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A RESEARCH OF FORMULATION AND EVALUATION OF ESOMEPRAZOLE ENTERIC COATED TABLETS USING CELLULOSE ACETATE PTHALATE

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ABSTRACT

Oral ingestion is the predominant and most preferable route for drug delivery mainly due to their convenience of administration, patient compliance and their suitability for delivery of drugs for systemic effects. Following oral administration most drugs have to be absorbed into the blood to produce therapeutic action. However certain drugs have a "region-specific absorption" or absorption window. Enteric-coated tablets with a low core pH will have longer *in vivo* disintegration time, due to the suppression of ionization of enteric coating polymers in the acidic environment. As a result, tablets with a high proportion of an acidic therapeutic agent or acidic excipients would probably exhibit retardation in dissolution if directly enteric coated. Considering the dissolution in general and stability in particular, the pH of the core tablet was basified using sodium bicarbonate (50 mg). Three different core tablets (C1- C3) of Esomeprazole (40 mg) were prepared with varying concentration of super disintegrants crospovidone (CP), Sodium starch Glycolate (SSG), croscarmellose sodium (CCS), Dissolution analysis was employed to assess the effect of the enteric coat composition and coverage levels on the release of the formulations. *In vitro* drug release was carried out for formulations with CAP 2%, 3%, 4% (C3F1-C3F3) in 0.1 N HCl for 2 h followed by phosphate buffer pH 6.8 for 60mins. Compares the dissolution profile of enteric coated Esomeprazole tablets prepared using CAP (2%, 3%, 4%) in phosphate buffer pH 6.8. It is evident that (C3F3) demonstrated excellent physical resistance to the acid medium with the acid uptake value 1.22±0.06 in 2 hrs. However, formulations which were enteric coated 2% and 3% CAP fail the disintegration test carried out at pH 1.2. The study indicates that 4% CAP suitable for enteric coating. It provides greater protection to the core under acidic

condition while at the same time show the fastest drug release under intestinal pH. The optimized formulation was C3F3.

INTRODUCTION

Oral drug delivery

Oral ingestion is the predominant and most preferable route for drug delivery mainly due to their convenience of administration, patient compliance and their suitability for delivery of drugs for systemic effects. Following oral administration most drugs have to be absorbed into the blood to produce therapeutic action. However certain drugs have a "region-specific absorption" or absorption window. The region specific absorption may be due to various reasons, such as poor solubility at different pH values, poor stability in some GI regions, presence or absence of absorptive or efflux transporters, and presystemic metabolism in the gut wall.[1]

The oral route is the most popular route to administer drugs. However, some factors should be considered when looking to administer drugs via this route.

In particular the transit time in the gastrointestinal tract may vary considerably
The pH conditions in the gastrointestinal tract also vary considerably, from a low pH in the stomach (1.5–2 in the fasted state to around 5 in the fed state) to a higher pH in the small and large intestine. The pH in the small intestine varies from 4 to 7, with an average value of approximately 6.5. This may affect stability and will influence the degree of ionization of ionizable drugs which in turn will influence their absorption (unionized forms of drugs are usually taken up better than ionized forms of the same drug) and solubility (unionized forms are usually less soluble than ionized forms of the same drug).

1.1 Anatomy and physiology of stomach and intestine

1.1.1 The Stomach

The stomach is a hollow muscular organ, located below the diaphragm and above the small intestine that receives and holds masticated food to begin the next phase of digestion. It produces acid and various enzymes that break down food into simple substances. The inside wall of the stomach is protected from the acid and enzymes by a mucous lining.

With a volume of as little as 50 ml when empty, the adult human stomach may comfortably contain about a liter of food after a meal, or uncomfortably as much as 4 liters of liquid.

Ulcers are caused when there is an imbalance between the digestive juices produced by the stomach and the various factors that protect the lining of the stomach. Symptoms of ulcers may include bleeding. On rare occasions, an ulcer may completely erode the stomach wall.

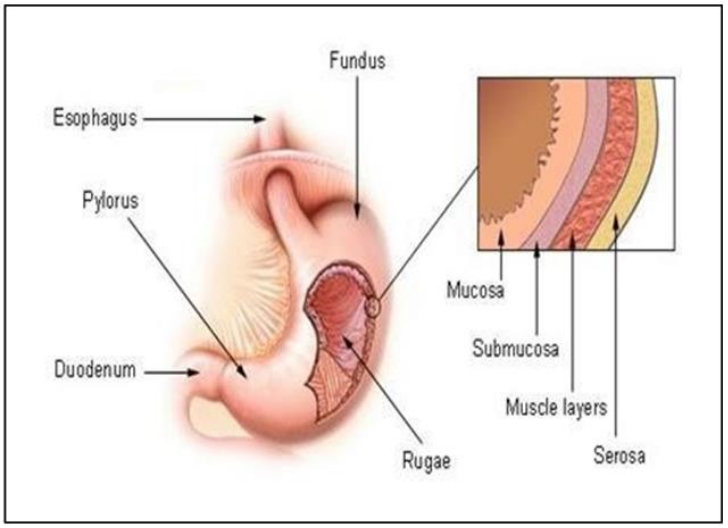

Figure 1.1: Schematic diagram of stomach.

- major cause of stomach ulcers is the bacteria called *Helicobacter pylori* Goodman and Gilman). Treatment regimens for ulcers caused this bacterium usually include medications to suppress the stomach acid as well as antibiotics to eradicate the infection.

The mucous layer lining the lumen is fairly effective at protecting the stomach wall, it is not impervious. Cells of the mucosa are constantly being damaged, and have an average lifespan of only a few days.

Pepsinogen is produced by chief cells and HCl by parietal cells deep in each gastric pit. They are forced into the lumen before much pepsinogen can be converted to pepsin. A mucus plug prevents "backwash" into the pit.

Diseases or disorders of the stomach affecting feeding can include: dyspepsia, stomach ache, chronic vomiting syndrome (CVS) **, peptic gastric ulcer, achlrohydria, hypochlorhydria, hyperchlorhydria, linitis plastica or Brinton's disease (a form of stomach cancer), Zollinger-Ellison syndrome (extremely rare in children), gastroparesis**, gastroenteritis**, borborygmus, and GERD*.

Most common GI diseases

- Erosive esophagitis (EE) associated with gastroesophageal reflux disease (GERD)

- Long – term maintanance of healing of erosive esophagitis
- Pathological hypersecretory conditions including zollinger-ellison syndrome
- Chronic use of anti-inflammatory medications, commonly referred to as NSAIDs (nonsteroidal anti-inflammatory drugs), including aspirin. Cigarette smoking also is an important cause of ulcer formation as well as failure of ulcer treatment.

NSAIDs are medications used for the treatment of arthritis and other painful inflammatory conditions in the body. Aspirin, ibuprofen (Motrin), naproxen (Naprosyn), and etodolac (Lodine) are a few of the examples of this class of medications.

