FORMULATION AND EVALUATION OF ENTERIC COATED TABLET OF PROTON PUMP INHIBITOR ESOMEPRAZOLE: A REVIEW

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ABSTRACT:

In this research, the Enteric Coated Tablet of Proton Pump Inhibitor Esomeprazole which evaluate the formulation for various parameter to release the active ingredient after predetermine time in a predetermine location with better pharmaceutical and therapeutic properties.

Different core tablets were prepared and formulation (F-1) was selected for further enteric coating, based on the disintegration time. Matrix coating was applied to achieve 6% weight gain using Enteric coating was carried out using different polymers like Eudragit FS 30 D, Eudragit S-100, Triethyl citrate to protecting all the drug formulation from acidic environment. Which results entric coating protect acid-liable drugs from the gastric fluid and inhance the bioavailability and reduce the toxicity by slowing drug absorption.

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, Stability studies indicate that the prepared formulations were stable for a period of three months. This study concluded that enteric coated tablets of esomeprazole can be prepared using any of the enteric coating polymer studied using a minimal weight gain of 6%.

KEYWORDS: Enteric coating tablets, Esomeprazole, Eudragit, HPMCP, CAP, stability.

INTRODUCTION:

Oral drug delivery has been known for decades as the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage forms. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process. The reasons that

the oral route achieved such popularity may be in part attributed to its ease of administration, belief that by oral administration of the drug is well absorbed.

All the pharmaceutical products formulated for systemic delivery via the oral route of administration irrespective of the mode of delivery and the design of dosage forms must be developed within the intrinsic characteristics of GIT physiology, pharmacokinetics and pharmacodynamics and formulation design to achieve a systemic approach to the successful development of an oral pharmaceutical dosage form.

ENTERIC COATINGS:

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, polyvinyl acetate, polyhydroxy propyl methyl cellulose, Methacrylic acid copolymers.

All these polymers have the common feature of containing the dicarboxylic, pthalic acid in partially esterified form. These polymers, being acid esters are insoluble in gastric 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 increased to a range of (pH 7-8). The primary mechanism, by which these polymers lose their integrity, is there by admitting the releasing drug to the intestinal fluid. In this ionization of the residual carboxyl groups on the chain and subsequent hydration.

IMPORTANT REASONS FOR ENTERIC COATING:

1. To protect acid-liable drugs from the gastric fluid.
2. To protect gastric distress or nausea due to irritation from drug.
3. To deliver drugs intended for local action in the intestines.
4. To provide a delayed release component to repeat actions.

ENTERIC COATING POLYMERS:

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
- Hydroxypropyl methyl cellulose phthalate (HPMCP)
- Polyvinyl acetate phthalate (PVAP)

- Hydroxy ethyl cellulose phthalate

MATRIX TABLETS:

Matrix tablets may be defined as the "oral solid dosage forms in which the drug or active ingredient is homogeneously dispersed throughout the hydrophilic or hydrophobic matrices which serves as release rate retardants". These are the type of controlled drug delivery systems, which release the drug in continuous manner by both dissolution controlled as well as diffusion controlled mechanisms. To control the release of the drugs, which are having different solubility properties, the drug is dispersed in swellable hydrophilic substances, an insoluble matrix of rigid non swellable hydrophobic materials or plastic materials.

ADVANTAGES OF MATRIX TABLET:

