



Research Article



Formulation and evaluation of esomeprazole magnesium delayed release tablets 40mg

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ABSTRACT

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ABSTRACT

The present study was an attempt to formulate and evaluate enteric coated tablets for esomeprazole magnesium dihydrate. Different core tablets were prepared and formulation was selected for further enteric coating, based on the disintegration time. Seal coating was applied to achieve 3% weight gain. Enteric coating was carried out using different polymers like hydroxyl propyl methylcellulose phthalate to achieve 5% weight gain. Disintegration studies showed that the formulations failed in 0.1 N HCl media. Hence the quantity of enteric coating was increased to 8% w/w. In vitro analysis of the developed tablets was carried out. Results from disintegration time and dissolution rate studies indicate that all the esomeprazole enteric tablets prepared possess good integrity, desirable for enteric coated tablets.

1. INTRODUCTION

Esomeprazole is a proton pump inhibitor which reduces acid secretion through inhibition of the H⁺ / K⁺ ATP as in gastric parietal cells. By inhibiting the functioning of this transporter, the drug prevents formation of gastric acid.

It is used in the treatment of dyspepsia, peptic ulcer disease (PUD), gastro esophageal reflux disease (GORD/GERD) and Zollinger-Ellison syndrome. Esomeprazole is the S-Enantiomer of Omeprazole.

Application : A proton pump inhibitor

Purity : ≥98%

Description:

A leading proton pumps inhibitor.

Technical Information

Appearance : Powder

Physical State : Solid

Solubility : Soluble in DMSO: 5 mg/ml

Storage : Desiccate at 4° C

Medical use:

The primary uses of esomeprazole are gastroesophageal reflux disease, treatment of duodenal ulcers caused by *H. pylori*, preventing of gastric ulcers in those on chronic NSAID therapy, and treatment of gastrointestinal ulcers associated with Crohn's disease.

Gastroesophageal reflux disease:

Gastroesophageal Reflux Disease (GERD) is a condition in which the digestive acid in the stomach comes in contact with the esophagus (food pipe). The irritation caused by this disorder is known as heartburn. Long term contact between the acid and esophagus can cause permanent damage to the esophagus. Esomeprazole reduces the production of digestive acids, thus minimizing their effect on the esophagus.

Duodenal ulcers:

Esomeprazole is combined with the antibiotics clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14 day eradication triple therapy for *Helicobacter pylori*. Infection by *H. pylori* is the causative factor in the majority of peptic and duodenal ulcers.

Adverse effects:

Common side effects include headache, diarrhea, nausea, flatulence, decreased appetite, constipation, dry mouth, and abdominal pain. More severe side effects are severe allergic reactions, chest pain, dark urine, fast heartbeat, fever, paresthesia, persistent sore throat, severe stomach pain, unusual bruising or bleeding, unusual tiredness, and yellowing of the eyes or skin. Proton pump inhibitors may be associated with a greater risk of hip fractures and clostridium difficile-associated diarrhea. By

suppressing acid-mediated break down of proteins, antacid preparations such as esomeprazole lead to an elevated risk of developing food and drug allergies. This happens due to undigested proteins then passing into the gastrointestinal tract where sensitisation occurs. It is unclear whether this risk occurs with only long-term use or with short-term use as well. Patients are frequently administered the drugs in intensive care as a protective measure against ulcers, but this use is also associated with a 30% increase in occurrence of pneumonia.

Interactions:

Esomeprazole is a competitive inhibitor of the enzymes CYP2C19 and CYP2C9, and may therefore interact with drugs that depend on them for metabolism, such as diazepam and warfarin; the concentrations of these drugs may increase if they are used concomitantly with esomeprazole. Conversely, Clopidogrel (Plavix) is an inactive prodrug that partially depends on CYP2C19 for conversion to its active form; inhibition of CYP2C19 blocks the activation of clopidogrel, thus reducing its effects.

Drugs that depend on stomach pH for absorption may interact with omeprazole; drugs that depend on an acidic environment (such as ketoconazole or atazanavir) will be poorly absorbed, whereas drugs that are broken down in acidic environments (such as erythromycin) will be absorbed to a greater extent than normal.