Peptic ulcer

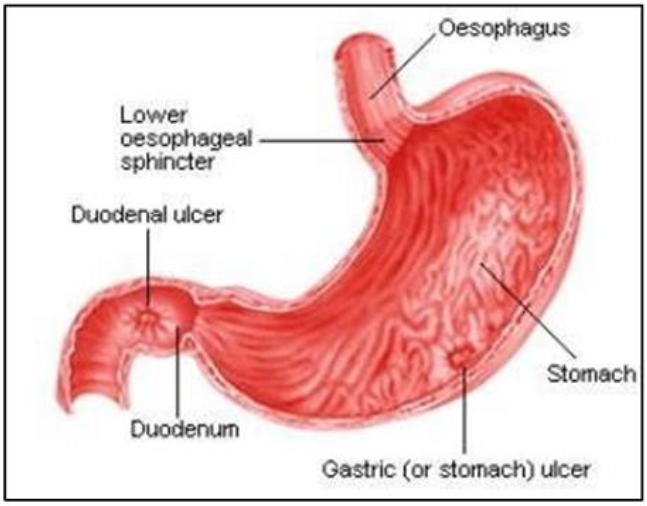

Figure 1.4: schematic diagram of peptic ulcer.

A peptic ulcer is a hole in the gut lining of the stomach, duodenum, or esophagus. A peptic ulcer of the stomach is called a gastric ulcer; of the duodenum, a duodenal ulcer; and of the esophagus, an esophageal ulcer. An ulcer occurs when the lining of these organs is corroded by the acidic digestive juices which are secreted by the stomach cells. Peptic ulcer disease is common, affecting millions of Americans yearly.

H. pylori is the major factor in the development of gastritis and ulcers. NSIADS (non- steroidal anti-inflammatory drugs), including aspirin and cigarette smoking is also an important cause of ulcer formation.

Table 1.1: Relationship between pH profile and transit times in human GIT.

Region	pH (Fasted)	pH (Fed)	Transit time
Esophagus	1-5	-	0.25-3hrs
Stomach	1.7 (1.4 – 2.1)	5	1-5 hrs
Small intestine	5.5-7.8	5.5	3-4hrs
Duodenum	4.6 (2.4 –6.8)	4.5 – 5.5	>5 hrs
Jejunum	6.1 (6.0 – 7.0)	4.5 – 5.5	1 -2 hrs
Ileum	6.5	6.5	2 -3 hrs
Colon	8	8	15 -48 hrs

1.2 Drug Profile

Drug name[21] Esomeprazole

Mechanism of action - Esomeprazole is a proton pump inhibitor that suppresses gastric acid secretion by specific inhibition of the H^+/K^+-ATPase in the gastric parietal cell. By acting specifically on the proton pump, Esomeprazole blocks the final step in acid production, thus reducing gastric acidity.

Use- In peptic ulcer, in gastro esophageal Reflux Disease, Zollinger -Ellison Syndrome

Physiochemical properties

Description - White fine powder

Chemical name - 5-methoxy-2-[(S)-(4-methoxy-3,5-dimethylpyridin-2-yl)methanesulfinyl]-1H-1,3- benzodiazole

Molecular formula - $C_{17}H_{19}N_3O_3S$

Molecular weight - 345.416

Solubility - Freely soluble in ethanol and very slightly soluble in water

Category - Proton pump inhibitor.

PHARMACOKINETIC PROPERTIES

(t_{max}) - 2.8h (oral)

Bioavailability - 85% (oral) **Plasma protein binding -** 97% **Volume of distribution -** 16 L.

Route of Metabolism - Esomeprazole is Completely Metabolized by The cytochrome P450 system via a CYP2C19 and CYP3A4.

Route of Elimination - Urine (80%), Feces (20%)

Biological half life- 1-1.5 hours

DRUG INTERACTION

Diazepam - Inhibit Oxidation.

Phenytoin - Inhibit Oxidation.

Ketoconazole - Decrease absorption.

Itraconazole - Decrease absorption

Contraindications

Known hypersensitivity to any component of the formulation or to substituted benzimidazoles.

Warnings and precautions

- Symptomatic response does not preclude presence of gastric malignancy
- Atrophic gastritis has been noted with long-term therapy

Adverse reactions

The most frequently occurring adverse reactions are as follows

- For adult use (>2%) are headache, diarrhea, nausea, abdominal pain, vomiting, flatulence, dizziness, and arthralgia.
- For pediatric use (>4%) are URI, headache, fever, diarrhea, vomiting, rash, and abdominal pain.

3.2 EXCIPIENT PROFILE

3.2.1 Sodium Starch Glycolate[22]

Chemical Name : Sodium carboxymethyl starch.

Empirical Formula : Sodium salt of carboxymethyl ether of starch. Molecular Weight : 98.033 g/mol.

Glycolate Functional Category : Tablet and capsule disintegrant.

Applications : Disintegrant in capsule and tablet formulations. The usual concentration employed in a formulation is between 2% and 8%.

Description : White to off-white, odorless, tasteless, free-flowing powder. Density (bulk) : 0.756 g/cm^3.

Density (tapped) : 0.945 g/cm^3. Density (true) : 1.56 g /cm^3.

Solubility: Practically insoluble in methylene chloride. It gives a translucent suspension in water.

3.3 Triethyl citrate[23]

Chemical Name : 2-Hydroxy-1, 2, 3 propanetricarboxylic acid triethyl ester Empirical Formula : $C_{12}H_{20}O_7$

Molecular Weight : 276.29

Functional Category : Plasticizer; solvent.

Application : It provides flexibility to coated film generally used in capsule, Tablets, beads, and granules for immediate release sustained and enteric coating. Sometimes used for taste masking.

Description : Triethyl citrate is a clear, viscous, odorless, and practically colorless, hygroscopic liquid.

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

Incompatibilities: Triethyl citrate is incompatible with strong alkalis and oxidizing materials.

3.4 Crospovidone[24]

Chemical Name: 1-Ethenyl-2-pyrrolidinone homopolymer Empirical Formula : $(C_6H_9NO)_n$

Molecular Weight: 111.143 g/mol

Functional Category: Tablet disintegrant.

Applications: Crospovidone is a water-insoluble tablet disintegrant and dissolution agent used at 2– 5% concentration in tablets prepared by direct compression or wet- and dry-granulation methods.

Description: Crospovidone is a white to creamy-white, finely divided, freeflowing, practically tasteless, odorless or nearly odorless.

Density: 1.22 g/cm^3

Solubility: P0ractically insoluble in water.

Storage Conditions: Since crospovidone is hygroscopic, it should be stored in an airtight container in a cool, dry place.

Incompatibilities: When exposed to a high water level, crospovidone may form molecular adduct with some materials.

3.5 Magnesium stearate[25]

Chemical Name: Octadecanoic acid magnesium salt Empirical Formula : $C_{36}H_{70}MgO_4$

Molecular Weight: 591.24

Structural Formula: $[CH_3 (CH_2)_{16}COO]_2Mg$ Functional Category : Tablet and capsule

Applications: Magnesium stearate is primarily used as a lubricant in capsule and tablet manufacture at concentrations between 0.25% and 5.0% w/w.

Description: Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, The powder is greasy to the touch and readily adheres to the skin.

