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RESEARCH ARTICLE

Formulation and Evaluation of Enteric Coated Delayed Release Tablets of Omeprazole for Duodenal Ulcer

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ABSTRACT

The objective of present study was to develop pharmaceutically elegant and stable enteric coated tablet formulation for highly unstable drug in acidic environment using pH dependent polymers. Omeprazole is a specific and non-competitive inhibitor of the enzyme H^+/K^+-ATPase. It is unstable in conditions of low pH and required protection from the effects of gastric acid when given orally so it is formulated in the form of enteric coated dosage forms. The core tablets were prepared by direct compression method using different concentration of crospovidone as a super disintegrant. Formulations showing less disintegration time were first subcoated with HPMC 15 cps upto 3% weight gain, followed by enteric coating with Eudragit L 100, Eudragit L 100-55 and Cellulose acetate phthalate. Pre and post compression evaluation of core and coated tablets were carried out. *In vitro* drug release studies were conducted in acidic and basic media to determine the appropriate coating ratio. All batches enteric coated with 8% weight gain of three polymers showed stable coating in 0.1 N HCl for 2 hours. Formulated batch F11 with 7% weight gain of Eudragit L 100-55 showed stable coating in 0.1 N HCl and had shown complete drug release in phosphate buffer pH 6.8. The prepared enteric coated tablets exhibited good physical and chemical stability, when subjected to accelerated stability studies. Further, when compared to marketed formulation (OPT tablet 20 mg Omeprazole), the prepared enteric coated tablets showed excellent similarities with marketed product (with respect to drug content, disintegration time and drug release) thereby establishing bioequivalence with marketed product.

KEYWORDS

Enteric coating, Eudragit L 100, Eudragit L 100-55, Cellulose acetate phthalate, Direct compression, Dissolution, Stability.

INTRODUCTION

A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted into a solid. Tablet dosage form is one of a most preferred dosage form all over the world.[1] Coating is a process by which an essentially dry, outer layer of coating material is applied to the surface of a dosage form in order to confer specific benefits that broadly ranges from facilitating product identification to modifying drug release from the dosage form. After making a good tablet, one must often coat it. Coating may be applied to a wide range of oral solid dosage form, including tablets, capsules, multiparticulates and drug crystals. [2]

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Enteric Coatings

Oral site-specific drug delivery systems have attracted a great deal of interest recently for the 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 cause 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.[3, 4]

Proton Pump Inhibitors (PPI's) are highly effective in the management of acid related diseases, including duodenal ulcer, gastric ulcer, gastro esophageal reflux disease, erosive esophagitis, hyper secretory syndromes like Zollinger-Ellison, and H.pylori infection.

There are currently five different proton pump inhibitors available including Omeprazole, lansoprazole, pantoprazole, rabeprazole and esomeprazole. These agents belong to a class of antisecretory drugs and are all substituted benzimidazoles that inhibit the final common pathway of gastric acid secretion. PPIs may also be used in combination with certain antibiotics (e.g. amoxycillin and clarithromycin) when treating H. Pylori infection (a bacterial infection of the stomach), which is thought to be one of the main causes of recurring stomach ulcers. [5]

In recent years, omeprazole has been widely used as a gastric acid secretion blocker and selectively inhibits the proton pump in the gastric mucosa. Omeprazole degrades very rapidly in aqueous solutions at low pH values. In aqueous solutions, the rate of degradation proceeds with a half-life of less than 10 min at pH values below 4, 18 h at pH 6.5 and about 300 days at pH 11. Omeprazole degradation is acid-catalysed; with an increase in the pH values, the rate of degradation decreases. In addition, the color of the solution changes immediately to pale yellow upon the addition of the acid and on heating, the color further changes to dark yellow, then becomes brownish. Preformulation studies have shown that moisture, solvents and acidic substances have deleterious effects on the stability of omeprazole and should be avoided in pharmaceutical formulations. To overcome the stability problems of omeprazole, the best solution seems to be to prepare enteric-coated dosage forms. The preparation must be perfectly coated, since if any drug leaks out of the dosage form in the stomach, it almost immediately degrades.

