FORMULATION AND CHARACTERIZATION OF ALGINATE BEADS FOR CONTROLLED RELEASE OF LANSOPRAZOLE

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SUMMARY

The objective of the present study is to develop alginate beads for Lansoprazole to enhance its bioavailability. Different polymers – HPMC. Eudragit R, Eudragit S- were used. Drug loaded beads have been developed using technique that involves a cross linking reaction. Several parameters such as particle size measurement, encapsulation efficiency, drug release profile, FTIR were investigated. Physicochemical characterization indicated the formation of novel Eudragit and HPMC alginate beads and showed that Lansoprazole does not interfere with the beads formation process. The release study showed the controlled release of Lansoprazole for 24 hours which was more satisfactory in Eudragit coated HPMC-alginate beads than HPMC coated Eudragit–alginate beads. FTIR spectroscopy showed that there was no interaction of Lansoprazole with polymers and solvents. Optical microscopy indicated that the beads after coating with Eudragit and HPMC had an irregular shape.

Keywords- Beads, Lansoprazole, controlled release, Eudragit, HPMC, Alginate.

Introduction

Nearly 2.5 liters of gastric juices secreted by the stomach daily which comprises of prorenin, pepsinogen, hydrochloric acid, intrinsic factor, mucus and bicarbonate ions. Disturbances in the secretory and protective mechanisms are responsible in the pathogenesis of peptic ulcer. Hence regulation of acid secretion by parietal cells provides a particular target for drug action. The major stimuli acting on parietal cells are gastrin, acetylcholine, histamine and prostaglandin E2 and I2. In parietal cells the cyclic AMP and Ca^{2+} dependent pathways activate H^+/K^+ ATPase (the proton pump) thereby exchanging the hydrogen and potassium ions across the parietal cell membrane. The high concentration of H^+ in the gastric lumen needs a robust mechanism to protect the esophagus and stomach. The defense mechanism includes the lower esophageal sphincter, secretion of mucous and bicarbonate ions[1,2]. H_2 antagonists as compared to Proton Pump Inhibitors (PPI's) provides control to both basal and food stimulated acid secretion thereby producing much more effective and longer lasting acid suppression[3]

Proton pump inhibitors such as Omeprazole, Lansoprazole, Pantoprazole, Rabeprazole, Esomeprazole, and Tenatoprazole are used for treatment of many acid related diseases such as gastroesophageal reflux disease (GERD), Barret's esophagus, peptic ulcer disease, Zollinger Ellison syndrome, gastrinomas and gastritis (inflammation of the esophagus/stomach)[4]

Lansoprazole is a very commonly used proton pump inhibitor. It has higher bioavailability, faster onset of action and slightly longer half-life than Omeprazole[5]. The pk_a value of Lansoprazole is 4.5.[6]

Alginates are among the most versatile biopolymers, which are used in a wide range of applications. Alginic acid, a polysaccharide, is a linear copolymer composed of residues of D-mannuronic acid (M) and L-mannuronic acid (G)[7,8]. One of the most important properties of alginate is its ability to form gel with divalent and multivalent ions[9]. It has been found that the gelation is due to the formation of egg-box junction between metal ions with GG block of alginate chain[10]. Conventionally alginate has been used as an excipient in drug products depending upon the thickening, gel-forming, and stabilizing properties. A requirement for prolonged and better control of drug administration has increased the demand for tailor-made polymers. Hydrocolloids like alginate can play a promising role in the design of a controlled-release product. At low pH alginic acid undergoes hydration leading to the formation of a high-viscosity "acid gel." Dried sodium alginate beads reswell which then creates a diffusion barrier lowering the migration of small molecules (e.g., drugs)[11]. Sodium alginate has been used in a variety of oral and topical pharmaceutical formulations. In tablet formulations, sodium alginate may be used as both a binder and disintegrant, it has been used as diluent in capsule formulations. In topical formulations, sodium alginate is widely used as thickening and suspending agent in a variety of pastes, creams and gels, and as stabilizing agent for oil-in-water emulsions[12]. Calcium alginate beads can be produced by dropping sodium alginate aqueous solution into calcium chloride solution.

