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AN OVERVIEW ON FORMULATIONS AND THEIR EVALUATION OF ESOMEPAROZLE – A PROTON PUMP INHIBITOR

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ABSTRACT

Esomeprazole, a proton pump inhibitor (PPI) is known to be widely used due to its properties and reduced side effects. There have been many publications in the literature concerning the various formulations with respect to treating various other diseases in combination with other drugs such as antibiotics. Therefore, it was found necessary to present a collective data on the various formulations. The present review is focused on briefing the literature on the formulations of esomeprazole which can be helpful to get further innovative ideas to develop new formulations with increased efficacy.

KEYWORDS: Esomeprazole, proton pump inhibitor, formulations, review

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INTRODUCTION

Esomeprazole is chemically 6-methoxy-2-[(*S*)-(4-methoxy-3,5-dimethylpyridin-2-yl)methylsulfinyl]-1*H*-benzimidazole. It is an S-isomer of the drug omeprazole as shown in figure 1.[1] It was first approved by the FDA in the year 2001 under the brand name Nexium over its dominance on other proton pump inhibitors such as omeprazole, pantoprazole, lansoprazole and rabeprazole in terms of side effects and pharmacokinetic profile.[2, 3] It is rapidly absorbed when administered orally and reaches the plasma concentration in a dose dependent manner.[4] It acts by inhibiting the H+/K+ ATPase enzyme which results in decreased secretion of HCL by the parietal cells of the gastro intestinal tract which is depicted in figure 2.[5] It is effective against Helicobacter pylori when used in combination with antibiotics.[3] Esomeprazole is poorly soluble in water and also gets easily degraded by the acid when reaches the stomach.[6] To overcome such problems and to increase the bioavailability of the drug, several formulations were developed. In this present review, we have briefly discussed the formulations that were developed to overcome the problems of esomeprazole and that which are currently being used to treat gastric ulcers caused due to various NSAIDS and antibiotics.

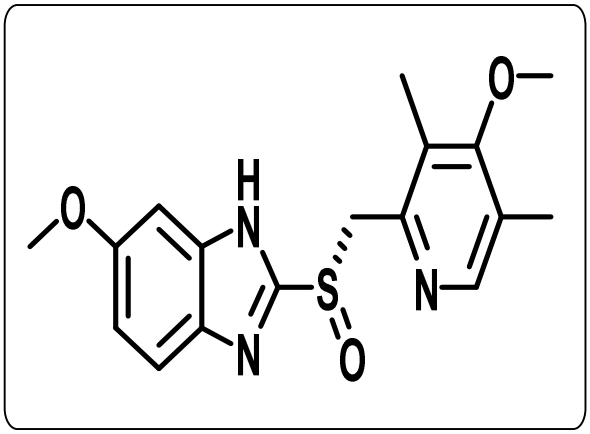

Figure 1: Structure of Esomeprazole

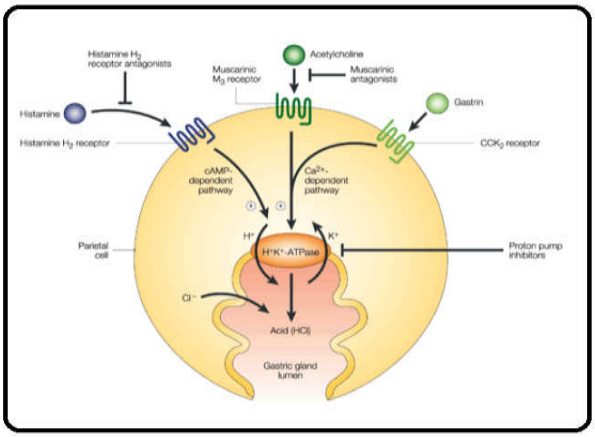

Figure 2: Mechanism of action of PPI's

Esomeprazole tablets were difficult to be swallowed by patients belonging to higher age and also by children. Therefore, to overcome such problem, in 2007, Nina Bladh *et al.,* developed sachet formulation in various strengths which was designed such that it contains acid-resistant pellets and the granules of the excipients which gets reconstituted easily in water. For the convenience of the patients, reconstitution was also investigated in the media other than water such as fruit juice and applesauce and the bioequivalence study was also studied on 94 healthy volunteers and compared with that of the capsule and tablet formulation having the dose of 40mg. The results obtained were quiet impressive as the formulation had short reconstitution time of 30minutes in water as well as the fruit juice and applesauce. The C_{max} of sachet formulation was 2.84 being closer to the capsule (3.16) and tablet (2.98) formulation. [7]