Pharmacokinetics:

Single 20–40 mg oral doses generally give rise to peak plasma esomeprazole concentrations of 0.5-1.0 mg/L within 1–4 hours, but after several days of once-daily administration these levels may increase by about 50%. A 30 minute intravenous infusion of a similar dose usually produces peak plasma levels on the order of 1–

3 mg/L. The drug is rapidly cleared from the body, largely by urinary excretion of pharmacologically-inactive metabolites such as 5-hydroxymethylomeprazole and 5-carboxyomeprazole. Esomeprazole and its metabolites are analytically indistinguishable from omeprazole and the corresponding omeprazole metabolites unless chiral techniques are employed.

Dosage forms:

Esomeprazole is available as delayed-release capsules in the United States or as delayed release tablets in Australia, the United Kingdom and Canada (containing esomeprazole magnesium) in strengths of 20 mg and 40 mg; and as esomeprazole sodium for intravenous injection/infusion. Oral esomeprazole preparations are enteric-coated, due to the rapid degradation of the drug in the acidic conditions of the stomach. This is achieved by formulating capsules using the multiple-unit pellet system.

Controversy:

There has been some controversy about AstraZeneca's behaviour in creating, patenting and marketing of the drug. Esomeprazole's successful predecessor omeprazole is a mixture of two mirror-imaged molecules (esomeprazole which is the S-enantiomer, and R-omeprazole); critics said that the company was trying to "evergreen" its omeprazole patent by patenting the pure esomeprazole and aggressively marketing to doctors that it is more effective than the mixture, claiming that omeprazole has no beneficial effects on the patient. In the acidic environment of the parietal cells, both esomeprazole and omeprazole are converted to the same active drug which stops the gastric acid production:

Esmoperazole. Gastro-esophageal reflux (GERD) is defined as the reflux of gastric contents into the esophagus leading to reflux

symptoms sufficient to affect patient well-being and/or cause complications. Population-based studies suggest that heartburn is a very common symptom in the general population with a prevalence of 10%–20% in the Western world but far from all are consulters. However, in Asia the prevalence of GERD-like symptoms is lower and has been reported to be less than 5%. When traditional endoscopy is used, GERD can be subdivided into reflux esophagitis (or erosive GERD) and endoscopy-negative reflux disease (or non-erosive reflux disease, NERD). About 50% of patients with the disease have a normal endoscopy in referral centers, but in primary care the occurrence of esophagitis is lower. Erosive GERD has been associated with complications such as esophageal strictures and Barrett's esophagus.

The proton pump inhibitors (PPIs) are substituted benzimidazoles administered as enteric-coated tablets or capsules that pass through the stomach and are absorbed in the duodenum. They act on the proton pump molecule on the luminal surface of gastric parietal cells, resulting in inhibition of acid secretion. Esomeprazole is the latest PPI and was developed as the S-isomer of omeprazole as an improvement in its pharmacokinetic properties. PPIs are the drugs of choice in the treatment of GERD.

Esomeprazole exhibits significantly higher bioavailability, leading to the greater inhibition of gastric acid secretion compared to Omeprazole.² Esomeprazole, the stereospecific S-isomer of Omeprazole, is the first proton pump inhibitor (PPI) to be developed as a single isomer for use in the treatment of acid-related diseases.³ The intragastric pH-monitoring data for esomeprazole, 20 mg once daily, show improvement over omeprazole, 20 mg once daily, but the esomeprazole, 40 mg once daily, intragastric pH data show a further convincing gain in control of gastric pH.

2. AIMS AND OBJECTIVES:

To formulation and evaluation of esomeprazole magnesium delayed release tablets 40 mg. Objective of present investigation is to design and evaluation of esomeprazole magnesium delayed release tablet. For the past two decades, there has been enhanced demand for more patient compliance dosage forms. As a result, the demand for their technologies has been increasing three-fold annually. Since the development cost of a new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize side effects. The present experiment is to formulate and evaluate the esomeprazole magnesium delayed release of tablet by Wet granulation method. These formulations are then evaluated to check whether the drug and polymer are compatible for this we use analytical methods such as HPLC was also used to determine the percentage drug release. After the analytical

results are obtained we go for punching, followed by pre compression studies, post compression studies.