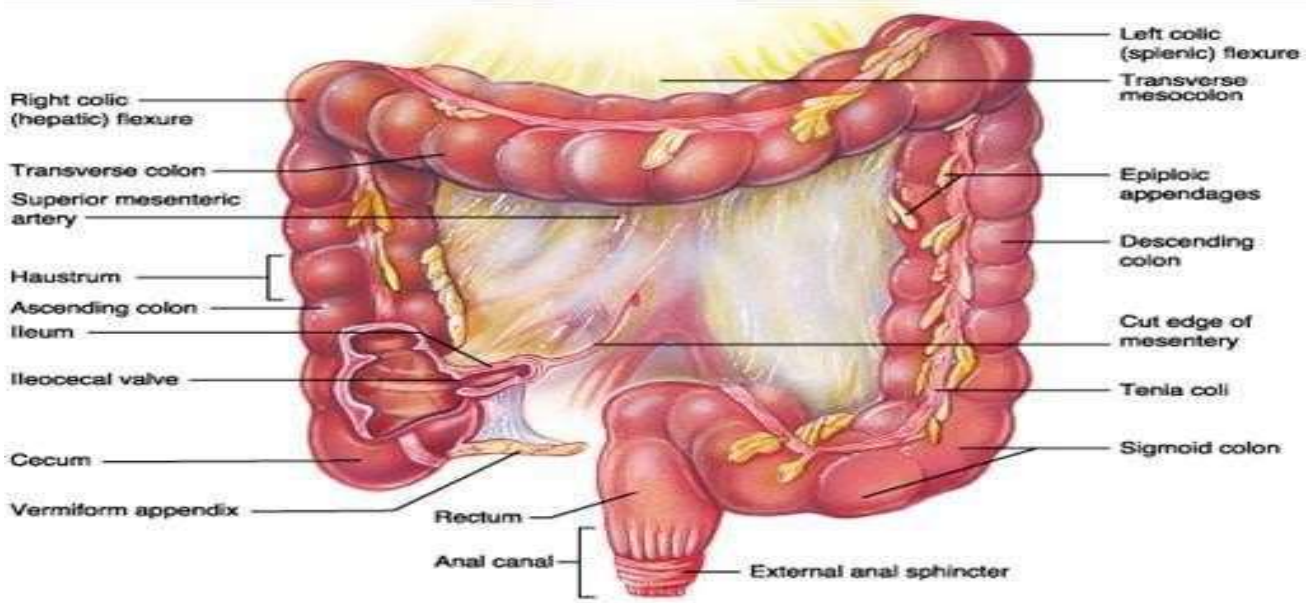
- Can be made to release high molecular weight compounds.
- The sustained release formulations may maintain therapeutic concentrations over prolonged periods.
- The use of sustain release formulations avoids the high blood concentration.
- Sustain release formulations have the potential to improve the patient compliance.
- Minimize drug accumulation with chronic dosing.

COLON TARGETED DRUG DELIVERY SYSTEM:

Colon Targeted Drug Delivery System (CTDDS) may be following the concept of Controlled or Sustained drug Delivery System. For CTDDS oral route of administration has received most attention. Local delivery allows topical treatment of inflammatory bowel disease. Colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, Crohn's disease, colonic cancer, local treatment of colonic pathologies and systemic delivery of protein and peptide drugs.

For effective and safe therapy of these colonic disorders, colon specific drug delivery is necessary i.e. drug release and absorption should not occur in the stomach as well as the small intestine, and neither the bioactive agent should be degraded in either of the dissolution sites but only released and absorbed once the system reaches the colon.

ANATOMY AND PHYSIOLOGY OF COLON



In GIT, large intestine starts from the ileocecal junction to the anus having a length of about 1.5m (adults) and is divided into three parts, viz. colon, rectum and anal canal. The colon consists of caecum, ascending colon, transverse colon, descending colon and sigmoid colon. Colon is made up of four layers, serosa, muscularis externa, submucosa and mucosa.Three major cell types found in the epithelium are the columnar absorptive cells, goblet (mucous) cells and entero endocrine cells. Mucus production in the colon is a function of goblet cells and the proportion of goblet cells increases in the elderly. The colon and the rectum have an anatomic blood supply. The arterial blood supply to the proximal colon is from the superior mesenteric artery and the inferior mesenteric artery supplies the distal colon.

FUNCTIONS OF THE COLON

The major function is the consolidation of the intestinal contents into feaces by the absorption of water and electrolytes. The absorptive capacity is very high. In healthy human colon, sodium and chloride ions are usually absorbed and potassium and bicarbonate ions are usually secreted. Activity in the colon can be divided into segmenting and propulsive movements. Segmenting movements caused by circular muscle and causing the appearance of the sac-like haustra, predominate and resulting in mixing of the luminal contents. Significant propulsive activity, associated with defecation and affected by longitudinal muscle, is less common and occurs an average of three or four times daily.