Gastro-esophageal reflux disease (GERD) is a very common problem faced by patients which was treated by prescribing esomeprazole in combination with domperidone by the physicians. To minimize the number of tablets, and for long term therapy, a fixed dose combination (FDC) capsule was developed with no pharmacokinetic profile. However, Sangita Agarwat *et al.,* in 2007 developed sustained release formulation containing esomeprazole 40mg and domperidone 30mg (test) and compared it with commercially available capsule (reference) having same strength to understand the pharmacokinetics.

The bioequivalence study was performed upon 24 volunteers belonging to the age group of 20-38. The

results of the study revealed the formulation to be stable within the equivalence range of 0.80-1.25 and also were well tolerated by the volunteer group as well as there were no drop outs during the study. Moreover, there were no adverse reactions reported. [8]

Esomeprazole in the salt form improves pharmacokinetic profile and metabolic properties there by giving enhanced therapeutic activity. Therefore, Kumar *et al.,* in 2004 first developed and patented the esomeprazole zinc (EZ) but were reported to have poor intestinal absorption and low water solubility. [9] Based on these findings, Yongmei Xie *et al.,* in 2008 prepared solid dispersions of esomeprazole zinc (SDEZ) by solvent method. Carrier for SDEZ used was PEG4000. The preparation when observed through DSC studies, the thermogram as shown in figure 3 reveals no endothermic peak corresponding to SDEZ where as the endothermic peak for EZ and PEG4000 were visible indicating their melting point. The study was conducted in 6 healthy volunteers and the results were shown to have 14.7 fold higher dissolution rates of SDEZ when compared to pure esomeprazole. However, the results when compared with Nexium, the absorption was relatively low for SDEZ. [10]

