ORIGINAL ARTICLE

Formulation and evaluation of press coated tablets of esomeprazole for colonic delivery

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The present study was aimed to formulate press-coated tablets of esomperazole magnesium trihydrate for colon specific delivery. Press coated tablets were formulated with an aim to prevent the gastric degradation of drug so as to improve the bioavailability of drug. Various polymers such as pH-dependent (Eudragit L100, Eudragit S100), enzyme-dependent (Pectin), and time-dependent (HPMC K4M) were selected for press coating the drug-incorporated core tablets. Fourier Transform Infrared (FTIR) analysis was performed to check the compatibility of drug and polymers. Core and coating materials were evaluated for pre-compression parameters like bulk density, tapped density, angle of repose, carrs index, and hausner's ratio. Press coated tablets were evaluated for hardness, thickness, friability, tensile strength, drug content, and *in vitro* drug release. *In vitro* release studies were performed for 24 hours, first 2 hours in 0.1 N HCl, 3 hours in phosphate buffer (pH 6.8), and then for 19 hours in phosphate buffer (pH 7.4). *In vitro* drug release studies revealed that the tablets coated with pH-dependent, enzyme-dependent, and time-dependent polymers showed no drug release in 0.1 N HCl, except for tablets coated with Pectin (25% and 50%, w/w). Kinetic modeling showed that the release exponent (n) value for all formulations was >0.89, indicating super case II transport to be the drug release mechanism. Press coated tablets for colonic delivery of esomeprazole magnesium trihydrate were successfully developed.

Key words: *Colon specific drug delivery system, eudragit L100, eudragit S100, Hydroxypropyl methyl cellulose K4M (HPMC K4M), pectin*

INTRODUCTION

Targeted drug delivery to colon is highly desirable for local treatment of a variety of bowel diseases such as ulcerative colitis, crohn's disease, amebiosis, colonic cancer, local treatment of colonic pathologies, and systemic delivery of protein and peptide drugs.[1] However, treatment can be made effective if the drugs can be targeted directly into the colon, thereby reducing the systemic side effects.[2] The colon specific drug delivery system (CDDS) should be capable of protecting the drug en route the colon, 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.[3] CDDS is applicable when localized delivery of drugs is required in colon, drugs are prone to degradation and poorly absorbed in the upper gastrointestinal tract (GIT). There are four major approaches for CDDS, viz. pH-dependent systems, time-dependent systems, colonic micro flora-activated systems, and use of prodrugs.[4,5] Whichever approach is adopted, the crucial concern is sufficient and successful delivery of the drug to the colon.

Press coating process involves compaction of coating material around a preformed core. Press coated tablets have two layers, an inner core containing the drug and an outer polymeric coat. This technique gained advantage over the conventional liquid coating, since the process does not need the use of solvents, requires a relatively short manufacturing process, and allows greater weight gain to the core tablet.[6] Different drug release patterns could be obtained depending upon the type and composition of the coating layer. Press coated tablets also offers other advantages like protecting hygroscopic, light-sensitive, oxygen labile, or acid-labile drugs, separating incompatible drugs from each other, modifying drug release pattern (delayed, sustained, pulsatile, and programmable release for different drugs in one tablet).[7]

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Esomeprazole magnesium trihydrate is a classical example of proton pump inhibitor used for the treatment of gastroesophageal reflux disease, duodenal ulcers caused by *H. pylori*, erosive esophagitis, nonerosive reflux disease (heartburn and regurgitation), gastrointestinal ulcers associated with Crohn's disease, and for prevention of gastric ulcers in patients on chronic NSAID therapy. Esomeprazole is an S-isomer of omeprazole and the first proton pump inhibitor to be developed as an optical isomer. 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.[8] Its bioavailability is 89% and plasma elimination half life is 1.5 hour. 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 in 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-hydroxymethylesomeprazole and 5-carboxyesomeprazole.[9]

The aim of the present study was to formulate press coat esomperazole magnesium trihydrate core tablet with different polymers viz. pH-dependent (Eudragit L100, Eudragit S100), enzyme-dependent (Pectin), and time-dependent (HPMC K4M) in different proportions to prevent the gastric degradation of drug in order to improve the bioavailability of the drugs. The formulated tablets were evaluated for various tablet parametric tests including hardness, thickness, friability, tensile strength, drug content, and *in vitro* drug release. The *in vitro* drug release data was fitted to various kinetic models namely zero order, first order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas for studying the mechanism of the drug release from the formulation.