The aim of this work was to formulate sodium alginate based matrix that effectively prolongs the Lansoprazole release. The acidic environment of the stomach causes significant degradation leading to reduced bioavailability of Lansoprazole. Encapsulation of Lansoprazole protects the drug from the acidic environment thereby improving the bioavailability. For Lansoprazole the stability is pH dependent and rate of

degradation increases with decreasing pH. Enteric coating of Lansoprazole starts to dissolve in the small intestine (high pH environment) and drug is released, resulting in improved bioavailability.

Materials and methods

Materials: Sodium alginate of medium viscosity (viscosity of 2% at 25ºC 3500cps) was obtained from S.D. Fine Chemicals, Mumbai. Calcium chloride was purchased from Merck. Eudragit (RS-100 and RL-100) was a gift sample from Degussa. All related chemicals and reagents were of analytical and reagent grade. Doubly distilled water was used throughout the study.

Preparation of sodium alginate beads of Lansoprazole: Lansoprazole-loaded beads were prepared by extrusion/ precipitation of sodium alginate aqueous suspension containing 1 % w/v Lansoprazole and 2% w/v of sodium alginate. This suspension was prepared by single mixing step which was added, using a peristaltic pump, through a 0.9 mm diameter needle into a gently stirred 10% w/v calcium chloride aqueous solution. Beads were then separated by filtration, washed with deionised water and dried in a fluid bed dryer at 37^0 C for 45 mins. Alginate beads were then coated with Eudragit solution (1:1 mixture of RL-100 and RS-100) and dried and followed by coating with HPMC solution having different concentrations. In another batch it was coated with HPMC solution firstly and dried and then with Eudragit solution. In total 8 formulations were prepared by varying the concentration of the coating solutions. Different formulation codes have been assigned as given in table I.

Ingredients	Formulations							
	F1	F2	F3	F4	F5	F6	F7	F8
Drug	1%	1%	1%	1%	1%	1%	1%	1%
Sodium alginate	2%	2%	2%	2%	2%	2%	2%	2%
Calcium chloride	10%	10%	10%	10%	10%	10%	10%	10%
Eudragit	1%	2%	5%	10%	20%	5%	10%	4%
HPMC	1%	1%	7.5%	5%	2.5%	7.5%	5%	1%

Table I: Composition of the formulations prepared

Particle size analysis: Microscopic examination was carried out for wet beads, placebo beads and dried coated beads using optical microscope (B1 series system microscope, Motic). For measurement of size of different formulation/batches, sample holder was cleaned with distilled water followed by acetone to prevent cross-contamination.

Encapsulation efficiency: Amount of Drug substance loaded in the beads was estimated by crushing beads equivalent to 15mg of Lansoprazole in 20ml of phosphate buffer at 70°C to extract the drug from beads. The solution was centrifuged to remove the suspended polymer particles and the clear supernatant liquid was diluted with buffer solution. Drug was assayed using the UV-VIS spectrophotometer (Lambda 25, Perkin Elmer) at λmax of 284 nm.

Fourier Transform infrared spectra (FTIR): Samples or beads were crushed to make KBr pellets under hydraulic pressure of 600kg/cm^2. FTIR (Spectrum RX I, Perkin Elmer) spectra were taken in the polymer wavelength range between 400 and 4000cm^{-1}.

***In-vitro* drug release:** In-vitro drug release was carried out 37°C in a USP-II rotating paddle dissolution test apparatus (TDT-08L, Electrolab) under sink conditions at a rotation speed of 50 rpm. Drug release from beads was studied both in simulated gastric (0.1N HCl) and intestinal (6.8 pH phosphate buffer) fluids. The dissolution medium was phosphate buffer pH-6.8. At appropriate intervals of time aliquot samples were withdrawn and analyzed for drug on UV-VIS spectrophotometer at 284nm. .

Results and discussion

Particle size analysis

Particle size analysis was done by optical microscope for dried coated sodium alginate beads of Lansoprazole (Figure I); wet beads (Figure II); as well as for placebo beads (Figure III). As expected, drug incorporation lead to increase in particle size. Table II shows the size of the beads.
Microscopic analysis showed that the beads prepared with sodium alginate and calcium chloride and coated with Eudragit and HPMC presented an irregular shape irrespective of the composition and preparation method.