Density (bulk): 0.159 g/cm^3

Density (tapped): 0.286 g/cm^3

Density (true): 1.092 g/cm^3

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

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

Incompatibilities: Incompatible with strong acids, alkalis, and iron salts. Avoid mixing with strong oxidizing materials.

3.6 Corn starch[26]

Chemical Name: Corn (maize) starch

Empirical Formula: $(C_6H_{10}O_5)_n$ where n = 300–1000. Functional Category: Directly compressible tablet excipient;

disintegrant; tablet and capsule diluent.

Applications: Corn starch can be used in tablets to improve compressibility, flowability and disintegration properties.

Description: Corn starch occurs as a white or almost white odorless 12–18% of corn (maize) starch. It is a free-flowing powder owing to its spherical structure.

Density (bulk): 0.57 g/cm^3

Density (tapped): 0.68 g/cm^3

Density (true): 1.478 g/cm^3

Solubility: Solubility Partially soluble in cold water Storage Conditions : Starch should be stored in an airtight containerin a cool, dry place.

Incompatibilities: Starch is incompatible with strongly oxidizing substances. Colored inclusion compounds are formed with iodine.

3.7 Sodium carbonate[27]

Chemical Name : Sodium carbonate anhydrous.

Empirical Formula : Na_2CO_3

Molecular Weight : 105.99.

Functional Category : Alkalizing agent; buffering agent.

Applications : Sodium carbonate is used as an alkalizing agent in injectable, ophthalmic, oral, and rectal formulations. As an alkalizing agent, concentrations of sodium carbonate between 2% and 5% w/w are used in compressed tablet formulations. As an effervescent agent, concentrations up to 10% w/w can be used.

Description: Sodium carbonate is a white, almost white, or colorless inorganic salt, produced as crystalline powder or granules. It is hygroscopic and odorless with an alkaline taste.

Solubility: Freely soluble in water, glycerin; practically insoluble in ethanol (95%).

Storage Conditions: Sodium carbonate converts to the monohydrate form when in contact with water and produces heat. Store in airtight containers.

Incompatibilities : Sodium carbonate decomposes when in contact with acids in the presence of water to produce carbon dioxide and effervescence.[28]

PREFORMULATION STUDY

6.1 PHYSICAL APPEARANCE

Small quantity of drug was taken on butter paper and viewed. The drug powder was examined For physical a property like colour, odor and physical state.

6.2 MELTING POINT STUDY: Melting point is determined by capillary tube method using digital melting point apparatus.

Table: Melting point study.

Sample	Specification	Observation
Famotidine	174°C	174 -176°C

It is one of the parameter to judge the purity of drug .In case of pure chemical or drug.[39,43]

6.3 SOLUBILITY OF DRUG

Solubility study

Table 6: solubility study of Famotidine in different solvent.

S.No.	Solvent used	Remarks
1	**Methanol**	Freely soluble
2	**Phosphate buffer pH 7.4**	Soluble
3	**Simulated Intestinal Fluid pH 6.8**	Soluble

4	**Phosphate buffer pH 6.8**	Soluble
5	**Simulated Gastric Fluid pH 1.2**	Less soluble
6	**0.1 N HCl**	Soluble
7	**Distilled water**	Soluble

6.4 DETERMINATION OF λ_{max} AND PREPARATION OF STANDARD CURVE

Determination of ƛ max and preparation of standard curve

6.4.1 Calibration curve of Esomeprazole

A standard curve of Esomeprazole was constructed using 0.1N HCl (1-10 µg/ml) and phosphate buffer 6.8 pH. Various concentrations 2, 4, 6, 8, 10, 15, 20, 25 and 30 µg/ml was prepared.

The absorbance of prepared concentrations was measured at **301nm** by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented in figure.

Table 6.2: Standard curve of Esomeprazole in 0.1N HCl (pH 1.2).

Concentration (µg/ml)	Absorbance
0	0
1	0.102
2	0.218
3	0.300
4	0.408
5	0.457
6	0.562
7	0.638
8	0.743
9	0.855
10	0.924

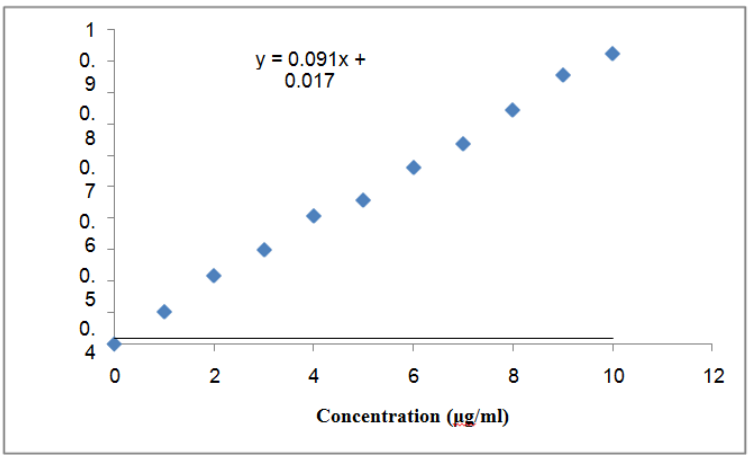

Figure 6.3: Standard curve of Esomeprazole in 0.1N H.

Cl (pH 1.2)

oncentration (µg/ml)	Absorbance
0	0
2	0.074
4	0.136
6	0.196
8	0.262
10	0.318
15	0.48
20	0.64
25	0.794
30	0.92

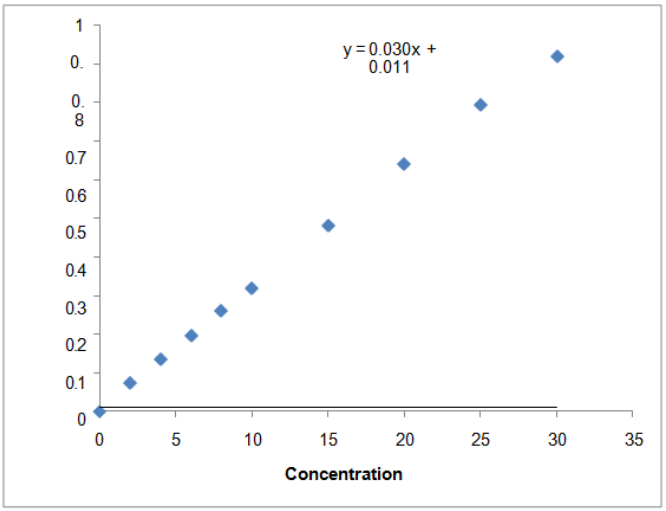

Figure 6.4: Standard curve of Esomeprazole in phosphate buffer pH 6.8.

6.5 Partition coefficient

Partition coefficient studies are carried out to find the extent of drug transfer in the aqueous and the other non aqueous layer. This type of phenomenon usually is done to obtain the drug concentration in the other layer. The partition coefficient value of famotidine is shown in table.

Table no. 8: Partition coefficient values of drug.