3. MATERIALS AND METHODOLOGY:

Materials:

Esomeprazole magnesium dihydrate, hydroxypropyl methyl cellulose phthalate and cellulose acetate phthalate and other additives were procured commercially. All the reagents and solvents used were of analytical grade. In vitro analysis of the prepared tablets was carried out as per the requirements of enteric coated tablets as specified in official pharmacopoeia.

Drug excipient interaction study:

Active drug blended with individual excipients were taken in 1:1 ratio, filled in closed vials and placed in stability chambers at 35°C •} 2°C / 60% •} 5% RH for a period of 4 weeks. Samples were analyzed by IR

Table No: 4.1
Master Formula: For 2000 tablets:

Sr no	Ingredients	Quantity/Unit[mg]	Quantity/ Batch[gm]
1	Esomeprazole magnesium dihydrate	43.5	0.087
2	Anhydrous lactose	52.1	0.105
3	Starch	13.9	0.027
4	HPC	2	0.004
5	CCS	3	0.006
6	Magnesium carbonate[light]	15	0.030
7	Meglumine	3	0.006
8	Povidone	6.5	0.013
9	IPA	54.95	0.110
10	Magnesium stearate	2	0.004
11	CCS	2.5	0.005
12	Crospovidone	5	0.010
13	Colloidal anhydrous silica	1.5	0.003

4. MANUFACTURING INSTRUCTIONS:

GRANULATION AND DRYING:

Dry mixing:

- Load the sifted material in to RMG.
- Mix the material for 20 min with mixer at slow speed.

Preparation of binder solution:

Stir isopropyl alcohol in a pre labeled paste vessel to form a vortex without drawing air in to the liquid. Add steadily providence to the vortex to get clear solution.

Wet mixing:

Add prepared binder solution in to the RMG over a period of 2-3 minutes while mixing at slow speed.

- Mix the wet mass 1-2 minutes mixer at

high speed. If required add extra quantity of iso propyl alcohol, while mixing with mixer at slow speed with regular interval checking for suitable granules formation.

Transfer the wet granular mass into a clean pre-labeled suitable container and transfer to drying area.

Drying:

Air- dry the wet mass until there is no perceptible smell of isopropyl alcohol to get LOD NMT 4.0% w/w at 105 °C , by auto mode using IR moisture analyzer.

Table No: 4.2

Load the blend in to hopper of tablet press. Adjust the tablet parameters as follows.

Sr no	Parameter	Specification
1	Description of core tablets	Pale yellow colored, circular, uncoated tablets.
2	Weight of 10 tablets [g]	1.50g+4% (1.440g to 1.560 g)
3	Hardness [kp]	Not less than 3 kp
4	Thickness [mm]	3.60mm+o.40 mm (3.20 mm -4.00 mm)
5	Disintegration time [Minutes]	Nmt 15 minutes[in water]
6	Friability [%w/w]	Nmt 1 .0%w/w
7	Uniformity of weight	150.00 mg +7.5%(138.750-161.250mg)
8	Tablet press speed	10-15rpm

Table No: 4.3 SUB COATING MATERIAL:

Sr No	Ingredients	Quantity/Unit[mg]	Quantity/ Batch[gm]
1	Hypromellose	5.42	0.011
2	Povidone	0.22	0.001
3	Titanium dioxide	0.22	0.001
4	Propylene glycol	0.14	0.001
5	Isopropyl alcohol	46.4	0.092
6	Dichloromethane	148.06	0.296
Sub coating tablet weight		156.00	

Sr no	Ingredients	Quantity/ Unit[mg]	Quantity/ Batch[gm]
1	Hypromellose phthalate	6.38	0.012
2	Cetyl alcohol	0.63	0.012
3	Triacetin	0.63	0.012
4	Titanium dioxide	0.06	0.010
5	Talc	0.06	0.010
6	Lake brilliant blue	0.04	0.008
7	Acetone	69.93	0.140
8	Isopropyl alcohol	30.30	0.060
Enteric coating tablet weight		163.80	

SUB COATING

SUB COATING PARAMETERS: Table No: 4.5

Set the spray guns and coating parameters as per the operating instructions to achieve the following parameters.

