Hardness (kg/cm^2)	6.7±0.208	6.5±0.252	6.9±0.153	6.9±0.15
Thickness (mm)	3.68±0.02	3.66±0.015	3.68±0.03	3.68±0.015
Disintegration time	125min 63sec ± 0.036	127min 7sec ± 0.076	128min 16sec ± 0.043	127min 32 sec ± 0.052
Assay (%)	103.47	103.18	102.58	102.25

*Pale yellow,Round enteric -coated tablet

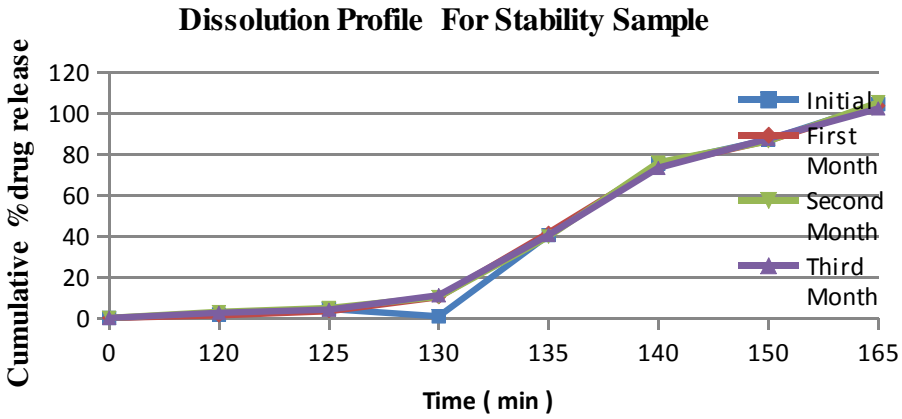
Inference: At 40˚C ± 2˚C / 75% RH ± 5% RH, for the first month and second month no physical changes were observed. Average weight gradually increased every month, this may be due to increase in moisture content. Assay data showed no significant variation during stability studies.

Sampling Time points (min)	**Storage condition 40˚C ± 2˚C / 75% RH ± 5% RH**			
	Initial	**1st month**	**2nd month**	**3rd month**
SIMULATED GASTRIC FLUID (0.1 N HCL)				
2 Hrs	1.59	1.67	1.79	1.56
SIMULATED INTESTINAL FLUID (p^H 6.8 PHOSPHATE BUFFER)				
5 Min	4.34	3.33 ± 0.497	4.89 ± 0.467	3.99 ± 0.419
10 Min	9.77	10.19 ± 0.365	10.20 ± 0.36	11.08 ± 0.42
15 Min	40.37	41.62 ± 0.695	39.69 ± 0.674	40.58 ± 0.646
20 Min	75.28	74.40 ± 0.37	75.94 ± 0.72	73.29 ± 0.409

30 Min	87.19	86.75 ± 0.659	86.31 ± 0.32	87.63 ± 0.59
45 Min	104.53	103.74 ± 0.442	105.42 ± 0.499	102.41 ± 0.173

Table No: 30 - Stability Study Dissolution Data for Sample

Fig. 17



Inference: Optimized formulation **F_5** ,was kept for stability studies and observed that drug content, and in vitro dissolution profile are remained with out any significant changes, at the end of 3rd month Hence it is concluded that the formulated Enteric coated tablets are stable and the data obtained could be used to predict the shelf life of the product.

9. CONCLUSION

Preformulation studies has been performed to study the nature of API and compatibility of API with excipients by physical observation and FT-IR studies. The results showed that there was no interaction between API and all the excipients selected.

Delayed release enteric coated tablets of Pantoprazole sodium. were successfully formulated by wet granulation method using the selected excipient quantities. The formulated tablets were evaluated for both pre-compression and post-compression parameters as per requirements of standards. And The results were complied with the pharmacopoeia specification.

From among the entire optimized batches, formulation F_5 has been selected for comparative dissolution profile study against marketed sample PROTONIX. since it provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. The results showed an $\mathbf{f_2}$ value of 81.7, thus it indicates that the two products were similar in terms of in vitro drug release.

The most satisfactory formulation has been subjected to Accelerated stability studies as per ICH guidelines. the results of stability studies showed no significant changes in the physical parameters of the tablets, drug content and *in-vitro* dissolution pattern until the end of 3 months from initial values. Hence the formulation is considered stable and the data can be employed for prediction of shelf life of the product.

Future scope

The present work may explore the following aspects in the future which may become a valuable assets in the field of pharmaceutical science.

- Manufacture Acid labile drug into formulations as cost effective & stable pharmaceutical compositon.
- The invitro studies can be extended to invivo studies by leading to a final conclusion of a sucessful formulation which can be marketed there after.

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