S.No.	Medium	Partition coefficient (LogP)
1	Octanol : water	613.75

6.6 Drug excipient compatibility study

Table No. 9: Drug excipient compatibility study.

S. No.	Composition	Absorbance at 301nm
1	Drug	0.6381
2	Drug + polymer	0.6401
3	Polymer + polymer	0.5512

Result: the drug and polymer are compatible mutually.

EXPERIMENTAL WORK

- **Preparation of standard curve**

A standard curve of Esomeprazole in suitable medium was prepared by plotting the concentrations on x-axis and absorbance values on y-axis.

Procedure for preparation of standard curve of Esomeprazole

Accurately weighed amount of 10mg of Esomeprazole was taken in a 10ml volumetric flask with volume make up distilled water, which constitutes the primary stock solution of 1mg/ml. by further diluting this stock solution suitably with distilled water various concentrations like 2, 4, 6, 8, 10, 15, 20, 25 and 30µg/ml were prepared. These solutions were checked for their absorbance using UV-visible spectrophotometer at λmax 301 nm against phosphate buffer pH 6.8 as blank and a standard graph was plotted.

- **Formulation of core tablet of Esomeprazole**
- **Formulation design**

Esomeprazole core tablets were prepared using direct compression technique. Direct compression technique is a convenient method but the excipients used in this method are costlier when compared to the excipients used in wet granulation technique.

Different formulations of Esomeprazole were designed to be prepared by direct compression method using three super disintegrants (sodium starch glycolate, crospovidone, croscarmellose) keeping all other ingredients constant.

Table 5.1: Formulation of Esomeprazole core tablets.

Formulation code	Esomeprazole	CCS	SSG	CP	MCC pH101	Starch (corn)	Magnesium stearate	Sodium carbonate	Total weight
C1	40	4	-	-	92	60	2	2	200mg
C2	40	-	4	-	92	60	2	2	200mg
C3	40	-	-	4	92	60	2	2	200mg

* Total batch size 50 Tablets

- **Procedure**

Esomeprazole and all other ingredients listed in Table 5.1, except magnesium stearate, were passed through sieve no 60 to get uniform size particles and weighed accurately. Finally, magnesium stearate [passed through a 60-mesh] was introduced to the powder mixture. The

final mixture was shaken manually for 5-10 min in a plastic bag. This powder was passed through the hopper of rotary tabletting machine and punched into tablets using 8mm. the process is similar for all core formulations, which are prepared by direct compression technique.

- **Evaluation of the powder blend**
- **Angle of repose**

The angle of repose of powder blend was determined by the funnel method. The height of the funnel was adjusted in such a way that the tip of the funnel just touched the apex of the heap of the powder blend (Patel *et al.,* 2010). The diameter of the powder cone was measured & angle of repose was calculated using the following equation:

$$\tan \theta = h/r$$

Where, h & r are the height & radius of the powder cone respectively.

Table 5.2: Angle of Repose Values.

S. No.	Angle of Repose	Properties
1	<25	Excellent
2	25-30	Good
3	30-40	Passable
4	>40	Poor flow

- **Bulk density**

Both loose bulk density (LBD) & tapped bulk density (TBD) were determined. A quantity of 2 g of powder from each formula, previously lightly shaken to break any agglomerates formed, was introduced into a 10 ml measuring cylinder. After the initial volume was observed, the cylinder was allowed to fall under its own weight onto a hard surface from the height of 2.5 cm at 2 second intervals. The tapping was continued until no further change in the volume was noted. LBD & TBD were calculated using the following formulas

LBD = weight of the powder / volume of the packing

TBD = weight of the powder / tapped volume of the packing

- **Compressibility Index**

The Compressibility Index of the powder blend was determined by Carr's compressibility index. The formula for Carr's Index is as below:

Carr's Index (%) = [(TD-BD) x100] / TD

Table 5.3: Carr's Index Values.

S. No.	Carr's Index	Properties
1	5-12	Free flowing
2	13-16	Good
3	18-21	Fair
4	23-35	Poor
5	33-38	Very poor
6	>40	Extremely poor

- **Hausner's ratio**

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is Hausner's ratio. It is calculated by the following equation.

$$H = \rho T / \rho B$$

Where ρT = tapped density, ρB = bulk density

- **Evaluation of tablets**
- **Weight variation test**

Twenty tablets were randomly selected from each formulations and their average weight was calculated using digital balance. Individual weight of each tablet was also calculated using the same and compared with the average weight. The mean ± S.D. were noted. The tablets meet USP specifications if no more than 2 tablets outside the percentage limit and if no tablet differs by more than 2 times the percentage limit.

Table 5.4: As per USP specifications, weight variation tolerances for uncoated tablets.

Average weight of tablets (mg)	Maximum % difference allowed
<130	± 10%
130-323	± 7.5%
<323	± 5%

The USP limit for weight variation in case of tablet weight between 107.3-124.7 mg is ± 7.5%.

- **Thickness measurement**

The tablet thickness should be controlled within a ± 5% variation of standard value.

- **Hardness**

The tablet hardness of different formulations was measured using the Monsanto hardness

tester. The force of fracture is recorded, and the zero force reading is deducted from it.

- **Friability**

The test is performed using a laboratory friability tester Roche friabilator. 20 tablets were weighed and placed in a plastic chambered friabilator attached to a motor, which revolves at a speed of 25rpm, dropping the tablets from a distance of 6 inches with each revolution. The tablets were subjected to 100 revolutions for 4 minutes. After the process, these tablets were dedusted and reweighed. Percentage loss of tablet weight was calculated. The limit for friability is NMT 1%.

$$\% \text{ Friability} = (W_1 - W_2) \times 100/W_1$$

Where,

W1=initial weight of the 20 tablets before testing W2=final weight of the 20 tablets after testing.

- **Disintegration test**

The disintegration test was performed in disintegration test apparatus by taking 1 tablet in each of the six tubes of the basket (Amitava roy *et al.*, 2009). The apparatus was operated using phosphate buffer pH 6.8 at 37 ± 0.5ºC temperature.

- ***In vitro* Release Studies**

Dissolution Test: The dissolution test was conducted using simulated intestinal fluid (phosphate buffer, pH-6.8) as dissolution medium for uncoated tablets (Saffar Mansoor *et al.*, 2007). Using simulated intestinal fluid 900 ml of phosphate buffer Ph 6.8 maintained 37 ± 0.5°C and placed in the vessel Then, Esomeprazole tablets were placed in six baskets, one in each basket and stirrer was rotated at 100 rpm for 1 hr. After 10, 20, 30, 40, 50 and 60 min, sample of 5 ml was pipetted out and same volume of fresh phosphate buffer was added to keep volume of the dissolution medium constant. Absorbance was measured at 301nm and calculation was done using Lambert beer's law. Similarly, the absorbance of known concentration of standard solution of Esomeprazole was measured and percent drug release was calculated.

Statistical analysis*:* The results are expressed as mean and standard deviation.

- **Formulation of enteric coated tablets of Esomeprazole**
- **Formulation design**

Different formulations of Esomeprazole enteric coated tablets were prepared using Cellulose acetate phthalate in different ratios keeping core tablet (C3) constant. They are assigned with formulation codes.