Parameters	Solace 8''
Pan speed	6-8 RPM
Spray rate	189.000-420.000 g/3guns/min.(63.000-140.000 g/gun/mm)
Spray type	Continues
Atomized air pressure	4-5 kg/cm ²
Tablet bed temperature	50±5 °C
Inlet air temperature	55±5 °C
Exhaust temperature	50±5 °C
Gun distance	10 Cm
% weight gain /tablet	4.0±0.8% w/w (3.20-4.80 % w/w)
peristaltic pump speed	18-22 RPM

EXCIPIENTS PROFILE

MAGNESIUM STEARATE:

Nonproprietary Names

BP: Magnesium Stearate, **JP:** Magnesium Stearate, **PhEur:** Magnesium Stearate, **USP-**

NF: Magnesium Stearate

MAGNESIUM STEARATE

Functional Category

Tablet and capsule lubricant.

Applications in Pharmaceutical Formulation or Technology:

Magnesium stearate is widely used in cosmetics, Foods, and pharmaceutical formulations. It is Primarily used as a lubricant in capsule and

Tablet manufacture at concentrations between 0.25% and 5.0% w/w. It is also used in barrier creams.

Description

Magnesium stearate is a very fine, light white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. The powder is greasy to the touch and readily adheres to the skin.

Stability and Storage Conditions

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

Incompatibilities

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

Safety

Magnesium stearate is widely used as pharmaceutical excipients and is generally regarded as being nontoxic following oral administration. However, oral consumption of large quantities may produce a laxative effect or mucosal irritation.

No toxicity information is available relating to normal routes of occupational exposure. Limits for heavy metals in magnesium stearate have been evaluated in terms of magnesium stearate worstcase daily intake and heavy metal composition. Toxicity assessments of magnesium stearate in rats have indicated that it is not irritating to the skin, and is nontoxic when administered orally or inhaled. Magnesium stearate has not been shown to be carcinogenic when implanted into the bladder of mice.

Handling Precautions

Observe normal precautions appropriate to the circumstances and quantity of material handled. Eye protection and gloves are recommended. Excessive inhalation of magnesium stearate dust may cause upper respiratory tract discomfort, coughing, and choking.

Magnesium stearate should be handled in a well-ventilated environment; a respirator is recommended. In the USA, the OSHA limit is 10 mg/m³ TWA for magnesium stearate.

Hydroxyl value: Between 218 and 238.

Iodine value: Not more than 2.0, determined by Method B in a 8% w/v solution in chloroform,

Saponification value: Not more than 2.0.

TITANIUM DIOXIDE:

1. Titanium dioxide, also known as titanium (IV) oxide or titania, is the naturally occurring oxide of titanium, chemical formula TiO.

2. When used as a pigment, it is called titanium white, Pigment White. Generally it is sourced from ilmenite, rutile and anatase. It has a wide range of applications, from paint to sunscreen to food colouring.

Applications

The most important application areas are paints and varnishes as well as paper and plastics: They process about 80% of the world's titanium dioxide consumption. Other pigment applications like printing inks, fibers, rubber, cosmetic products and foodstuffs account for another 8%. The rest is used in other applications, for instance the production of technical pure titanium, glass and glass ceramics, electrical ceramics, catalysts, electric conductors and chemical intermediates.

Other applications

Synthetic single crystals of TiO₂, ca. 2–3 mm in size, cut from a larger plate.

- Titanium dioxide in solution or suspension can be used to cleave protein that contains the amino acid [HYPERLINK "http://en.wikipedia.org/wiki/Proline"](http://en.wikipedia.org/wiki/Proline) proline at the site where proline is present.
- Titanium dioxide is also used as a material in the memristor, a new electronic circuit element. It can be employed for solar energy conversion based on dye, polymer, or quantum dot sensitized nanocrystalline TiO₂ solar cells using conjugated polymers as solid electrolytes.
- Synthetic single crystals and films of TiO₂ are used as a semiconductor, and also in Bragg-stack style dielectric mirrors due to the high refractive index of TiO₂ (2.5–2.9).

5. RESULTS

Esomeprazole magnesium delayed release tablets were prepared by wet granulation method.