MATERIALS AND METHODS

Materials

Omeprazole was obtained from Yerrow Chem Ltd. HPMC 15 cps was received from Colorcon India Pvt Ltd. Eudragit L 100; Eudragit L 100-55 was gifted from Evonic Industries. Talc (Luzenac) was purchased from Imerys Talc Industries, France. Microcrystalline cellulose, crospovidone, cellulose acetate phthalate were purchased from SD Fine Chemicals. Sodium lauryl sulphate and magnesium stearate obtained from Finar chemicals. Dibutyl phthalate, iso propyl alcohol, acetone and ethanol were obtained from Renkem India. All the reagents and solvents used were of analytical grade.

Identification of Omeprazole

Identification of Omeprazole by FT-IR

Fourier-transform infrared (FT-IR) spectra were obtained using an FT-IR spectrometer. The pure Omeprazole were mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample: KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Identification of Omeprazole by DSC

The DSC study was carried out using differential scanning calorimeter instrument. The instrument comprises of calorimeter, flow controller, thermal analyzer and operating software. Drug sample was heated in sealed aluminum pans under nitrogen flows (30 ml/min) at a scanning rate of 5^0C/min from 25 to 300^0C. Empty aluminum pan was used as a

reference. The heat flow as a function of temperature was measured for the sample.

Drug Excipient Compatibility Study

Drug-Excipients Compatibility Study by FT-IR

Fourier-transform Infrared (FT-IR) spectra were obtained using an FT -IR spectrometer. The compatibility of Omeprazole with microcrystalline sodium, crospovidone, Eudragit L 100, Eudragit L 100-55, cellulose acetate phthalate, HPMC 15cps individually and combine in physical mixture were previously ground and mixed thoroughly with potassium bromide, an infrared transparent matrix, at 1:5 (Sample:KBr) ratio, respectively. The KBr discs were prepared by compressing the powders at a pressure of 5 tons for 5 min in a hydraulic press. Forty scans were obtained at a resolution of 4 cm^{-1}, from 4000 to 400 cm^{-1}.

Preparation of Core Tablets

The enteric coating tablet was prepared by direct compression method. Accurately weighed required quantity of Omeprazole, microcrystalline cellulose, sodium lauryl sulphate and crospovidone were sieved through 40# size. The above shifted materials were mixed using planetary mixture for 10min. The shifted materials were lubricated with magnesium stearate and talc for 5 min octagonal blender. All the required ingredients were passed individually through sieve no. # 30. The core tablets were prepared by direct compression method using 8 mm concave punch and die set. Formulation P4 was selected for further coating, as blend of formulation showed good flow property and its disintegration time was less as compared to the other formulations. The core tablets were subjected to apply subcoat and finally enteric coating was applied with pH dependent enteric coating polymers. The subcoating and enteric coating were carried out by pan coating method.

Coating of Core Tablets

Preparation of Subcoating Solution

Weigh accurately required quantity of HPMC 15 cps as a seal coating material. Required quantity of ethanol was taken into mixing vessel. HPMC 15 cps was added slowly with constant stirring provided by magnetic stirrer. Required quantity of water was added to above vessel with constant stirring to get clear solution. Finally titanium dioxide was added. The above solution was prepared and used freshly. And finally the coating was carried out in coating pan.[6, 7]

Table 1: Composition of core tablet batches

Ingredients (mg/tablet)	P1	P2	P3	P4	P5
Omeprazole	20	20	20	20	20
Microcrystalline Cellulose	168	164	162	160	158
Crospovidone	0	4	6	8	10
Sodium Lauryl Sulphate	4	4	4	4	4
Talc	6	6	6	6	6
Magnesium Stearate	2	2	2	2	2
Total Weight	**200**	**200**	**200**	**200**	**200**

Table 2: Parameters for coating process

Sr. No.	Parameters	Limits
1	Pan Speed	25 rpm
2	Inlet Air Temperature	45 ^{0}C
3	Outlet Air Temperature	40 ^{0}C
4	Bed Temperature	40 ^{0}C
5	Atomizing air Pressure	1 kg/cm^2
6	Spray Gun Nozzle Diameter	1.0 mm
7	Spray Rate	12 to 15 ml/min

Table 3: Composition of subcoating

Ingredients	Quantity
HPMC 15 cps	1%
Water : Ethanol (up to) (2:8)	100%
Titanium Dioxide	0.2%

Preparation of Enteric Coating Solution

Weighed required quantity of Eudragit L 100 as an enteric coating polymer. In a mixing vessel organic solvent was taken and with constant stirring coating polymer was added to the mixing vessel with constant stirring provided by magnetic stirrer. Then the required quantity of dibutyl phthalate as plasticizer was added to above solution. Similarly following above procedure, enteric coating solutions of different polymer Eudragit L 100-55 and cellulose acetate phthalate were prepared. Finally the subcoated tablets were enteric coated with above solution in conventional pan coater. Tablet subcoating was performed in a conventional coating pan