COLONIC ABSORPTION

As absorption capacity of colon is very high which is attributed to the colon transit time, which can be as long as 20-35 hours, hence it is ideally suited for absorption

The absorption is influenced by the transport of water, electrolytes and ammonia across the mucus and it is more in the proximal colon than the distal colon. Drug molecules pass from the apical to basolateral surface of epithelial cells by

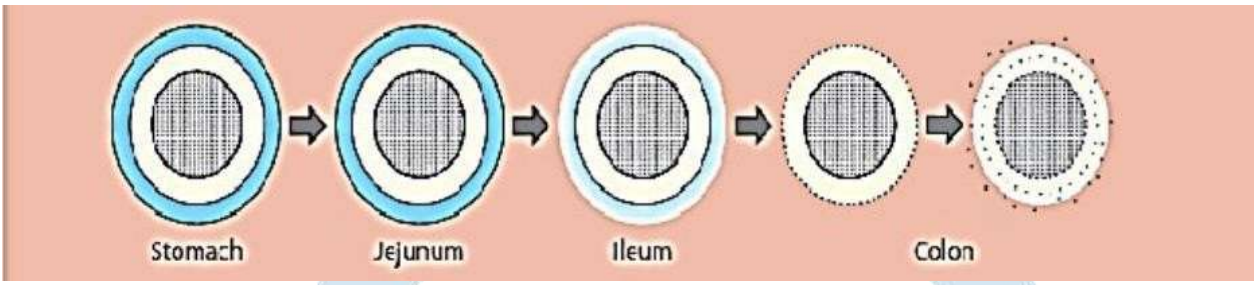


Figure:- Drug release pattern of coated system at different pH conditions in GIT

- Passing through colonocytes (trans cellular transport), or
- Passing between adjacent colonocytes (para cellular transport)

INFLAMMATORY BOWEL DISEASE:

Inflammatory bowel disease (IBD) is a group of inflammatory conditions of the colon and small intestine. Crohn's disease and ulcerative colitis are the principal types of inflammatory bowel disease. It is important to note that not only does Crohn's disease affect the small intestine and large intestine, it can also affect the mouth, esophagus, stomach and the anus whereas ulcerative colitis primarily affects the colon and the rectum.

ULCERATIVE COLITIS:

Ulcerative colitis is an idiopathic, chronic inflammatory disorder of the colonic mucosa, which starts in the rectum and generally extends proximally in a continuous manner through part of or the entire colon however, some patients with proctitis or left-sided colitis might have a caecal patch of inflammation. Bloody diarrhoea is the characteristic symptom of the disease.

Ulcerative colitis is a nonspecific inflammatory bowel disease of unknown etiology that effects the mucosa of the colon and rectum. The treatment of ulcerative colitis depends on the amount of the large bowel affected and the severity of the inflammation.

These disease are chronic, or long lasting, disease that causes inflammation irritation or swelling and sores called ulcers on the inner lining of the large intestine.

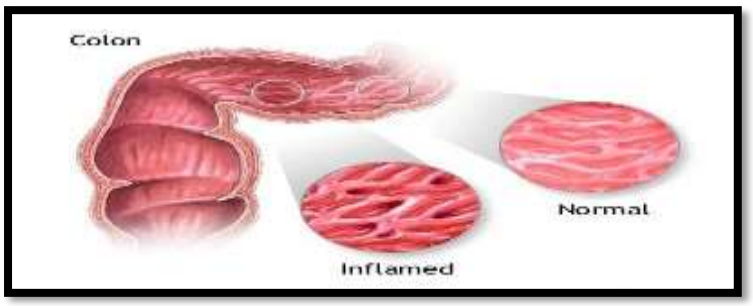


Figure:- Diagram of Inflamed and normal colon

SIGNS AND SYMPTOMS OF ULCERATIVE COLITIS:

The most common signs and symptoms of ulcerative colitis are diarrhea with blood or pus and abdominal discomfort. Other signs and symptoms include

- An urgent need to have a bowel movement
- Nausea or loss of appetite, Weight loss, Fever, Joint pain or sorenes
- Weight loss, Fever, Joint pain or sorenes
- Anemia is a condition in which the body has fewer red blood cells than normal Less common symptoms include.