Table 5.5: Formulation codes of Esomeprazole enteric coated tablets.

Polymers	% Weight gain	FORMULATION CODE
	5%	C3F1
Cellulose acetate	10%	C3F2
Phthalate	15%	C3F3
	20%	C3F4

General formulation

A formulation is set using following ingredients

Coating polymer	-	Cellulose acetate phthalate
Solvent	-	Isopropyl alcohol, Dichloromethane, Water
Plasticizer	-	Triethyl citrate
Anti adherent	-	Talc
Colorant	-	Tatrazine

Steps involved in the preparation of enteric coated tablets

1. Preparation of core tablets
2. Sub coating of core tablets
3. Enteric coating of sub coated tablets

- **Sub coating of core tablets**

Barrier coating was given to prevent the interaction of drug and excipients with enteric coating polymers as the drug is acid labile.

- **Formulation of Esomeprazole subcoated tablets using HPMC 5cps**

Table 5.6: Subcoating formulation of Esomeprazole tablets.

Sub coating 3% weight gain	Amount taken
HPMC 5cps	1gm
Triethyl citrate	1ml
Talc	40mg
Water	20ml
Color	q.s

- **Preparation of sub-coating dispersion**
- **Enteric coating of Esomeprazole using Cellulose acetate phthalate (CAP)**
- **Enteric coating with Cellulose acetate phthalate (CAP) Composition of coating dispersion.**

Cellulose acetate phthalate 4.0%

Triethyl citrate 2ml

Talc 1gm

Isopropyl alcohol 50ml

Dichloromethane 50ml

Preparation of enteric coating dispersion

Isopropyl alcohol and dichloromethane were taken in 1:1 ratio in a beaker. Cellulose acetate phthalate was slowly added to this solvent with stirring and the contents were mixed for 15 minutes under continuous stirring. Talc was added to the above solution, under continuous stirring till a homogenous dispersion was formed.

Table 5.7: Enteric coating of Esomeprazole with CAP.

S. No.	Enteric coating	A	B	C
1.	Sub coated tablets	206mg	206mg	206mg
2.	CAP	2%	3%	4%
3.	Triethyl citrate	2ml	2ml	2ml
4.	Talc	1gm	1gm	1gm
5.	Isopropyl alcohol	50ml	50ml	50ml
6.	Dichloromethane	50ml	50ml	50ml
7.	Color	q.s	q.s	q.s

Statistical analysis*:* The results are expressed as mean and standard deviation.

RESULTS

Preformulation study

Preformulation studies are primarily done to investigate the physicochemical properties of drug and to establish its compatibility with other excipients.

- **FTIR Compatibility Studies**

FTIR spectra of IR spectrum of pure Esomeprazole, croscarmellose sodium, crospovidone, sodium starch glycolate, Cellulose acetate phthalate, and combination thereof were recorded on Bruker spectrophotometer. The scans were evaluated for presence of polymer. The FTIR

spectra of pure Esomeprazole, crospovidone, sodium starch glycolate, Cellulose acetate phthalate and combination thereof are shown in following figures.

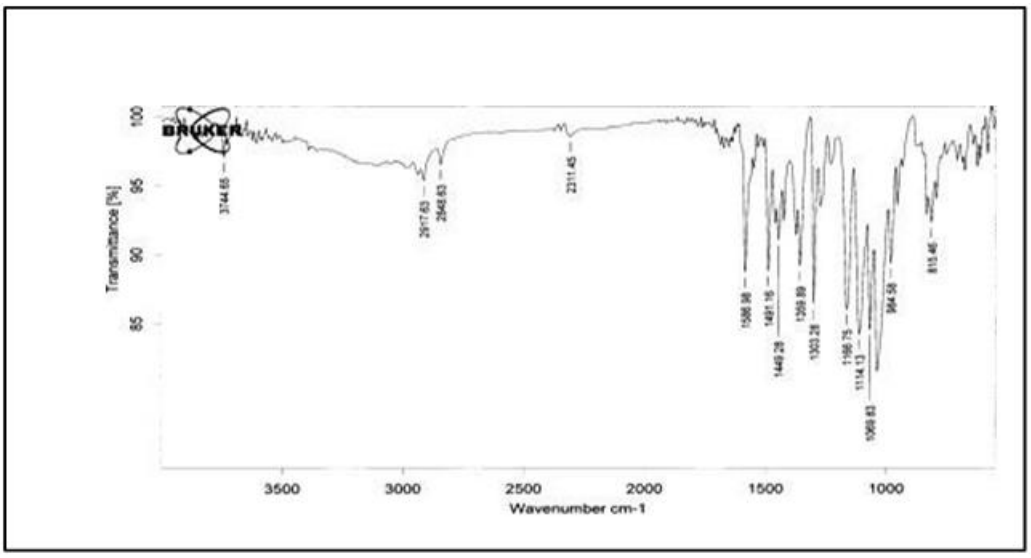

Figure 6.1: FTIR spectra of Esomeprazole.

Sulfoxide 1076 S=O stretching methoxy 1199 C-O stretching, methoxy 1228 C-O stretching, amine 1409 N-H bending, pyridine 1569 C=N stretching, benzimidazole 1612, 1588 C=N stretching, aromatic 2970 C=C-H asymmetric stretching , alcohol/water 3100–2800 O-H stretching.

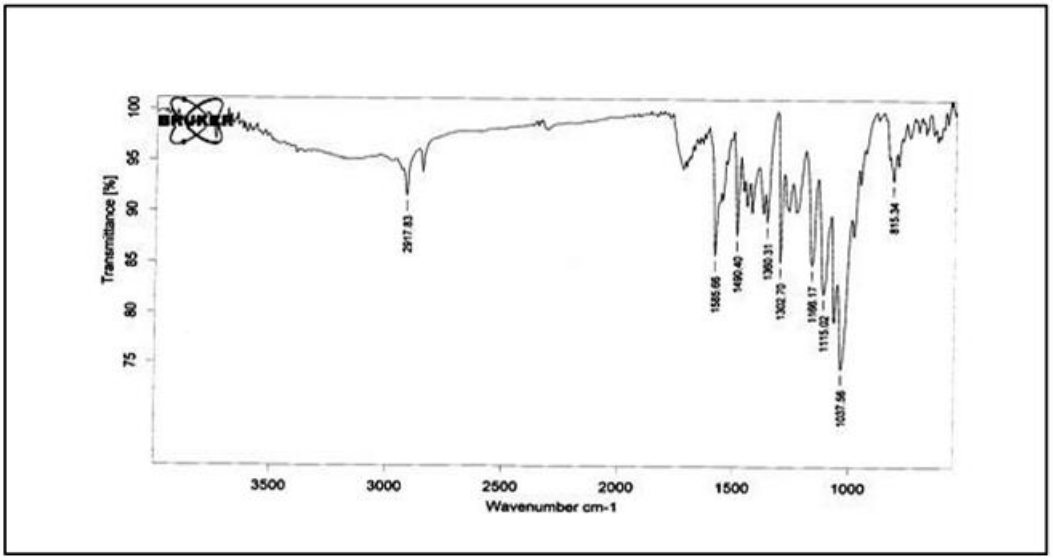

Figure 6.2: FTIR spectra of Esomeprazole with all polymers.