Description [visual inspection] : pale yellow colored powder.

Identification [by HPLC]: The retention time of the major peak in the chromatogram of the sample solution corresponds to that in the chromatogram of the standard solution, as obtained in the assay. Esomeprazole magnesium Dihydrate equivalent to Esomeprazole in mg: each uncoated tablet contains 40.1mg of Esomeprazole. Each enteric coated tablets contains 39.56mg of esomeprazole, percentage of labeled amount is 98.9% assay by HPLC. in acid stage not more than 10% of the labeled amount of drug release after 2 hours and in buffer stage not less than 70% of the labeled claim is dissolved in 45 minutes.

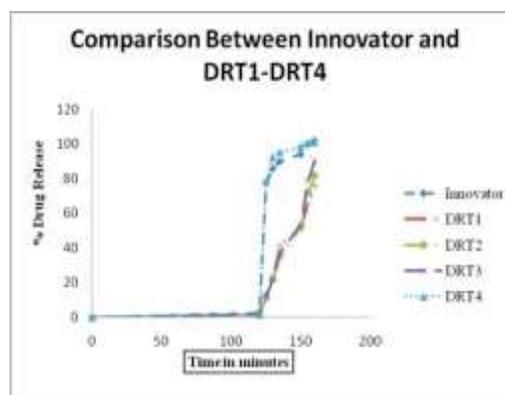
Drug content studies: The drug content in tablets were determined by randomly choosing twenty tablets of each formulation and

Powdered using mortar & pestle. A quantity equivalent to 40 mg of esomeprazole magnesium trihydrate was weighed, dissolved in mobile phase and diluted suitably. The amount of drug was determined by injecting 20 µl of the sample in a HPLC system (Shimadzu, LC-10ATVP, Japan) consisting of a Phenomenex C18 analytical column (4.6 X 250mm, Luna, 5.0 µm). The column was maintained at ambient temperature. The compounds were eluted at a flow rate of 1.0 ml/min using a mobile phase of Acetonitrile: Phosphate buffer pH 6.8 (60:40 v/v). The column effluent was monitored at 203 nm.

In vitro Dissolution tests

Drug release profile was evaluated in vitro using a dissolution test apparatus (Electro Lab, TDT-08L, Mumbai, India). The USP XIII Type II (paddle type) method was selected to perform the dissolution profile of esomeprazole magnesium trihydrate. The dissolution for all the formulations was carried out according to US Pharmacopoeia [13] for 2 h in 0.1N HCl and then media was changed into phosphate buffer pH 6.8. The temperature was maintained at 37 ± 0.5°C and a constant paddle rotation speed of 100 rpm. Samples (10 ml) were withdrawn at regular intervals and filtered through membrane filter (pore size 0.22 µm). The samples were analyzed by HPLC.

Table no: 5.1 dissolution profile



It shows dissolution profile for innovator and delayed release tablets

6. DISCUSSION

In the present work emphasize on Esomeprazole magnesium is formulated as delayed release tablets to provide desired effect at certain time in maintained drug concentration without any unwanted effect with patient compliance also to improve its bioavailability by decreasing its exposure to gastric acid. A delayed release dosage form is designed to release the drug from the dosage form at a time other than promptly after administration. UV spectrophotometric method has been developed for the estimation of Esomeprazole in pharmaceutical formulations. Then the tablets were prepared by wet granulation method rather than direct compression because of cohesive property of the drug. Optimized core tablet then subjected for enteric coating by selected base coat polymer cellulose derivative for preventing core tablet from moisture. The coated formulations were compared with marketed sample for optimization. Dissolution results of tablets with enteric coating have shown release of Esomeprazole in simulated gastrointestinal fluid pH 1.2, but most of the drug released in pH 6.8 Phosphate buffer. At the end it was found that prepared formulation gave satisfactory results compared with marketed sample dissolution profile. Hence prepared formulation by-pass the degradation of Esomeprazole by enteric coating approach and can be used as single unit dosage for the treatment of acid-related diseases. Thus a pharmaceutically equivalent, robust formulation of Esomeprazole delayed release tablet was developed.