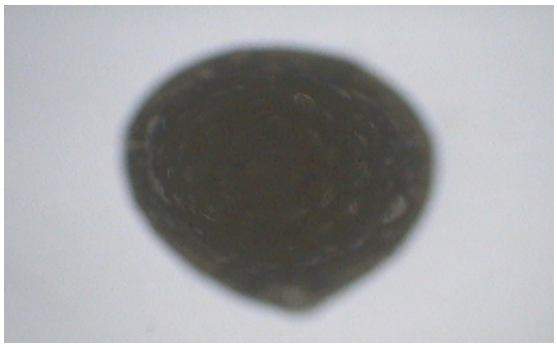

Fig.I. Picture of coated sodium alginate bead of Lansoprazole taken under optical microscope

Fig.II. Picture of wet alginate bead of Lansoprazole

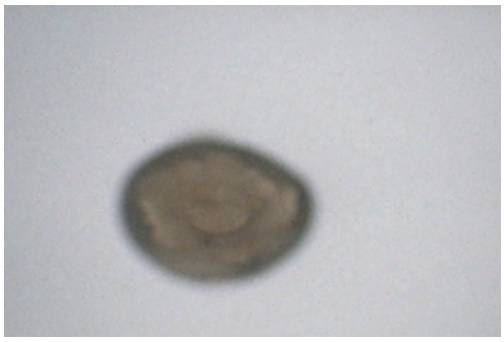

Fig.III. Picture of placebo bead

Type	Size
Placebo beads	700-800µm
Wet beads	2000-2100µm
Beads after coating	900-1000µm

Table II: Size of beads

Encapsulation efficiency

High encapsulation efficiencies (Figure IV) were achieved for all formulations (> 90%). This may be due to low solubility of Lansoprazole in calcium chloride solution.

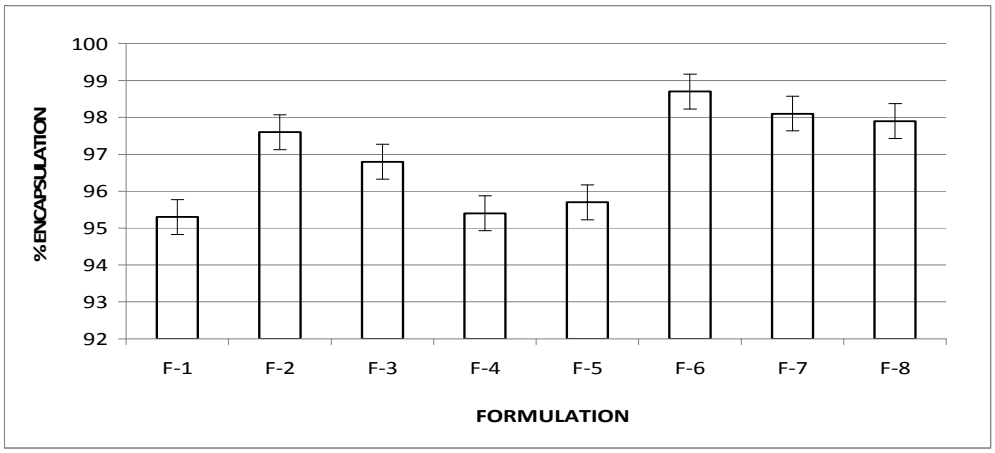

Fig.IV. % encapsulation of formulations

FTIR spectroscopic study

Beads were scanned in the range of 400 to 4000 cm^{-1}.The FTIR spectral analysis of Lansoprazole alone showed that the principal peaks were observed at wave numbers of 3176, 1581. 1400, 1265, 1117, 1039 and 750 confirming the purity of the drug. In the FTIR spectra of Lansoprazole sodium alginate beads peaks were observed at 1581, 1403, 1039, 750. However some additional peaks were observed which could be due to the presence of polymers. FTIR spectra for drug and formulation are shown in Figure V and VI.