Table 4: Composition of enteric coating (F1 to F6 batches)

Ingredients	F1	F2	F3	F4	F5	F6
Eudragit L 100 (%)	3	3	3	-	-	-
Eudragit L 100-55 (%)	-	-	-	3	3	3
Dibutyl phthalate (%w/w of Polymer)	10	10	10	10	10	10
Isopropyl alcohol (q.s. to)	100	100	100	100	100	100
% Weight Gain	**6**	**8**	**10**	**6**	**8**	**10**

Table 5: Composition of Enteric coating (F7 to F12 batches)

Ingredients	F7	F8	F9	F10	F11	F12
Eudragit L 100 (%)	-	-	-	3	-	-
Eudragit L 100-55 (%)	-	-	-	-	3	-
Cellulose acetate phthalate (%)	3	3	3	-	-	3
Dibutyl phthalate (%w/w of Polymer)	10	10	10	10	10	10
Isopropyl alcohol (q.s. to)	-	-	-	100	100	-
Acetone : Isopropyl alcohol (1:1)(q.s. to)	100	100	100	-	-	100
% Weight Gain	**6**	**8**	**10**	**7**	**7**	**7**

with one spray gun. Sub coat of HPMC 15 cps was applied to the tablets up to a weight gain of 3%. Then the subcoated tablets were enteric coated with different enteric coating materials such as Eudragit L100, Eudragit L100-55 and cellulose acetate phthalate. The detailed compositions of omeprazole enteric coated tablet formulations are given in Table 4 and 5.[8,9]

Evaluation of Enteric Coated Tablet

Pre compression Evaluation

Angle of Repose

The angle of repose was determined by the funnel method. The determination of angle of repose by this method is referred to as static angle of repose. Powder is poured onto the center of the dish from the funnel that can be raised vertically until the maximum cone height (h) is obtained.

The angle of repose can be calculated by the given formula,

$$\alpha = \tan^{-1}(h/r)$$

Where **h** is height of pile and **r** is radius of pile.

Bulk Density

The apparent true density (ρb) was measured by pouring the pre weighed (M) blend into a graduated cylinder. The bulk volume (Vb) of the blend was determined by this method. Then the true density was determined by the given below formula.

$$\rho b = M/Vb$$

Tap Density

The measured cylinder containing a known mass (M) of blend was tapped for a fixed time, and the minimum volume (Vt) occupied in the cylinder was measured. The tapped density was calculated by the formula mentioned below.

$$\text{Tap density} = M/Vt$$

Carr's Index

Based on the apparent bulk density and the tapped density, the percentage compressibility of the bulk drug was determined by using the following formula.

% Compressibility = (tapped density - bulk density/tapped density) X100[10]

Table 6: Relationships between % Compressibility and Flowability[11]

Carr's Index (%)	Flow Character
≤ 10	Excellent
11–15	Good
16–20	Fair
21–25	Passable
26–31	Poor
32–37	Very poor
>38	Very, very poor

Porosity

The porosity of voids and of the powder is defined as the ratio of void volume to the bulk volume of the packaging.

$$E = (Vb-Vp)/Vb = 1 - (Vp/Vb)$$

Hausner's Ratio

The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. [12]

Table 7: Relationship between Hausner's Ratio and Flowability[11]

Hausner's ratio	Type of Flow
Less than 1.25	Good
Between 1.25 - 1.5	Moderate
More than 1.5	Poor

Post-Compression Evaluation

Thickness and Dimension

The thickness and dimension of the tablet in mm was measured using vernier calipers.

Hardness

The tablet crushing strength was tested by commonly used monsanto type tablet hardness tester. A tablet was placed between the anvils and the crushing strength, which caused the tablet to break, was recorded.

Friability

Tablet strength was tested by Roche friabilator. Pre weighed tablets were given 100 revolutions in 4 min and were dedusted. The percentage weight loss was calculated by reweighing the tablets.[44]

Weight Variation Test

It was performed as per the method given in the US pharmacopoeia. Tablets were randomly checked to ensure that uniform weight tablets were being made. Twenty tablets were selected randomly from each formulation, weighed individually and the average weight and % variation of weight was calculated.