CAUSES OF ULCERATIVE COLITIS

The exact cause of ulcerative colitis is unknown. Researchers believe the following factors may play a role in causing ulcerative colitis:

- Overactive intestinal immune system
- Genes
- Environment

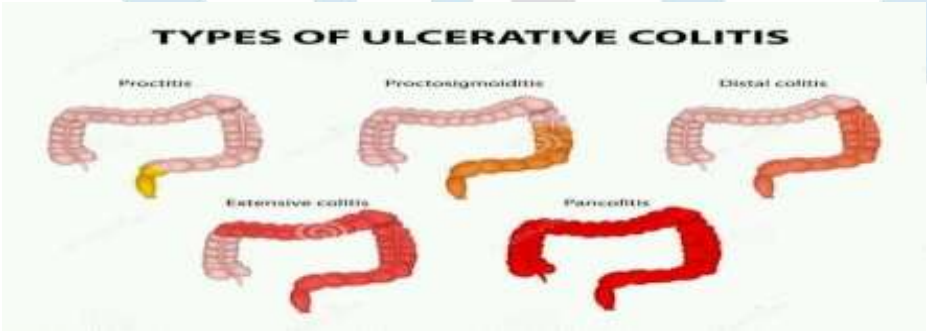


Figure:- Types of ulcerative colitis

- Proctitis – Involves only the rectum
- Distal colitis –Involve only the left side of the colon
- Pancolitis –Involves the entire colon
- Backwash ileitis – Involves the distal ileum

DRUG FORMULATION:

S.No	Drug name	Label Claim	Brand name	Company
1	Esomeprazole	40 mg	Actipraz	Invision Medie Science Pvt Ltd

METHODOLOGY:

FORMULATION OF COLON TARGETED MATRIX TABLET ESOMEPRAZOLE:

The method used in the formulation of colon targeted matrix tablet of Esomeprazole was direct compression method. All the batch formulations in these studies are formulated by direct compression method.

FORMULATION CHART:

S. No	INGREDIENTS	QUANTITY OF INGRIDIENTS (mg/tab)					
		F1	F2	F3	F4	F5	F6
1	Esomeprazole (mg)	40	40	40	40	40	40
2	Eudragit S-100	150	300	450	-	-	-
3	Ethyl cellulose	-	-	-	150	300	450
4	Lactose	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
5	Talc	15	15	15	15	15	15
6	Magnesium stearate	20	20	20	20	20	20
Total weight (mg)		600	600	600	600	600	600

Composition of Ingredient for Enteric Coating

S. No	Ingredients	Quantity/450 Tablet (gm)
1	Eudragit FS 30 D	129
2	Triethyl citrate	1.915
3	Talc	19.20
4	Purified water	123

6% coating has been given for all the formulations to protect the drug from acidic environment.

PREPARATION OF ENTERIC COATING SOLUTION:

A required quantity of Eudragit FS 30 D was weighed accurately and stirred. Mean while Triethylcitrate was added to it, purified talc were triturated separately in a mortar. And added to the solution and stirred. Finally the volume was making up to required quantity with purified water**.** Filtered the above solution with #100 mesh.

Weight built up calculation for enteric coating: [6 %]

800 x 6 % (6 gm ⟶ 100ml) 0.06 =24

800 + 20 = 820

The weight of enteric coated tablet = 820mg.