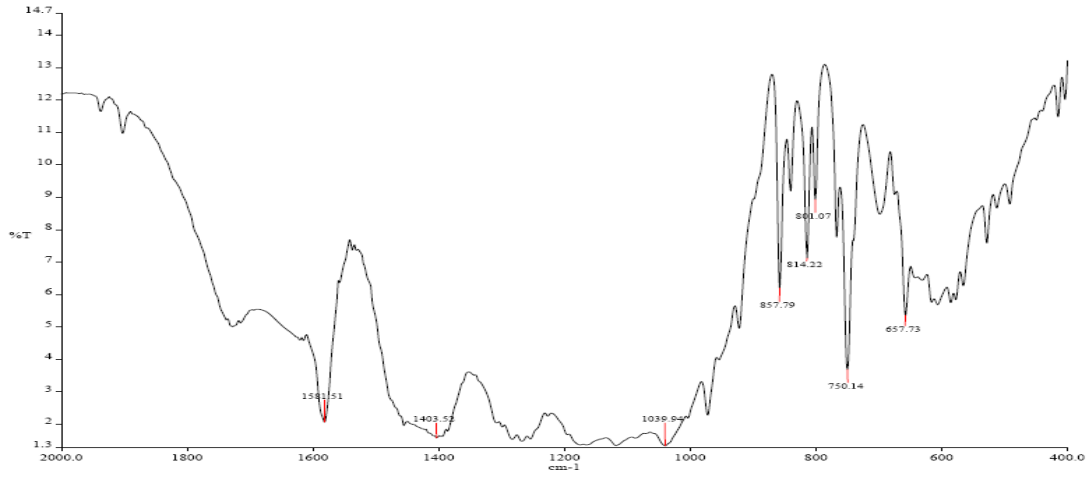

Fig. V. FTIR spectra for Lansoprazole

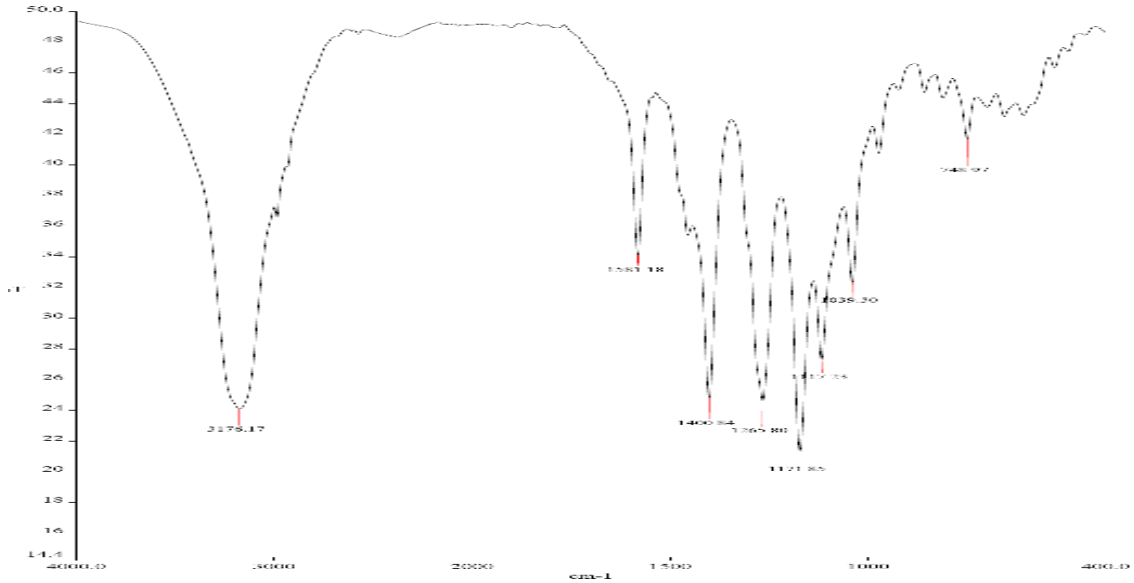

Fig.VI. FTIR spectra for beads of Lansoprazole

***In- vitro* Drug release**

Dissolution studies were carried out for all the 8 formulations. In formulations 1, 2, 3, 4, 5 HPMC was the inner coat and Eudragit was the outer coat whereas in formulations 6, 7, 8 Eudragit was the inner coat and HPMC was the outer coat. Different concentrations of Eudragit and HPMC used are shown in table I. Formulations F1, F2,F3,F4 and F5 showed a good release profile in which nearly 75 % of the drug was released till 12th hour (Figure VII). Formulations F6,F7 and F8 also showed good release profile but more than 85% of drug is release till 12th hour (Figure VIII). So according to the results obtained the formulations in which eudragit is the outer coat gives a better controlled and optimum release of the drug from the beads.