In the FTIR spectra of pure drug and polymers it is observed that the peaks of major functional groups which are present in spectrum of pure drug are observed in combination of

drug and polymers. There was no appearance or disappearance of any characteristics peak in the FTIR spectrum of optimized formulation. This shows that there is no chemical interaction between the drug and the polymers used. The presence of peaks at the expected range confirms that the materials taken for the study are genuine and there were no possible interactions occurred.

- **Preformulation characteristics**

Table 6.1: Preformulation of powder blend of Esomeprazole core tablet.

Formulation code	Angle of repose	Bulk density (gm/cm^2)	Tapped density (gm/cm^2)	Hausners ratio	% compressibility
C1	25.7±0.03	0.34±0.02	0.42±0.03	1.24	19.04±0.01
C2	26.8±0.01	0.36±0.02	0.45±0.05	1.26	22.32±0.05
C3	24.9±0.02	0.36±0.05	0.47±0.02	1.31	18.53±0.04

(n=3)

- **Calibration curve of Esomeprazole**

A standard curve of Esomeprazole was constructed using 0.1N HCl (1-10 µg/ml) and phosphate buffer 6.8 pH. Various concentrations 2, 4, 6, 8, 10, 15, 20, 25 and 30 µg/ml was prepared.

The absorbance of prepared concentrations was measured at 301nm by adjusting to zero with blank sample. A graph was plotted by taking concentration on x-axis and absorbance on y-axis and best fit line was drawn and regression value and equation was calculated represented in figure.

Table 6.2: Standard curve of Esomeprazole in 0.1N HCl (pH 1.2)

Concentration (µg/ml)	Absorbance
0	0
1	0.102
2	0.218
3	0.300
4	0.408
5	0.457
6	0.562
7	0.638
8	0.743
9	0.855
10	0.924

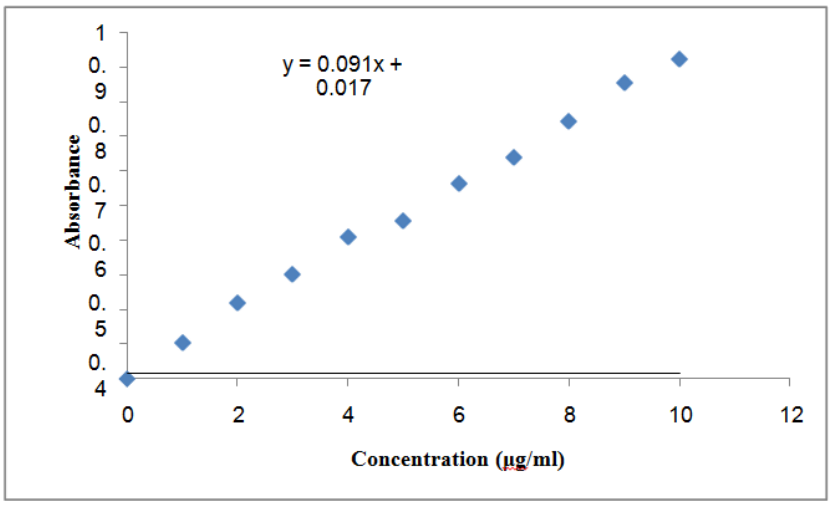

Figure 6.3: Standard curve of Esomeprazole in 0.1N HCl (pH 1.2).

Table 6.4: Standard curve of Esomeprazole in phosphate buffer pH 6.8.

Concentration (µg/ml)	Absorbance
0	0
2	0.074
4	0.136
6	0.196
8	0.262
10	0.318
15	0.48
20	0.64
25	0.794
30	0.92

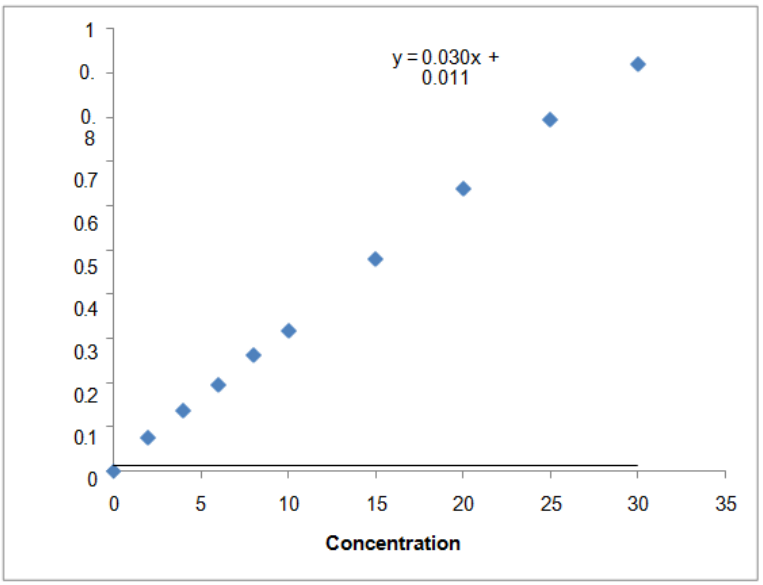

Figure 6.5: Standard curve of Esomeprazole in phosphate buffer pH 6.8.

- **Evaluation of Esomeprazole core tablets**

Table 6.4: Physical characteristics of Esomeprazole core tablets (C1-C3)

Formulation Code	Av.wt (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability %	Assay %	Disintegration Time (min)
C1	200±0.6	2.63±0.02	6.47±0.06	0.34±0.07	99.49±0.92	6.45±0.93
C2	199±0.5	2.60±0.02	6.53±0.21	0.71±0.13	98.7±0.61	5.56±0.28
C3	202±0.9	2.66±0.03	6.6±0.17	0.60±0.08	99.86±0.84	4.5±0.33

(n=3)

Weight variation

Acceptable physicochemical properties were observed for the prepared core tablets of Esomeprazole and all the formulated tablets passed the weight variation test. The weight variations of all compressed tablets were within the limits as per USP.

Thickness

The thickness of the core tablets varied from 2.60 to 2.66 mm and all the batches showed uniform thickness.

Hardness

Acceptable physicochemical properties were observed for of the prepared core tablets. Hardness of the tablets was found to be good depending upon compression force applied (6-8 kg/cm^2).

Friability

Acceptable physicochemical properties were observed for of the prepared core tablets. Friability was obtained between the ranges 0.34 to 0.60, which was below 1% indicating sufficient mechanical integrity of the tablets.

Assay

Acceptable physicochemical properties were observed for of the prepared core tablets. The drug content estimation showed values in the range of 98.7 ± 0.92 to 99.86 ± 0.84 which reflects good uniformity in the drug content among different formulations. Assay of all compressed tablets were within the limits as per USP.