MATERIALS AND METHODS

Materials

Esomeprazole was received as a gift sample from Ranbaxy Laboratories Ltd., Ponta Sahib (HP), India. Avicel 102 was kindly gifted by Signet Chemical Cooperation Pvt. Ltd., Mumbai, India. Pectin CU 201 was received as a gift sample from Herbstreith and Fox KG, Neuenberg, Germany. HPMC K4M was received from Cadila Healthcare, Baddi (HP), India. Eudragit L 100 and Eudragit S 100 were received as gift samples from Evonik Degussa India Pvt. Ltd., Mumbai, India.

Drug-excipient compatibility studies

Drug-excipient compatibility was studied using ATR-FTIR (Bruker spectrophotometer, Model-Alpha 200385), and the spectra were recorded in the wavelength region of 4000-450 cm^{-1}. Samples of pure drug, pure polymer, and the physical mixtures containing both the drug and polymer were scanned in the mentioned wavelength region.

Pre-compression evaluation

Flow properties and compressibility properties of powder mixture were evaluated by measurement of angle of repose, bulk density, tapped density, carr's index, and hausner ratio.

Formulation of core tablets

Core tablets were prepared as per the formula given in Table 1. All the ingredients were passed through 60# sieve, followed by mixing for 15 minutes by tumbling. Tablets with a theoretical weight of 70 mg were obtained using multipunch tableting machine (A K Industries, Nakodar, India) fitted with 6-mm concave-round die-punch tooling.

Press coating of core tablets

The formulated core tablets were press coated with an appropriate blend of coating polymer [Table 2]. Half the quantity of the coating polymer was filled into the die cavity (8.5-mm diameter). The core tablet was placed in the centre of the die cavity, which was then filled with the remainder of the coating material. Then, it was compressed around the core tablets at

Table 1: Formulation of core tablet

Ingredients	Quantity (mg)
Esomperazole magnesium trihydrate	20
Sodium starch glycolate	4
Magnesium stearate	1
Talc	1
Avicel 102	44
Total weight	70

Table 2: Press-coat composition of the different formulations

Batches	Polymer %				
	pH dependent		Time dependent HPMC K4M	Enzyme dependent Pectin CU201	Avicel 102
	Eudragit L100	Eudragit S100			
F1	100	-	-	-	-
F2	75	25	-	-	-
F3	50	50	-	-	-
F4	25	75	-	-	-
F5	-	100	-	-	-
F6	-	-	25	-	75
F7	-	-	50	-	50
F8	-	-	75	-	25
F9	-	-	100	-	-
F10	-	-	-	25	75
F11	-	-	-	50	50
F12	-	-	-	75	25
F13	-	-	-	100	-

an applied force of 5000 kg using 8.5-mm concave punches fitted to multipunch tableting machine.

Evaluation of press-coated tablets

Hardness and friability

Hardness and friability were determined using the validated Monsanto hardness tester and the Roche friabilator (Camp-bell Electronics, Mumbai, India), respectively.

Thickness

The thickness of the tablets was determined using Digital Vernier Caliper (Mitutoyo Absolute Digimatic Caliper, Japan). Five tablets from each formulation were used and the average values were calculated.

Tablet tensile strength

The tablet tensile strength is the force required to break a tablet by compressing it in the radial direction and is measured using a Monsanto hardness tester. For measuring the hardness of the tablets, the plunger of the hardness tester is driven down at a speed of 20 mm/min. Tensile strength for crushing (T) is calculated using the following equation:

$$T = 2F/\pi dt \quad (1)$$

Where, F is the crushing load and d and t signify the diameter and thickness of the tablet respectively.