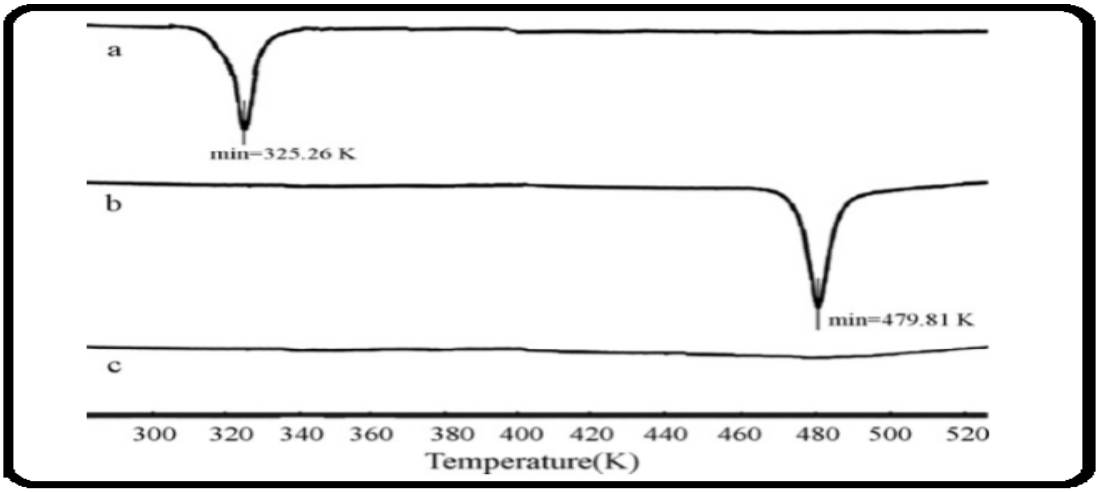

Figure 3: DSC thermogram of (a) PEG4000 (b) EZ powder (c) Solid dispersion

Capsule formulation are not stable for longer duration unlike tablets and may not be favorable to use if the formulation is intended to be dissolved in the intestine as it may degrade due to acidic nature of the stomach. Therefore, there was a need to develop a tablet formulation that could be economical and also be used when desired to disintegrate in the alkaline environment by coating with the enteric polymers which dissolve in the desired pH. Anroop B Nair *et al.,* in 2010, formulated enteric coated tablets using various enteric coating polymers such as Eudragit L-30 D-55, HPMC-P, CAP and Acryl-EZE. When the weight gain was upto 5%, the tablets failed to disintegrate at 0.1N HCl. However, when the weight gain was increased to 8%, they passed the disintegration test at pH 1.2. Among the four different enteric polymers used, methacrylic polymer (Acryl-EZE) showed better dissolution rate when compared to other polymers. [11]

Similar study was done by Shahrzad Missaghi *et al.,* in 2010, they have formulated delayed release multiparticulates of esomeprazole using sugar spheres, hypromellose and polysorbate with the seal coating of hydroxypropyl cellulose followed by enteric coating with Acryl-EXE 93A (aqueous acrylic enteric system) along with other excipients. The results of the drug release profile were found to be excellent as the release of drug in 0.1N HCl or acetate buffer of pH 6.8 was nearly equal. The drug

was shown to be protected in the media for 2 hours followed by their rapid release in the respective media. Moreover, the formulation was shown to be stable for 3 months under accelerated conditions. Following figure 4 shows the drug release profile of esomeprazole. [12]

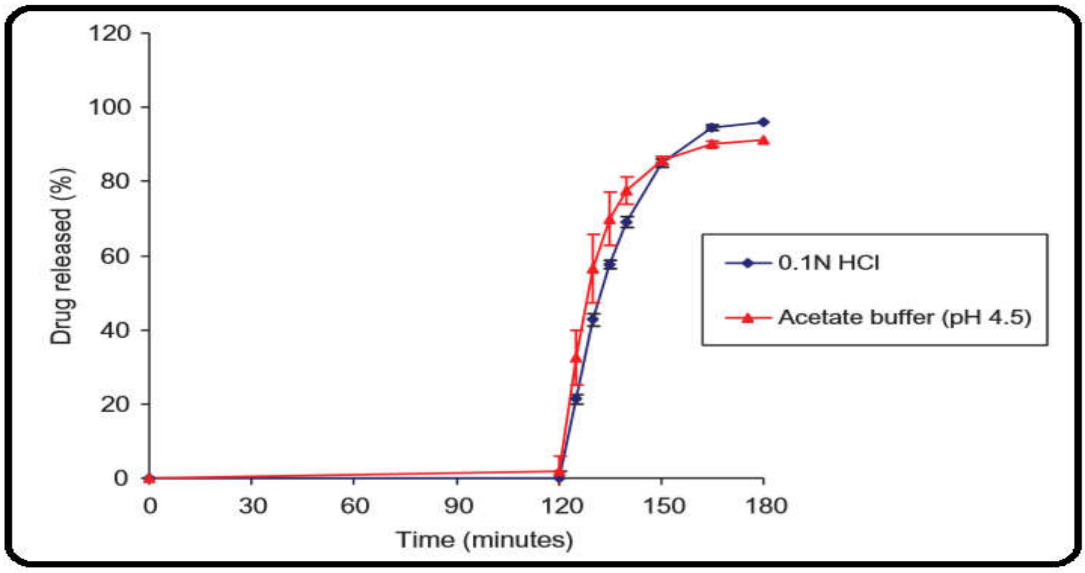

Figure 4: Release profile of enteric coated multiparticulates of esomeprazole

NSAIDS are prescribed to relieve pain and inflammation as these are associated with the inhibition of cyclo oxygenase enzyme (COX). There are two types of COX enzymes and they are COX1 which is associated with gastric mucosal integrity and COX2 which is found in the area of inflammation. [13] The NSAIDS which are used bind irreversible to COX1 during which prostaglandins are released which stimulate the release of bicarbonate and mucous thereby preventing duodenal ulcers but has no effect in preventing gastric ulcers. [14] David N Roberts and Philip B Miner in 2011 developed non enteric coated PN400 FDC formulation for immediate release of esomeprazole 20mg followed by sustained release enteric coated naproxen 500mg. The formulation was subjected to clinical trials. In phase I study was conducted on 28 patients and the formuation was administered 60 minutes before the meals in the morning. The results obtained were consistent and sustained increase of the esomeprazole was observed in the gastric pH > 4. Phase III study which was conducted on 301 volunteers showed significant reduction of gastric ulcers. [15]