***In vitro* drug release studies**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Esomeprazole from different formulations of core tablets with different

superdisintegrants, crospovidone (CP), Sodium starch Glycolate (SSG), croscarmellose sodium (CCS), the best drug release and disintegration is with crospovidone (CP). By taking the crospovidone as superdisintegrant in core tablet the enteric coating was carried out.

Table 6.5: Cumulative percent drug release of Esomeprazole core tablets prepared by using different superdisintegrants (C1, C2, C3).

Time (min)	Cumulative % Drug release		
	C1	C2	C3
10	20.55±2.58	21.58±2.11	24.42±1.18
20	38.28±2.66	34.53±0.94	36.3±1.15
30	52.77±1.15	53.52±1.77	56.27±1.75
40	69.25±2.65	72.5±1.07	73±1.13
50	82.26±2.62	85.08±0.86	87.5±2.17
60	92.25±0.75	94.98±0.83	98.59±0.93

(n=3)

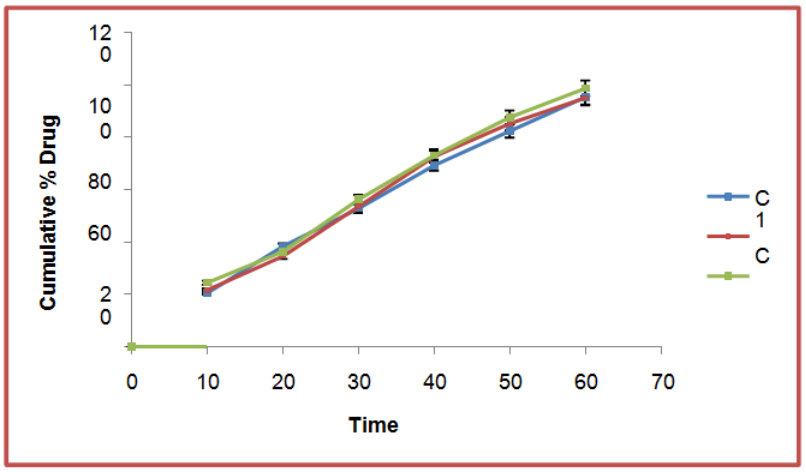

Figure 6.5: Graphical representation of cumulative percent drug release from Esomeprazole core tablets (C1, C2, and C3).

- **Evaluation of Esomeprazole enteric coated tablets**

Table 6.6: Physical characteristics of Esomeprazole enteric coated tablets.

Formulation code	Avg. wt (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability %	Assay %
C3F1	222.46±0.01	3.77±0.02	6.22±0.1	0.41±0.29	94.28±0.27
C3F2	226.59±0.01	3.81±0.1	6.41±0.07	0.32±0.21	95.7±0.48
C3F3	236.89±0.02	3.84±0.81	6.38±0.05	0.284±0.83	91.25±0.47

(n=3)

Weight variation

Acceptable physicochemical properties were observed for the prepared enteric- coated tablets,

all the formulated tablets passed the weight variation test. The weight variations of all compressed tablets were within the limits as per USP.

Thickness

The thickness of the enteric-coated tablets varied from 3.77 mm to 3.84 mm all the batches showed uniform thickness.

Hardness

Acceptable physicochemical properties were observed for of the prepared enteric coated tablets. Hardness of the tablets was found to be good depending upon compression force applied (6-7 kg/cm^2).

Friability

Acceptable physicochemical properties were observed for of the prepared enteric coated tablets. Friability was obtained between the ranges 0.26 to 0.82%, which was below 1% indicating sufficient mechanical integrity of the tablets.

Assay

Acceptable physicochemical properties were observed for of the prepared enteric coated tablets. The drug content estimation showed values in the range of 91.27±0.47 to 99.97±0.36 which reflects good uniformity in the drug content among different formulations. Assay of all compressed tablets were within the limits as per USP.

***In vitro* drug release studies**

In vitro drug release studies were conducted in phosphate buffer pH 6.8 and the studies revealed that the release of Esomeprazole from different formulations varies with composition and % weight gain of enteric coating polymers as shown in graphs 6.6.

Table 6.7: Disintegration of Esomeprazole enteric coated tablets in 0.1 N HCl (pH 1.2) followed by phosphate buffer pH 6.8.

Formulation code	Disintegration time at 0.1 N HCl (2hrs)	Disintegration time at Phosphate Buffer pH 6.8 (min)
C3F1	Slight softening and cracking observed after 1hr	5 ± 0.78
C3F2	Slight softening and cracking observed after 1hr 32min	7.5 ± 0.12
C3F3	No disintegration in 2hrs	11± 0.42

Table 6.8: Dissolution test conditions in 0.1 N HCl.

Parameter	Specification
Dissolution medium	0.1N HCl
Volume of medium	900 ml
Temp. medium	37 ± 0.5ºC
Paddle Rotation speed	100 rpm
Sampling time interval	1hr, 2hr
Detection wavelength	301nm

Table 6.9: Cumulative % Drug release of Esomeprazole enteric coated tablets in 0.1N HCl.

S. No	Formulation code	% Drug release in pH 0.1N HCl (time in hrs)	
		1hr	2hr
1	C3F1	13.6±0.21	31.53±1.01
2	C3F2	12.8±0.31	22.55±0.13
3	C3F3	9.5±0.46	17.11±0.18

(n=3)

Table 6.10: Dissolution test conditions in phosphate buffer pH 6.8.

Parameter	Specification
Dissolution medium	phosphate buffer pH 6.8
Volume of medium	900 ml
Temp.medium	37±0.5ºC
Paddle Rotation speed	100 rpm
Sampling time interval	10-60 min
Detection wavelength	301 nm

Table 6.11: Cumulative percent drug release of Esomeprazole enteric coated tablets in phosphate buffer 6.8 pH (C3F1, C3F2, and C3F3)

Time (min)	Cumulative % Drug release		
	C3F1	C3F2	C3F3
10	10.50 ± 0.61	13.2 ± 0.42	15±1.98
20	27.9 ± 0.79	35.52 ± 0.43	38.99 ± 1.06
30	38.65 ± 0.38	47 ± 1.13	55.25 ± 3.85
40	45.1 ± 1.28	58.15 ± 0.36	68.25 ± 3
50	54.5 ± 0.42	72.88 ± 0.42	76.53 ± 0.74
60	65.48 ± 0.61	81.5 ± 1.15	89.13 ± 1.09

(n=3)

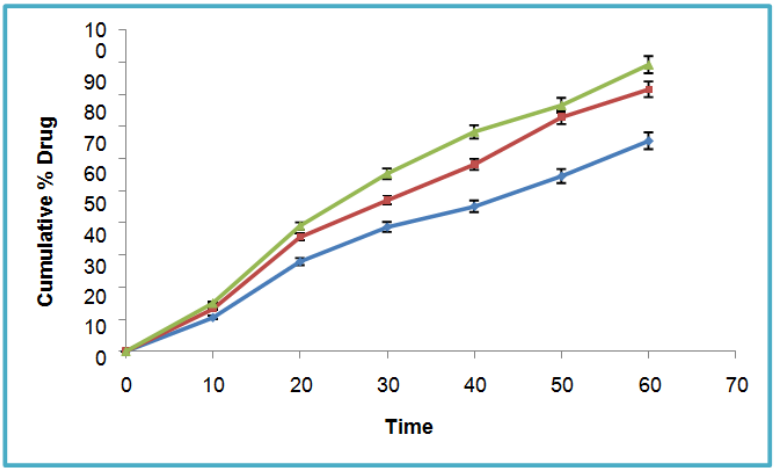

Figure 6.6: Graphical representation of cumulative percent drug release of Esomeprazole enteric coated tablets prepared by using Cellulose acetate phthalate (C3F1, C3F2, and C3F3).