Uniformity of content

Ten tablets were finely powdered and quantity of powder equivalent to 20 mg of esomeprazole magnesium trihydrate was accurately weighed and transferred to 100 ml volumetric flask containing phosphate buffer (pH 7.4) and mixed thoroughly and filtered. One milliliter of filtrate with suitable dilution was estimated for esomeprazole magnesium hydrochloride content at 295 nm using double beam UV spectrophotometer (AU 2701, Systronics, Mumbai, India).

In-vitro drug release studies

The dissolution study was performed using USP dissolution apparatus II paddle assembly (DS 8000, LABINDIA, Mumbai, India) at 75 rpm and 900 ml of dissolution fluid at 37 ± 1°C. The formulations were tested individually in 0.1 N HCl (pH 1.2) for first 2 hours, in phosphate buffer (pH 6.8) for the next 3 hours, and then in phosphate buffer (pH 7.4) for the next 19 hours. These media were selected to mimic the conditions in stomach, small intestine, and colon, respectively. Aliquot samples were withdrawn at specified time intervals and were analyzed spectrophotometrically (AU-2701, Systronics, Mumbai, India) at 297, 295, and 295.6 nm for the three media, respectively. The volume of the sample withdrawn each time was replaced with the same volume of the respective buffer solution. The dissolution study of enzyme dependent formulations was performed in presence of pectinolytic enzyme (4 mL/L). The studies were conducted in triplicate and the mean values were plotted versus time with standard error of mean, indicating the reproducibility of the results.

Kinetics of drug release

The dissolution data obtained were fitted into various kinetic models, namely, zero order, first order, Higuchi, Hixson–Crowell, and Korsmeyer–Peppas. This was to determine the mechanism of a drug release.

Higuchi model relates the relationship between the quantity of drug released and the square root of time.

$$Q = K_H t^{1/2} \quad (2)$$

The quantity of drug released was plotted against square root of time. The Higuchi release constant K_H and r^2 value were extracted from the graph. The Higuchi constant reflects the design variables of the system. Hence, drug release rate is proportional to the reciprocal of the square root of time.[10]

For zero order, from the equation $C = K_0 t$, drug concentration was plotted against time. The zero order rate constant K_0 and the regression line (r^2) values were also extracted from the graph.

For First order release kinetics, Log cumulative percent drug remaining was plotted against time. The first order rate constant K_1 and the regression line value (r^2) were extracted from the graph.

For Hixson–Crowell (Hixson and Crowell, 1931) release mechanism, cube root of percent drug remaining at time *t* was plotted against time in hour. Then, the rate constant of release and the regression line value (r^2) were extracted from the graph.[11]

Mechanism of drug release

Korsmeyer *et al.* derived a simple relationship that described drug release from a polymeric system, Equation 2. To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model:

$$M_t/M_\infty = Kt^n \quad (3)$$

Where, Mt/M_∞ is a fraction of drug released at time *t*, *k* is the rate constant, and *n* is the release exponent. The *n* value is used to characterize different release mechanisms as given in Table 3.[12]

Table 3: Different release mechanisms

Diffusion exponent (*n*)	Overall solute diffusion mechanism
0.45	Fickian diffusion
0.45<*n*<0.89	Anomalous (non-Fickian) diffusion
0.89	Case-II transport
n>0.89	Super case-II transport

RESULTS AND DISCUSSION

Compatibility studies by FTIR analysis

FTIR spectrum of Esomeprazole magnesium trihydrate is characterized by the absorption band of sulphonyl group at 1077 cm^{-1}, secondary amine C-N stretch at 1152 cm^{-1}, methylene C-H bend at 1475 cm^{-1}, aromatic C-H out of plane bend at 768 cm^{-1}, alkyne C-H bend at 634 cm^{-1}, and weak band at 2830-2800 cm^{-1} shows the presence of methoxy groups [Figure 1]. The presence of characteristic peaks of drug in the FTIR spectra of physical mixture (Drug: Polymer) indicates the absence of chemical interaction between the drug and the polymers employed in the study.