7. SUMMARY AND CONCLUSION

Esomeprazole is a proton pump inhibitor which reduces acid secretion through inhibition of the H⁺ / K⁺ ATPase in gastric parietal cells. By inhibiting the functioning of this transporter, the drug prevents formation of gastric acid.

Medical use

The primary uses of esomeprazole are gastroesophageal reflux disease, treatment of duodenal ulcers caused by H. pylori, preventing of gastric ulcers in those on chronic NSAID therapy, and treatment of gastrointestinal ulcers associated with Crohn's disease.

Gastro esophageal reflux disease

Gastroesophageal Reflux Disease (GERD) is a condition in which the digestive acid in the stomach comes in contact with the esophagus (food pipe). The irritation caused by this disorder is known as heartburn. Long term contact between the acid and esophagus can cause permanent damage to the esophagus. Esomeprazole reduces the production of digestive acids, thus minimizing their effect on the esophagus.

Duodenal ulcers

Esomeprazole is combined with the antibiotics clarithromycin and amoxicillin (or metronidazole in penicillin-hypersensitive patients) in the 7-14 day eradication triple therapy for Helicobacter pylori. Infection by H. pylori is the causative factor in the majority of peptic and duodenal ulcers.

In addition, Esomeprazole treatment yields higher erosive esophagitis healing rates and provides sustained resolution of heartburn in more patients than any other oral site-specific drug delivery systems have attracted a great deal of interest recently for the local treatment of a variety of bowel diseases and also for improving systemic absorption of drugs, which are unstable in the stomach. However, the micro environment in the gastrointestinal tract and varying absorption mechanisms generally causes hindrance for the formulation scientist in the development and optimization of oral drug delivery. Delivery of therapeutic agent into the intestinal region could be accomplished by the

application of an enteric coating on a solid dosage form. Several approaches have been attempted and reported during the last decade to develop new methodologies for site-specific drug release, including pH-sensitive drug release and time-controlled drug release. Among these, the time-controlled release systems such as sustained or delayed-release dosage forms are very promising. Nevertheless, due to the potentially large variation of gastric emptying time of dosage forms in humans, these dosage form may show high inter patient variability in the site of drug delivery. On the other hand, pH-sensitive delivery systems such as enteric-coated dosage form offer a simple and practical means for intestinal drug delivery. Esomeprazole magnesium dihydrate, is a classical example of proton pump inhibitors and is approved by FDA for the treatment of symptomatic gastro esophageal reflux disease, short-term treatment and maintenance of erosive esophagitis. Esomeprazole is an S-isomer of omeprazole and the first proton pump inhibitor to be developed as an optical isomer. The drug has an improved pharmacokinetic profile, resulting in increased systemic exposure and less inter individual variability compared with omeprazole, and more effective suppression of gastric acid production compared with other proton pump inhibitors. Its bioavailability is 89% and plasma elimination half-life is 1.5 h. The stability of esomeprazole magnesium trihydrate decreases with a corresponding decrease in the pH of the media. Hence, the exposure of esomeprazole magnesium trihydrate to the acidic contents of the stomach would lead to significant degradation of the drug and would result in reduced bioavailability. Few attempts have been made to deliver this drug by peroral route in the form of enteric coated granules, solid dispersion, suspension. A number of enteric coating polymers are available and capable of protecting the drug core from the aggressive environments of the stomach. Being soluble at higher pH values, these polymers dissolve in the intestine and release the core for ready action. These polymers include several synthetic

polymers like hydroxy propyl methyl cellulose phthalate (HPMCP). The aim of the present study was to compare the suitability of these renowned polymers to develop enteric coated tablets of a very sensitive proton pump inhibitor.

Esomeprazole core tablets were prepared and stabilized using Magnesium carbonate as a stabilizer. A sealcoat of 3% weight gained and using Hypromellose phthalate was sufficient to protect the tablets from the acid coat of the enteric layer. Enteric coating was done using different enteric coating materials hydroxyl propyl cellulose to achieve 5% weight gain. Which were enteric coated to 8% weight gain could pass the disintegration test carried out at pH 1.2. The study indicates that HPC, HPMCP polymers are most suitable for enteric coating. These provide greater protection to the core under acidic condition while at the same time show the fastest drug release under intestinal pH.

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