CONCLUSIONS

Esomeprazole core tablets were prepared using different superdisintegrants. A seal coat of 3% weight gain using HPMC 5cps was sufficient to protect the tablets from the acid coat of the enteric layer. Enteric coating was done using enteric coating material (Cellulose acetate phthalate). Evaluation of these tablets indicated that the tablets coated disintegrated in 0.1 N HCl. However, formulations which were enteric coated 2% and 3% CAP fail the disintegration test carried out at pH 1.2. The study indicates that 4% CAP suitable for enteric coating. It provides greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH. The optimized formulation was C3F3 in 0.1 N HCl for 2 h followed by phosphate buffer pH 6.8 for 60mins. Compares the dissolution profile of enteric coated Esomeprazole tablets prepared using CAP (2%, 3%, 4%) in phosphate buffer pH 6.8. It is evident that (C3F3) demonstrated excellent physical resistance to the acid medium with the acid uptake value 1.22±0.06 in 2 hrs. Altering the media to basic (phosphate buffer-pH 6.8) leads to rapid release of the Esomeprazole from all the formulations evaluated. The cumulative percentage released at the end of the study was found to be relatively high with formulations made by enteric coating with 4% CAP (C3F3, 85.75 ± 0.97%).

REFERENCES

1. Kagan, L., Hoffman, A., Systems for region selective drug delivery in the gastrointestinal tract: biopharmaceutical considerations. Expert Opin. Drug Deliv., 2008; 5(6): 681-92.

2. Leon Shargel and Andrew B.C. Yu. Encyclopedia of Pharmaceutical Technology, Third Edition, 2006; 304-16.
3. Degussa creating essential, Guideline for formulation development & process Technology for Enteric coatings, 2007; 29.
4. Karl Thoma and Karoline Bechtold. Enteric coated hard gelatin capsules, 1987; 1-16:
5. Krishna Vamshi Allam, Gannu Praveen Kumar. Colorants the cosmetics for the pharmaceutical dosage forms. Int J Pharm Pharm Sci., 2011; 3(3): 13-21.
6. Muhammad F. Akhtar, Muhammad Hanif, Abdul Majeed & Shahid Shah. Formulation Development and Optimization of Captopril Containing Tablets through Box-Behnken Design. Latin American Journal of Pharmacy, 2018; 37(7): 1414-23.
7. Krutika A. Kulkarni, Jaymin Patel, and Shreeraj Shah. Formulation and evaluation of colon targeted drug delivery of budesonide using modified codes system. International Journal of Current Advanced Research, 2018; 7(4): 11387-11392.
8. Christopher Oswald Migoha, Eliangiringa Kaale, Godliver Kagashe. Formulation Development of Generic Omeprazole 20mg Enteric Coated Tablets. Pharmacology & Pharmacy, 2015; 6: 293-301.
9. Wilson B, Babubhai PP, Sajeev MS, Jenita JL, Priyadarshini SR. Sustained release enteric coated tablets of pantoprazole: formulation, *in vitro* and *in vivo* evaluation. Acta Pharm., 2013; 63(1): 131-40.
10. T. Neelima Rani, Ch. T. Lalitha Kumari, B. Mallikarjun Reddy, D.R. Brahma Reddy. Comparitive *in vitro* evaluation of different commercially available brands of pantoprazole tablets. IJPSR, 2012; 1107-1111.
11. Malay R Patel, Amit A. Patel, Laxman M Prajapati, Natvarlal M Patel. Formulation and evaluation of doxycycline hydrochloride delayed release enteric coated tablets. Der Pharmacia Lettre, 2012; 4(1): 249-55.
12. Ajit Patil, Santosh Payghan. Formulation and Evaluation of Enteric coated tablets of Azithromycin dehydrate. Int J of Chem Tech Research, 2011; 1479- 1484.
13. Preethi Mylavarapu, Prathima Srinivas, Venkata Ramana Reddy and M.Sadanandam. Formulation and evaluation of duloxetine hydrochloride delayed release enteric coated capsules. Int J Pharma and Bio Sci., 2011; 152- 172.
14. Rakesh. N. Tirpude, Prashant. K. Puranik. Rabeprazole delayed release multiparticulates: effect of enteric coated layers on product performance. J. Adv. Pharma. Tech. Res., 2011; 184-191.
15. A B Hawthorne, Y R Mahida, A T Cole, and C J Hawkey. Aspirin-induced gastric

mucosal damage: prevention by enteric-coating and relation to prostaglandin synthesis. Br J Clin Pharmacol., 1991; 77–83.

16. Subramaniam Kannan, Rangasamy Manivannan, Ayyasamy Balasubramaniam and Natesan Senthil Kumar. Formulation and evaluation of aspirin delayed release tablet. International journal of comprehensive pharmacy, 2010; 4(2): 1-3.
17. Sanjay R. Patel, Priyal R. Patel, Chintan N. Vora, Nitin D. Patel, Jayvadan K. Patel. Formulation, process parameters optimization and evaluation of delayed release tablets of rabeprazole sodium. Int J Pharmacy Pharm Sci., 2010; 144-156.
18. Singh Chhater, Kumar Rajesh, Agarwal Kshitij, Nema R.K. Development and evaluation of enteric coated tablet containing diclofenac sodium. Int J PharmSci and nanotechnology., 2009; 443-449.
19. Crotts G, Sheth A, Twist J, Ghebre-Sellassie I. Development of an enteric coating formulation and process for tablets primarily composed of a highly water-soluble, organic acid. Eur J Pharm Biopharm., 71-6: 2001.
20. S. C Basak, P Sampath Kumar, R Manavalan, K. A Narendranath. Preparation and Evaluation of Enteric Coated Pancreatin Tablets. Indian Journal of Pharmacy, 2002.
21. https://www.drugbank.ca/drugs/DB00736
22. https://www.drugs.com/inactive/sodium-starch-glycolate-128.html
23. https://en.wikipedia.org/wiki/Triethyl_citrate
24. https://en.wikipedia.org/wiki/Polyvinylpolypyrrolidone
25. https://en.wikipedia.org/wiki/Magnesium_stearate
26. https://en.wikipedia.org/wiki/Corn_starch
27. https://en.wikipedia.org/wiki/Sodium_carbonate
28. https://en.wikipedia.org/wiki/Cellulose_acetate_phthalate
29. https://en.wikipedia.org/wiki/Microcrystalline_cellulose
30. https://en.wikipedia.org/wiki/Sodium_croscarmellose