Precompression parameters

Powder blends used for preparing core tablets and polymeric compositions used for press coating the core tablets were evaluated for angle of repose, bulk density, tapped density, hausner ratio, and carr's index. The values for angle of repose, hausner ratio, and compressibility index were found to be in good correlation, indicating that all formulations possess good flow property and compressibility [Table 4].

The values of angle of repose of formulations F1, F2, F3, F4, F5, F6, and F10 were <25, indicating excellent flow properties. The values for angle of repose of other prepared formulas was in the range of 25-30, indicating good flow properties. Carr's index for powder blends of F1, F2, F3, F4, F5, F6, and F10 were in the range of 5-15, indicating excellent flow properties. Carr's index value of rest formulations indicates good flow. However, Carr's index is a one-point determination and does not reflect the ease or speed with which consolidation occurs. Hausner ratio is related to interparticle friction. Powders with low interparticle friction have ratios of approximately 1.2, whereas more cohesive, less flowing powders have ratios >1.6. Hausner ratio values for all the formulas were approximately 1.2, indicating low interparticle friction.

Characterization of core and press coated tablet

The core tablets were tested for diameter, thickness, hardness, tensile strength, friability, and drug content uniformity. Diameter, thickness, hardness, and tensile strength were found to be within acceptable limit. The

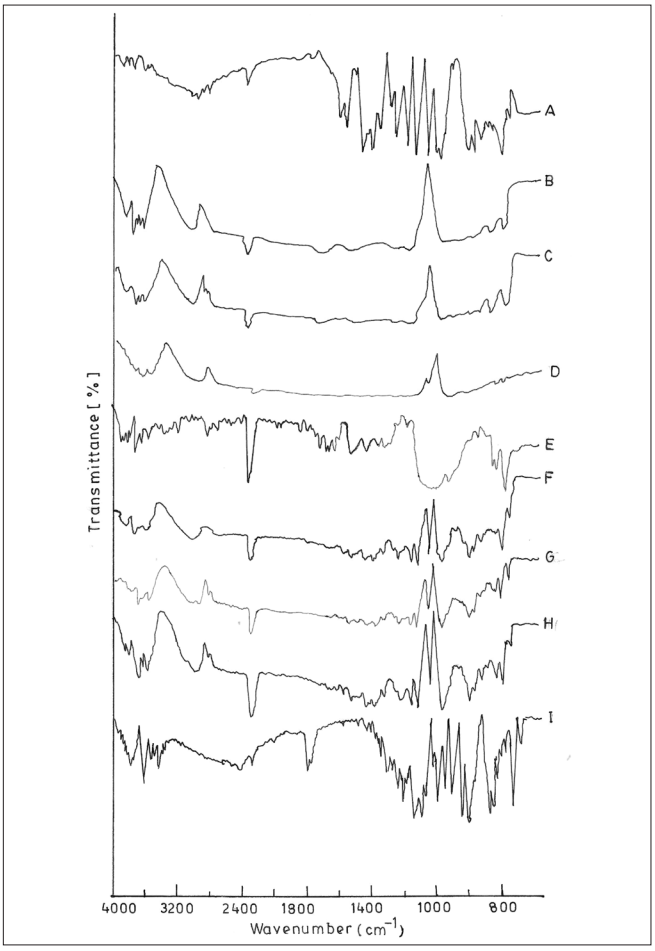

Figure 1: FTIR Spectra of drug, polymers, and physical mixture of drug and polymers. A - Drug, B-Eudragit L100, C-Eudragit S100, D-Pectin CU201, E-HPMC K4M, F-Drug+Eudragit L100, G-Drug+Eudragit S100, H-Drug+Pectin CU201, I-Drug+HPMC K4M