Table 8: Weight variation range as per USP

Average weight of Tablets (mg)	Maximum % 0f differenceAllowed
130 or less	10
130-324	7.5
> 324	5.0

Disintegration Time

Disintegration time was determined using the disintegration apparatus USP (Electrolab, Bangalore, India) in 0.1N HCl for 2 h and then in phosphate buffer pH 6.8 maintaining the temperature at 37 ±2°C.

According to Indian Pharmacopoeia the conditions for enteric-coated tablets are

- All the six tablets tested should not disintegrate in 2 hour in 0.1N HCl and should not show any sign of cracks or swelling.
- All the six tablets tested in 0.1N HCl for 2 hour should disintegrate within 60 min in phosphate buffer pH 6.8[10]

In vitro Drug Release Study

Dissolution of the Omeprazole enteric coated tablets was determined using the USP XXII apparatus 2 at 37 ± 0.5°C with a paddle which rotated at 100 rpm. The dissolution medium was 0.1 N HC1 (750 ml) solution and phosphate buffer pH 6.8 (1000 ml). The dissolution for all the formulations was carried out according to US Pharmacopoeia for 2 hours in 0.1N HCl and then media was changed into phosphate buffer pH 6.8 for further 1 hour. 10 ml samples were removed from the release medium, filtered and the concentration were determined by means of UV spectrophotometry at 304.8 nm. The same procedure was used in the stability studies for the evaluation of dissolution properties.[13, 14]

Curve Fitting Analysis

To analyze the release pattern of the drug from the dosage form, the data obtained were graphed as;

Cumulative percent drug release Vs. Time [Zero order Plot]

Log % CDR Vs. Time [First order Plot]

Cumulative percent drug release Vs. square root of time [Higuchi's Plot]

Log % CDR Vs. Log time [Peppas Plot]

Cube root of percent drug remain Vs. Time [Hixon-Crowell plot]

For the determination of the drug release kinetics from the Omeprazole enteric coated tablet, the *in vitro* release data were analyzed by zero order, first order, Higuchi and Korsmeyer and Peppas equations:

A. Zero Order Release Kinetics

To study the zero order release kinetics the release data was fitted into the following equation:

$$dQ/dt = K_0$$

Where, Q is the amount of drug release, K_0 is the zero order release rate constant and t is drug release time. The graph is plotted %cumulative drug release (% CDR) vs. time.

B. First Order Release Kinetics

To study the first order release kinetics the release rate data are fitted into the following equation:

$$dQ/dt = K_1Q$$

Where, Q is the fraction of drug release, K_1 is first order release rate constant and t is the release time. The graph is plotted log % CDR remaining versus time.

C. Higuchi Release Model

To study the higuchi release model the drug release rate data are fitted into the following equation:

$$Q = K_H t_{1/2}$$

Where, Q is the fraction of drug release, K_H is release rate constant and t is the release time. The graph is plotted % CDR versus square root of time.

D. Korsmeyer and Peppas Kinetics

To study the korsmeyer and peppas release kinetics the release rate data are fitted into the following equation:

$$Mt/M\infty = KK_P\ t\ n$$

Where, $Mt/M\infty$ is the fraction of drug release, KK_P is the release rate constant and t is the release time and n is the diffusion component related to mechanism of drug release. The graph is plotted log % CDR vs. log t.[15, 16, 17]

Comparison of Developed Formulation with Marketed Product

Optimized formulation was selected for comparison with marketed formulation of Omeprazole (OPT TABLETS – 20 mg). The parameters compared with marketed formulations were drug content, disintegration time and % cumulative drug release.

Similarity Study[18]

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. The dissolution profiles of products were compared using f_2. This similarity factor is calculated by following formula,

$$f_2 = 50 \text{ x } \log \{[1+(1/n) \Sigma | R_j - T_j |^2]^{-0.5} \text{ x } 100\}$$

Where, n = number of time points

R_j = Dissolution value of the reference batch at time t

T_j = Dissolution value of the test batch at time t

Dissimilarity Study[19]

Difference factor focuses on the difference in percent dissolved between reference and test at various time intervals. It can be mathematically computed by using following equation.

$$f1 = \{[\Sigma\ t=1n|Rt-Tt|] / [\Sigma\ t=1nRt]\} \times 100$$

Where, n is the number of dissolution time points

Rt- The reference profile at the time point t

Tt- The test profile at the same point

As per US FDA guidelines difference factor of 0-15 ensures minor difference between two products.