In 2012, Dhruv Malik and Inderbir Singh formulated press coated tablets of esomeprazole to enhance the bioavailability of the drug. The formulation was done using various polymers which include pH dependent such as Eudragit L100 and Eudragit S100, enzyme dependent such as Pectin and time dependent such as HPMC K4M with varying concentrations (25%, 50%, 75% and 100%). All the pre-formulation studies were performed and the results were found to be in the acceptance criterion. From the drug release results of post formulation studies which was conducted for 24 hours (2h in 0.1N HCL, 3h in phosphate buffer of pH 6.8 and 19h in phosphate buffer of pH 7.4), there was no drug release in 0.1N HCL by the pH dependent and enzyme dependent polymers except for pectin (25% and 50%). All the concentrations of pH dependent, enzyme dependent and time dependent (except for 25% and 50% of pectin) have shown optimum results of drug release and was considered to be optimum for the press coated formulation of esomeprazole. [16]

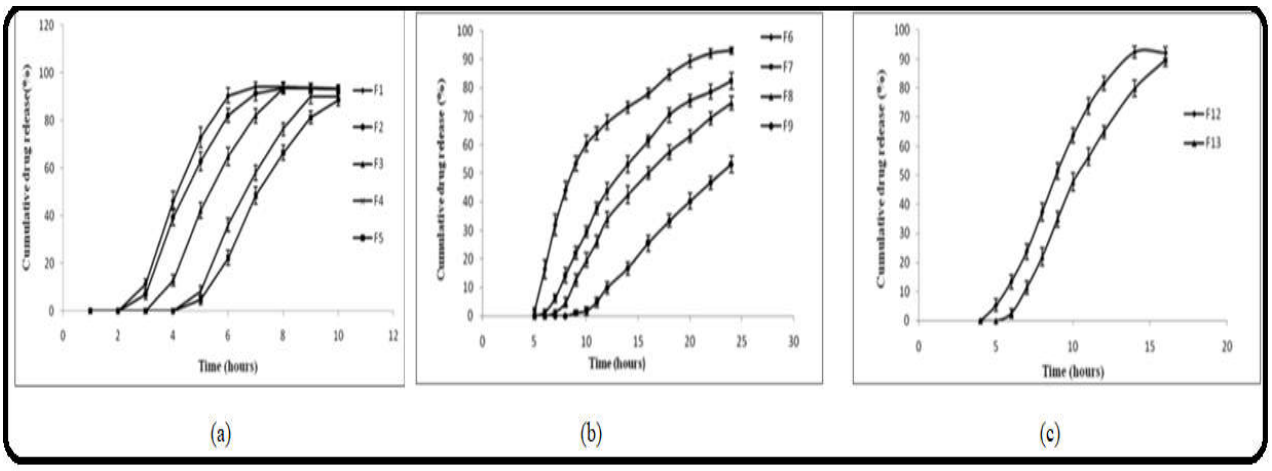

Figure 5: Drug release patter of (a) pH dependent (b) Enzyme dependent (c) Time dependent

In 2013, Prakash Goudanavar *et al.,* formulated floating microspheres of esomeprazole with an objective to increase the gastric retention time. The formulation was done using polymers such as hydroxy propyl methyl cellulose (HPMC) of grade K4M and K15M by double emulsion solvent diffusion technique. The shape of the floating microspheres was determined using scanning electron microscope (SEM) which is shown in the figure **6.** The percentage drug entrapment was around 80% and from the drug release profile in 0.1M HCL, it was observed that the formulation having HPMC K15M along with ethyl cellulose (F5) have good entrapment efficiency with good *in vitro* drug release pattern as shown in figure 7. [17]