Table 4: Pre-compression evaluation result

Batch	Angle of repose (Degrees)	Bulk density (gm/cm³)	Tapped density (gm/cm³)	Carr's index (%)	Hausner ratio
F1	20.13±0.08	0.476±0.001	0.547±0.002	12.97±0.14	1.14±0.01
F2	20.92±0.07	0.483±0.001	0.557±0.002	13.30±0.16	1.15±0.01
F3	21.33±0.09	0.487±0.001	0.564±0.001	13.40±0.14	1.16±0.01
F4	22.46±0.08	0.493±0.002	0.572±0.002	13.80±0.18	1.16±0.02
F5	24.09±0.10	0.502±0.002	0.583±0.002	13.90±0.17	1.16±0.01
F6	24.33±0.06	0.513±0.002	0.596±0.002	13.90±0.16	1.16±0.01
F7	26.26±0.08	0.494±0.002	0.583±0.002	15.20±0.17	1.18±0.02
F8	27.82±0.07	0.470±0.002	0.565±0.001	16.81±0.14	1.20±0.01
F9	29.24±0.10	0.457±0.002	0.553±0.002	17.35±0.16	1.21±0.01
F10	23.33±0.06	0.526±0.002	0.615±0.001	14.47±0.15	1.17±0.01
F11	25.45±0.08	0.519±0.001	0.611±0.001	15.05±0.14	1.17±0.01
F12	27.14±0.08	0.513±0.001	0.614±0.002	16.44±0.16	1.20±0.01
F13	29.23±0.10	0.508±0.001	0.612±0.001	16.99±0.13	1.20±0.01

friability was <1%, indicating good mechanical resistance of the tablet. Drug content of core tablets was observed in the range 96.2-99.5%.

The press coated tablets were also tested for various tablet parametric tests viz. diameter, thickness, hardness, tensile strength, and friability. The results of the same are shown in Table 5.

In vitro dissolution testing

pH-dependent polymers

Core tablets press coated with pH-dependent polymers (Eudragit S 100 and Eudragit L 100) in different proportions showed no drug release in 0.1 N HCl after 2 hours. Formulation F1 coated with Eudragit L100 alone exhibited fastest release among all pH-dependent polymers formulations. F1 released >90% drug in 7 hours. This might be due to the pH-dependent solubility of Eudragit L100 in pH 6, which, upon addition of phosphate buffer (pH 6.8), dissolved rapidly. On the other hand, formulation F5 coated with Eudragit S100 alone exhibited slowest release, and most of the drug release occurred after the addition of phosphate buffer (pH 7.4), this might be due to pH-dependent solubility of Eudragit S100 in pH above 7. F5 released 88.57% of drug in 10 hours. F2 released >90% drug in 7 hours, and F3 released 90% drug in 8 hours, whereas F4 started releasing drug after 4 hours and released 90% drug in 9 hours [Figure 2]. This might be due to the formation of pores/channels in the formulation because of solublization of Eudragit L 100, which constitutes 75% of the polymer composition in F2. Comparatively lesser channels/pores for the release would be available in case formulation F4 because of the presence of Eudragit S 100 contributing 75% of polymer concentration. As the concentration of Eudragit S 100 is increased in the formulation, rate of drug release from tablets reduced because of pH-dependent solubility of the polymer.[13]

All pH dependent formulations followed zero-order release, except F2 that followed Hixson–Crowell release model [Table 6]. Although Hixson–Crowell appeared to be the predominant release mechanism in F2 due to its higher regression line slope value, its Korsemeyer–Peppas "n" value was 2.84 (Super case II transport), which still confirms the