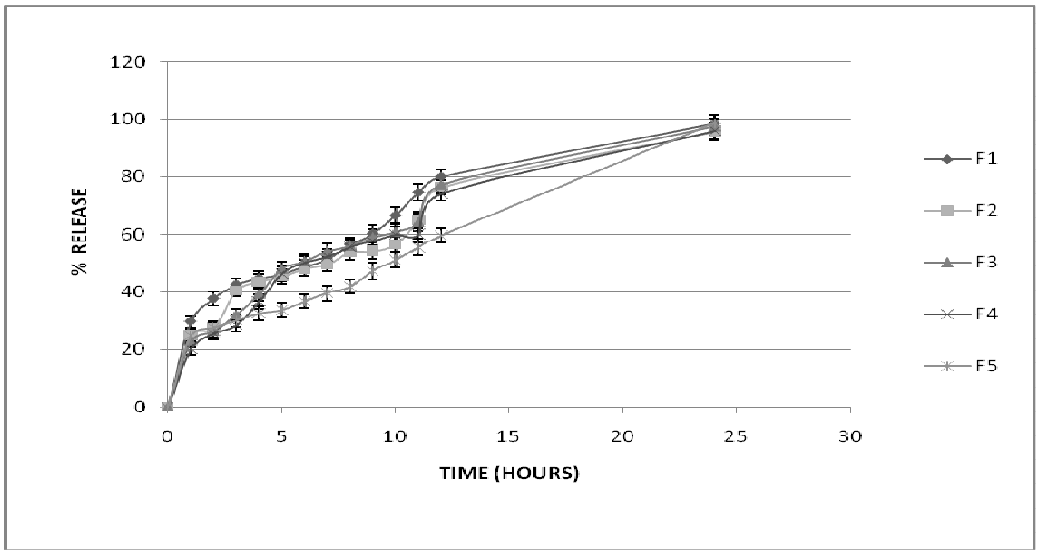

Fig.VII. Graph showing the % release of Lansoprazole from the beads in which HPMC is the inner coat and Eudragit is the outer coat.

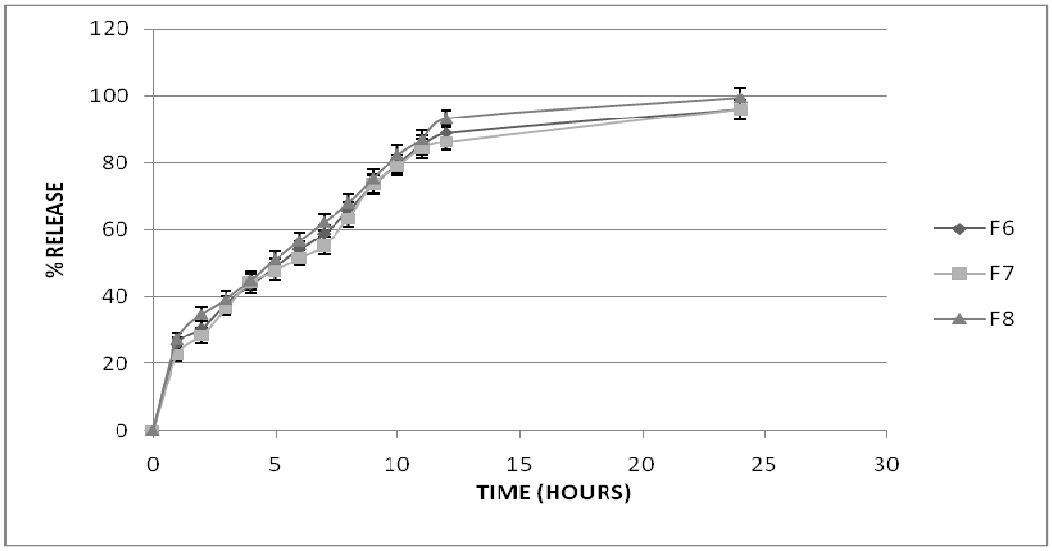

Fig.VIII. Graph showing the % release of Lansoprazole from the beads in which Eudragit is the inner coat and HPMC is the outer coat.

Conclusion

Physicochemical characterization indicated the formation of novel Eudragit and HPMC alginate beads and showed that Lansoprazole does not interfere with the beads formation process. The release study showed the controlled release of Lansoprazole for 24 h which is more satisfactory in Eudragit coated HPMC-alginate beads than HPMC coated Eudragit–alginate beads. FTIR spectroscopy showed that there was no interaction of Lansoprazole with polymers and solvents.

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