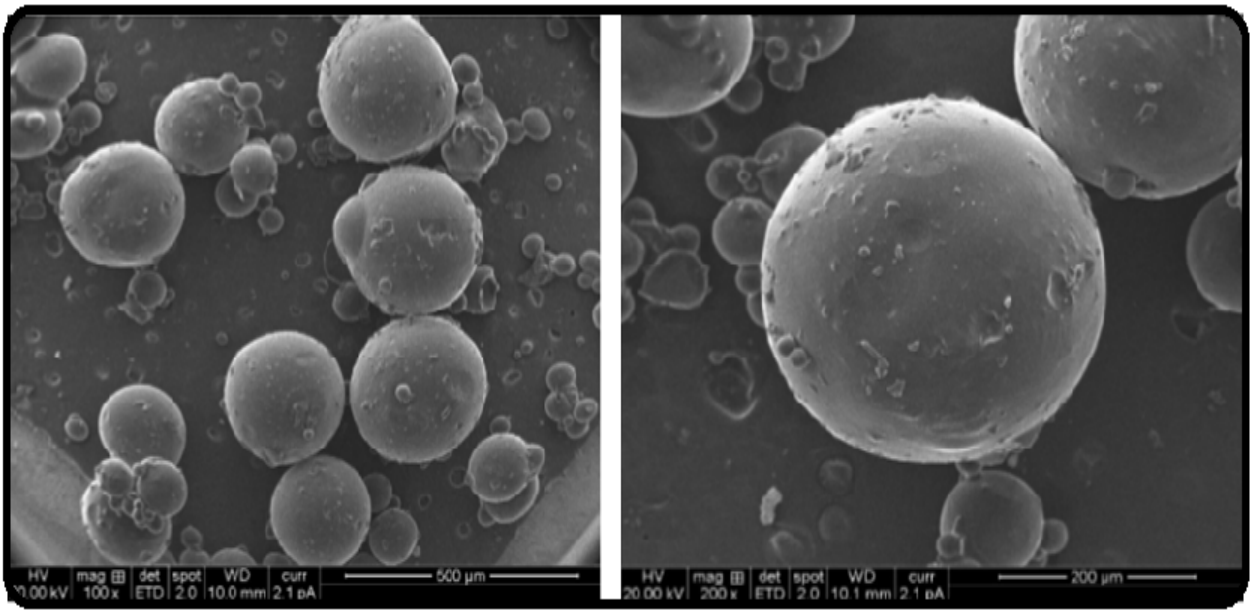

Figure 6: SEM images of floating microspheres

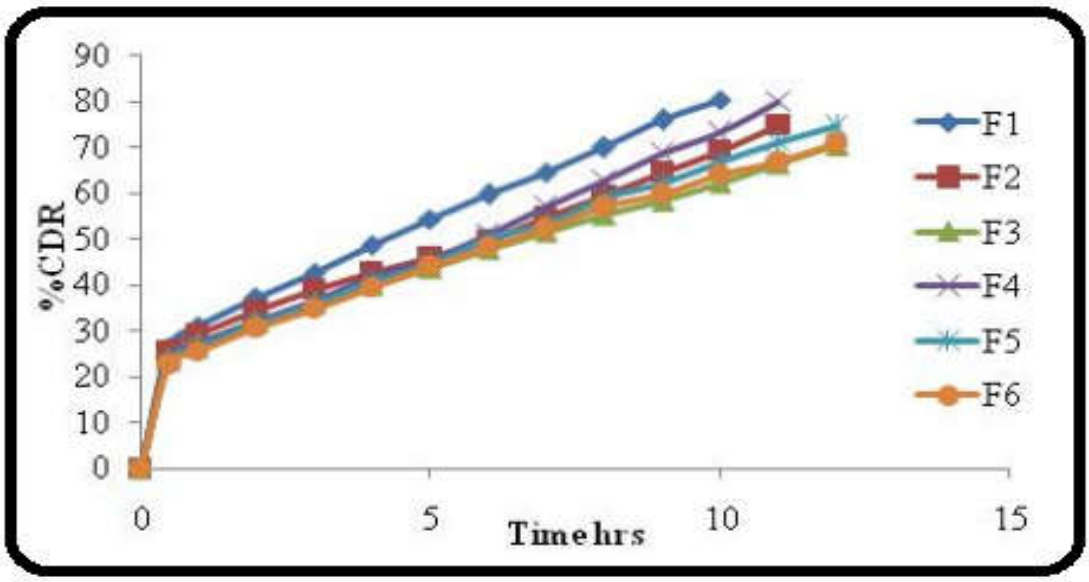

Figure 7: In vitro drug release of floating microspheres

The same year, Achin Jain *et al.,* has developed microsphere formulation using spray dried technique. The microspheres were prepared dissolving in locust bean and xanthun gum. The crosslinking polymer used was gluteraldehyde. Post formulating, it was enteric coated with Eudragit L100. All the post formulation parameters were within the acceptance criteria and the shape of microspheres was determined by SEM. From the entrapment results, it was observed that the formulation was efficient (60.5-92.3% entrapment of the drug). Moreover, the drug release studies, the formulation was found to be suitable as the drug release was sustained (99.8% released at the end of 12th h). [18]

Pellet formulations has wide applications such as they are more predictable, cause less local irritation, has reduced risk of systemic toxicity, etc. [19] Keeping in view of the advantages, Shu-Ling Kan *et al.,* in 2014 has prepared modified release pellets (MRP's) of esomeprazole magnesium using fluidized bed technology. For the sustained release of the formulation, the pellets were coated with Eudragit RS30D/RL30D. To undergo *in vitro* as well as *in vivo* study, final pellets were filled in hard gelatin capsules. For the studies, the optimal formulation was compared with the commercially available formulation NEXIUM. The results achieved good sustained release feature with relative bioavailability of 103.50% and a good correlation was achieved between the *in vitro* and *in vivo* results with the correlation coefficient of 0.9945. [20]

In 2015, Pankaj Kumar *et a1.,* prepared pH sensitive hydroxypropylated maize starch hydrogels by graft polymerization of methyl methacrylate. The prepared hydrogels were analysed through SEM to confirm the entrapment of the drug as shown in figure 8. Drug encapsulation efficiency form the results were found to be >78% and the swelling capability behavior of the hydrogels were found to be pH-responsive. From the *in vitro* drug release study, the formulation was observed to have sustained release of 80-90% up to 14hrs at pH 6.8. The results confirm the efficiency and ability of graft co-polymer hydrogel to release the drug in a controlled manner after a desired time period. [21]