COATING PARAMETERS:

OPERATION CONDITION FOR ENTIRE COATING PROCESS:

Specifications	Enteric coating range
Pan diameter	12
Speed of pan revolution	20-25 rpm
Distance of spray gun	5-6
Spray nozzle diameter	1.2 mm
Spray rate	1.5 -2.0 ml /min
Dry air temperature	50 ± 5^0C / 30 mins
Coating time	5 hours
Bed temperature	30-40^0C

EVALUATION OF POST COMPRESSION PARAMETERS FOR PREPARED TABLETS:

The designed formulation tablets were studied for their physicochemical properties like weight variation, hardness, thickness, friability and drug content.

WEIGHT VARIATION TEST:

To study the weight variation, twenty tablets were taken and their weight was determined individually and collectively on a digital weighing balance. The average weight of one tablet was determined from the collective weight. The weight variation test would be a satisfactory method of determining the drug content uniformity.

HARDNESS:

Hardness of tablet is defined as the force applied across the diameter of the tablet in order to break the tablet. The resistance of the tablet to chipping, abrasion or breakage under condition of storage transformation and handling before usage depends on its hardness. For each formulation, the hardness of three tablets was determined using Monsanto hardness tester and the average is calculated and presented with deviation.

THICKNESS:

Tablet thickness is an important characteristic in reproducing appearance. Tablet thickness is an important characteristic in reproducing appearance. Average thickness for core and coated tablets is calculated and presented with deviation.

FRIABILITY %:

It is measured of mechanical strength of tablets. Roche friabilator was used to determine the friability by following procedure. Pre weighed tablets were placed in the friabilator. The tablets were rotated at 25 rpm for 4 minutes (100 rotations). At the end of test, the tablets were re weighed, loss in the weight of tablet is the measure of friability and is expressed in percentage as.

% Friability = [(W1-W2) / W] × 100

In-vitro DRUG RELEASE STUDIES:

DISSOLUTION PARAMETERS:

Apparatus

-

-

USP-II, Paddle Method

Dissolution Medium

-

-

0.1 N HCl, pH 7.4 Phosphate buffer

RPM

-

-

50

Sampling intervals (hrs) -

-

2, 5, 8, 12, 16, 20, 24 hrs

Temperature

-

-

37°C ± 0.5°C

PROCEDURE:

900ml 0f 0.1 HCl was placed in vessel and the USP apparatus –II (Paddle Method) was assembled. The medium was allowed to equilibrate to temp of 37°C ± 0.5°C. Tablet was placed in the vessel and apparatus was operated for 2 hours and then the media 0.1 N HCl were removed and pH 6.8 phosphate buffer was added process was continued up to 24 hrs at 50 rpm. At definite time intervals withdrawn 10 ml of sample, filtered and again 10ml media was replaced. Suitable dilutions were done with media and analyzed by spectrophotometrically at required wavelength using UV-spectrophotometer at 262.

ADVANTAGES OF ENTRIC COATED TABLETS

- To protect acid-liable drugs from the gastric fluid.
- Reducing the adverse effects in the treatment of colonic diseases (ulcerative colitis, colorectal cancer, Crohn's disease etc.)
- Prevents gastric irritation resulting due to the administration of NSAIDs.
- Delay delivery of drug to achieve high concentration in treatment of disease of distal gut
- 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 (Eg, omeprazole, pantaprazole)
- Sustain release formulations have the potential to improve the patient compliance.

DISADVANTAGES OF ENTRIC COATED TABLETS

- The pH level in the small intestine and caecum are similar which reduces site specificity of formulation.
- Increase the cost of manufacturing
- Diet and diseases can affect colonic micro flora which can negatively affect drug targeting to colon.
- Nature of food present in GIT can affect drug pharmacokinetics.

CONCLUSON:

It is here by concluded that, enteric coated tablets emerged as a promising drug delivery system, offering improved bioavailability, prolonged release, and enhanced patient compliance. This review highlights the various formulation strategies,entric coating polymer nd evaluation techniques employed to design and optimize, enteric coated tablets. However, further research is needed to overcome the challenges

associated with enteric coated tablets such as limited intestinal surface area, variable colonal pH, and potential irritation. Overall, enteric coated tablet offer a promising platform for the delivery of therapeutic agents, and continued research and development are necessary to fully realize their potential.

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