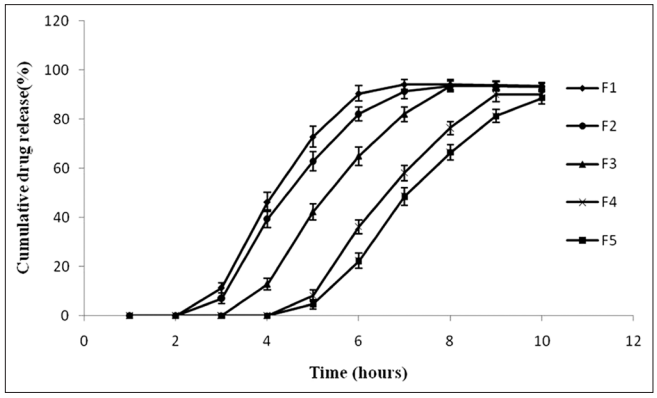

Figure 2: *In vitro* drug release from formulations comprising of pH-dependent polymers

Table 5: Post-compression evaluation results

Batches	Hardness (kg/cm²)	Friability (%)	Thickness (mm)	Tensile strength (MN/m²)
F1	6.08±0.12	0.52±0.09	4.65±0.016	0.959±0.016
F2	5.83±0.23	0.58±0.11	4.71±0.016	0.908±0.019
F3	5.66±0.23	0.59±0.14	4.72±0.012	0.880±0.020
F4	5.66±0.23	0.63±0.10	4.79±0.029	0.867±0.017
F5	5.33±0.11	0.64±0.13	4.83±0.032	0.809±0.013
F6	7.41±0.12	0.48±0.09	4.05±0.016	1.342±0.028
F7	7.16±0.23	0.50±0.13	4.21±0.016	1.244±0.026
F8	6.41±0.12	0.53±0.10	4.37±0.012	1.068±0.019
F9	6.16±0.23	0.57±0.11	4.43±0.024	1.059±0.018
F10	7.16±0.23	0.58±0.12	4.82±0.036	1.087±0.023
F11	7.08±0.12	0.61±0.14	4.73±0.016	1.097±0.022
F12	7.33±0.11	0.68±0.15	4.62±0.012	1.156±0.029
F13	7.83±0.23	0.79±0.14	4.73±0.016	1.215±0.026
Core tablet	4.66±0.23	0.46±0.08	3.12±0.008	1.548±0.031

Table 6: Various release models and their release parameters

Batch	Zero order		First order		Higuchi		Hixson-Crowell		Korsmeyer-Peppas		
	k_0	r^2	k_1	r^2	k_H	r^2	k_{HC}	r^2	k_{KP}	*n*	r^2
F1	−29.9	0.942	2.44	0.902	−85.5	0.903	5.63	0.932	−0.314	2.95	0.846
F2	−30.1	0.945	2.39	0.927	−81.5	0.893	5.52	0.948	−0.331	2.84	0.873
F3	−32.0	0.922	2.38	0.827	−79.6	0.845	5.57	0.880	−0.44	2.53	0.715
F4	−31.4	0.909	2.33	0.819	−75.6	0.824	5.48	0.865	−0.43	2.40	0.705
F5	−30.8	0.901	2.25	0.800	−67.7	0.761	5.34	0.828	−0.42	1.95	0.506
F6	−4.46	0.893	2.18	0.982	−46.1	0.928	4.97	0.973	−0.61	2.16	0.707
F7	−14.6	0.958	2.15	0.955	−48.3	0.906	5.05	0.964	−0.70	1.95	0.767
F8	−15.5	0.951	2.12	0.936	−43.8	0.870	5.01	0.947	−0.76	1.85	0.751
F9	−13.2	0.878	2.07	0.852	−29.8	0.742	4.89	0.862	−0.77	1.53	0.646
F12	−24.8	0.936	2.28	0.839	−63.5	0.849	5.35	0.893	−0.52	2.02	0.727
F13	−24.0	0.918	2.25	0.833	−58.8	0.815	5.28	0.879	−0.62	1.92	0.665

k_0: Zero-order release rate constant, k_1: First-order release rate constant, k_H: Higuchi release rate constant, k_{KP}: Korsemeyer–Peppas release rate constant, k_{HC}: Hixson–Crowell release rate constant, r^2: Regression line value