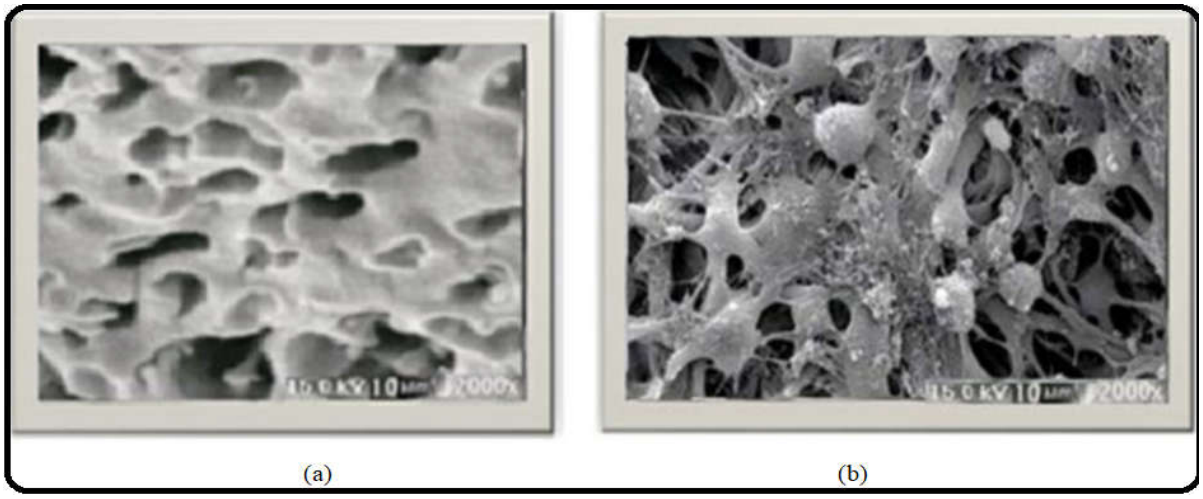

Figure 8: SEM image of (a) Hydrogels (b) Drug entrapped in hydrogel

During the formulation of enteric coated tablets, the polymer is directly in contact with the drug. Despite the fact, that the polymer protects the drug from degrading due to gastric acid, the direct contact of the drug with polymer results in stability problems. Therefore, to overocome such incombatibility, Panagiotis Barmpalexis and Agni Grypioti, in 2017 formulated delayed release formulation with enhanced stability in a three stepped process drug coating, sub (seal) coating and enteric coating on sugar spheres. This prevents the direct contact of the drug with the polymer. Eudragir L30D-55 was used as coating polymer whereas sub(seal) coating polymers used were HPC and HPMC (Image shown in figure 9). From the results obtained after evaluations, the formulation was bserved to have good gastric resistance even in 0.1N HCL as well as pH 4.5 media. Only the HPMC sub(seal) polymer was observed to be stable at 40±2°C/75±5%RH. [22]

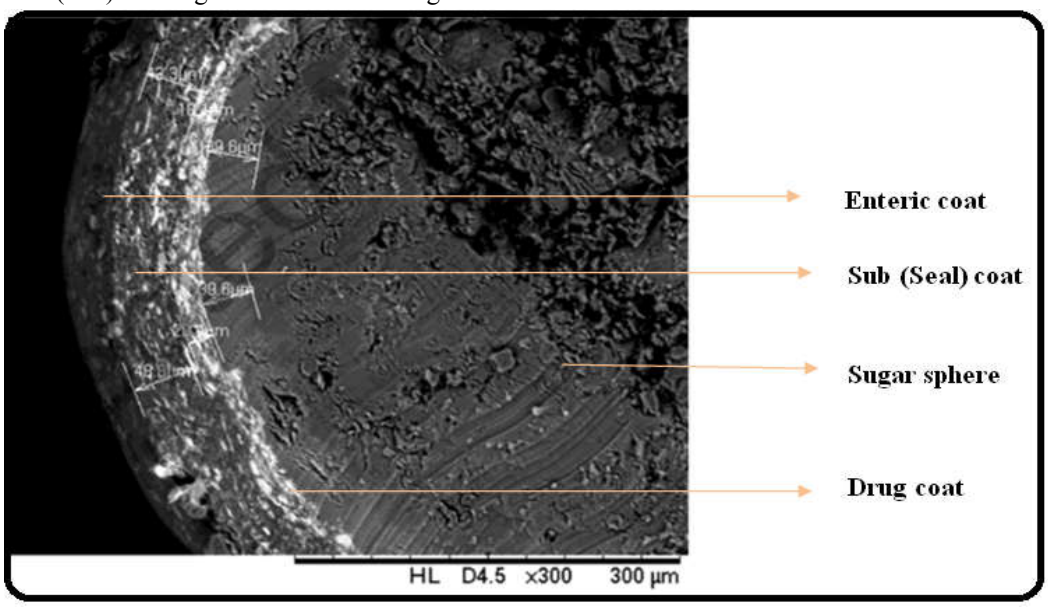

Figure 9: Three step enteric coated formulation

CONCLUSION

The main objective of this review was to collect all the information of various formulations of esomeprazole that were prepared and compare for the best formulation that could be used for further development of new formulation. From the information gathered, the formulation of microspheres, hydrogels were observed to be innovative as the drug entrapment efficiency and their bioavailability were found to be better when compared to other formulations. Therefore, keeping in view of the above literature, one can develop new ideas that may help in developing new formulations which has high efficiency and better drug release properties.

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