zero order to be the predominant drug release mechanism. The values of release exponent (n) for all formulations of pH-dependent polymers (F1–F5) were >0.89, indicating Super case II transport. From the study, it is evident that pH-dependent solubility of the polymers plays role in the release of drug from the dosage form. Moreover, polymer chain disentanglement and erosion caused by the dissolution media might also be contributing to the drug release. As drug release from polymeric matrix formulation is a complex phenomenon, another possible theory that could be used to explain the drug release mechanism from the dosage form is the increase in the polymeric chain mobility caused by the dissolution media that initiates the glass to rubbery transition of the polymeric dosage form, thereby allowing the drug molecules to dissolve and diffuse through the gel layer.

Time-dependent polymers

Tablets coated with HPMC K4M 100% showed lag time of 8 hours and released only 53.17% drug after complete dissolution studies. F7 and F8 coated with 50% and 75% of HPMC K4M released 82.42% and 74.72% in 24 hours of the dissolution studies. F6 coated with 25% HPMC K4M showed minimum lag time of 4 hours and released maximum amount of 93.07% drug among all time-dependent formulations (F6-F9) in the target area. The rate and extent of drug release from the formulations increases with the decrease in concentration of HPMC K4M in the coat. The decrease in drug release and increase in lag time by increasing HPMC K4M concentration in the coat could be due to swelling of the polymer, thereby formation of a thick viscous gel layer around the core tablet on exposure to the dissolution fluids. This viscous gel layer retards the seeping of the dissolution fluids into the core tablets and reduces the diffusion of drug from the core leading to retardation of the drug release from the formulation.[13] The extent of drug release from the formulations coated with time-dependent polymers could be arranged in the following order: F6 (93.07%) > F7 (82.42%) > F8 (74.72%) > F9 (53.17%) > F9 (17.462%) [Figure 3]. By studying the kinetic release data, it was found that the values of *n* for time-dependent polymers coated formulations were >0.89 [Table 6], indicating Super case II transport, which reflects involvement of polymer chain relaxation and plasticization process in the gel layer. At lower HPMC concentrations, swelling and relaxation of the polymeric chains leading to increased mobility of the polymeric threads might be responsible for the drug release. At higher HPMC concentrations, decrease in polymeric chain mobility and relaxation might play role in the retardation of drug release from the tablets. Also, at higher HPMC concentrations, reduction in wettability, media uptake and erosion can also contribute in the retardation of drug release from the formulation. Moreover, the formation of a thick viscous gel layer around the core tablet at higher HPMC concentrations retards seeping of dissolution fluids and reduces the diffusion of drug from the formulation.

Enzyme-dependent polymers

Formulations F10 and F11 coated with Pectin 25% and Pectin 50% were unable to prevent the release of drug in 0.1 N HCl (pH 1.2). But when the concentration of Pectin was increased to 75%, the formulation showed significant drug release in the target area and showed no drug release in acidic environment. Formulation F12 coated with Pectin 75% showed lag time of 4 hours and released maximum amount of 92.36% drug in 14 hours, while formulation F13 coated with 100% Pectin showed lag time of 5 hours and released drug at slower rate and released maximum amount of 89.76% drug in 16 hours [Figure 4]. In acidic medium, about 99% of the acidic groups on the pectin molecules are in the unionized form. Due to the lack of columbic repulsion, the linear pectin molecules interact with each other and form insoluble complexes, inhibiting the drug release from the formulation. This could be the probable reason for no drug release from F12 and F13 formulation in the acidic media. F10 and F11 formulations could not resist the drug release in the acidic environment; this could be due to lesser concentration of pectin; hence, non formation of insoluble complexes responsible for the drug release from the formulation in acidic media. It was found that the rate and extent of drug release from the tablets coated with pectin was dependent on the polymer concentration in the coat. The rate and extent of drug release decreases with

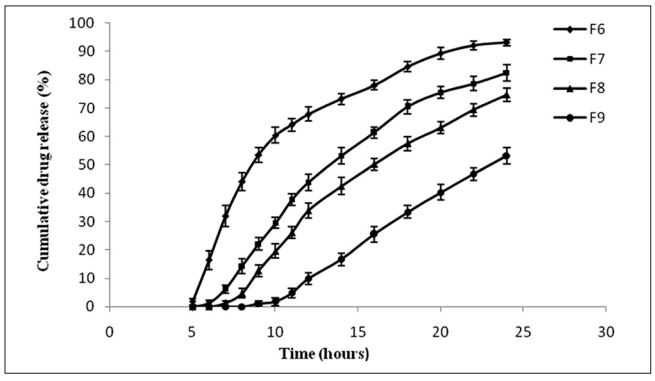

Figure 3: *In vitro* drug release from formulations comprising of time-dependent polymer

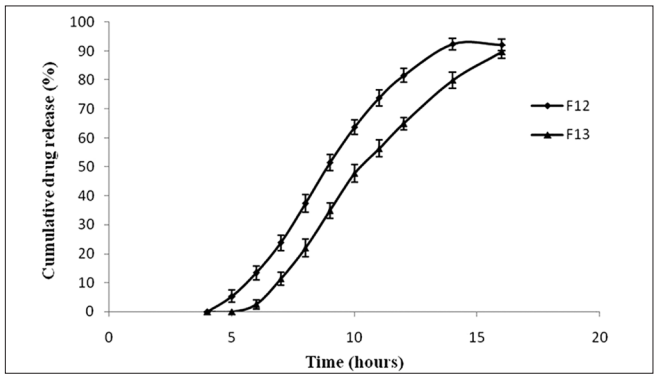

Figure 4: *In vitro* drug release from formulations comprising of enzyme-dependent polymer

increase in the concentration of pectin. However, as HM pectin has a low number of free carboxyl groups and, therefore, a low electrostatic repulsion between the molecules, gelation was more likely to occur.[14] The reduction in the rate and amount of drug released on increasing the proportion of pectin may be due to the increase in the gel strength of the swollen pectin layers. On exposure to the aqueous dissolution medium, being a hydrophilic polymer, pectin hydrated, swelled, and formed a hydrogel layer. Drug release from hydrophilic polymers occurs by diffusion through the gel layer. Because of which mechanical erosion of the swollen layer occurs, allowing further hydration and swelling of the polymer and further drug release.[15] As the pH is increased towards alkalinity, ionization of the galacturonic acid and formation of gel layer responsible for the retardation of the drug release occur. Moreover, the presence of pectinolytic enzymes in the dissolution fluids would also contribute towards faster drug release due to increased destruction of pectin chains that might lead to faster erosion rate. The drug release was found to be 92.12% and 89.76% for F12 and F13 formulations, respectively. All enzyme-dependent formulations follow zero-order release.

By fitting the release data up to 60% of the tablets to the Korsmeyer–Peppas model, the values of *n* for all formulas of enzyme-dependent polymers were >0.89 [Table 6], indicating Super case II transport, indicating involvement of more than one mechanism responsible for release from the formulation.

CONCLUSION

Successful delivery of drugs, specifically to the colon, requires the protection of drug from being released in the upper GIT. From the above results, it can be concluded that the esomeprazole press coated tablet could be successfully colon targeted by using pH-dependent (Eudragit L-100 and Eudragit S100), time-dependent (HPMC K4M), and enzyme-dependent (Pectin) polymers. Amongst all formulations, tablets press coated with 25% Pectin and 50% Pectin were unable to resist the drug release in the upper GIT. Based on the rate and amount of drug released in the colon, all concentrations of Eudragit L100 and Eudragit S100 as pH-dependent polymers, Pectin 75% and Pectin 100% as enzyme-dependent polymer, and HPMC 25% as time-dependent polymer were considered optimum for the formulation of esomeprazole press coated tablets for colonic delivery.

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