Stability Studies[20]

Stability studies on the optimized formulation was carried out to determine the effect of presence of formulation additives on the stability of the drug and also to determine the physical stability of the formulation under accelerated storage conditions.

The tablets were stored in an aluminum foil and subjected to elevated temperature and humidity conditions of 40 ± 2°C/ 75 ± 5 % RH for time period of one month.

Samples were withdrawn at the end of every week and evaluated for % drug content, disintegration time, % drug release.

RESULT AND DISCUSSION

Identification of Omeprazole

Identification of Omeprazole by FT-IR

The FT-IR spectrum shows characteristic peaks corresponding to various functional groups

present in Omeprazole structure. Various functional groups and their respective peaks were illustrated in the table 9, which were identical to the reference spectra given in Japanese Pharmacopeia which proves purity of test sample of Omeprazole.

Table 9: Interpretation of FT-IR spectra of Omeprazole

Frequency(cm^{-1})	**Interpretation**	**Frequency(cm^{-1})**	**Interpretation**
3431	N-H stretch	**1510**	CH_2 bending
3071	Aromatic C-H stretch	**1402 and 1309**	CH bending
2943 and 2904	C-H stretch	**1157**	C=O stretch
1621	C=C stretch	**1075**	C=S stretch
1587	C=N stretch	**966, 885, and 821**	C-H bending

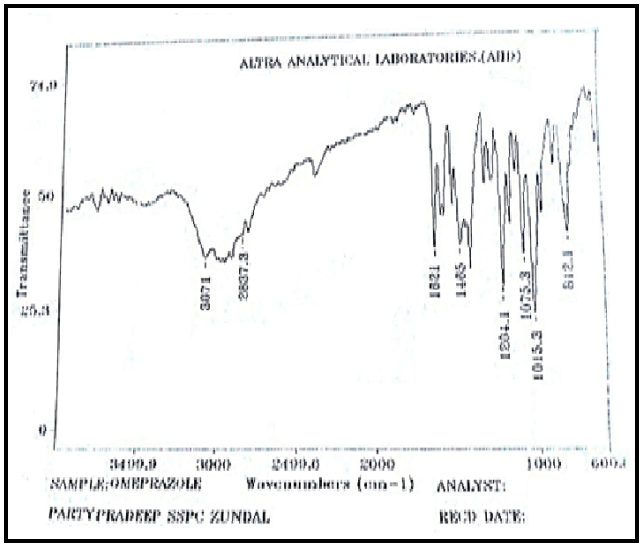

Figure 1: FT-IR Spectra of Omeprazole

Identification of Omeprazole by DSC

The DSC thermogram of the Omeprazole was conducted to explore the melting activities of drug. DSC analysis showed a sharp endothermic peak at 159.65°C which is an indication of melting point of Omeprazole. The melting range of Omeprazole is 155-160°C as per British pharmacopoeia. So, it was found to be very close to authentic range of official standard.

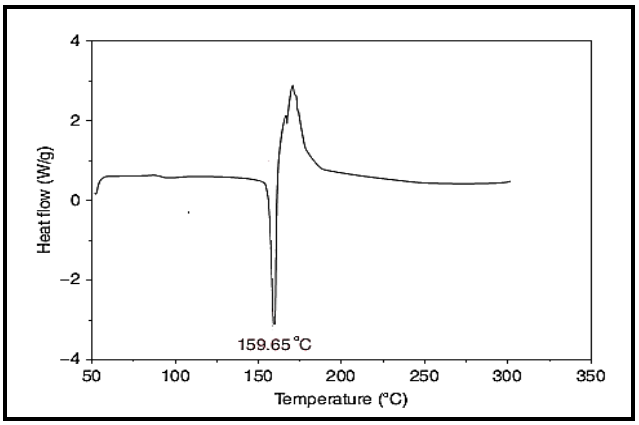

Figure 2: DSC spectra of Omeprazole

Drug-Excipients Compatibility Study

Drug-Excipients Compatibility Study by FT-IR

Drug and excipients compatibility study was performed by FT-IR spectrometer. Here the peak of the pure Omeprazole was correlated with drug in presence of the other excipients. In all the FT-IR spectra identical peaks of the Omeprazole could not varied than of its original peak. So, it can be concluded that the drug is compatible with all the excipients used in the formulation. The FT-IR spectra of the Omeprazole and with other excipients are shown in figure 3.

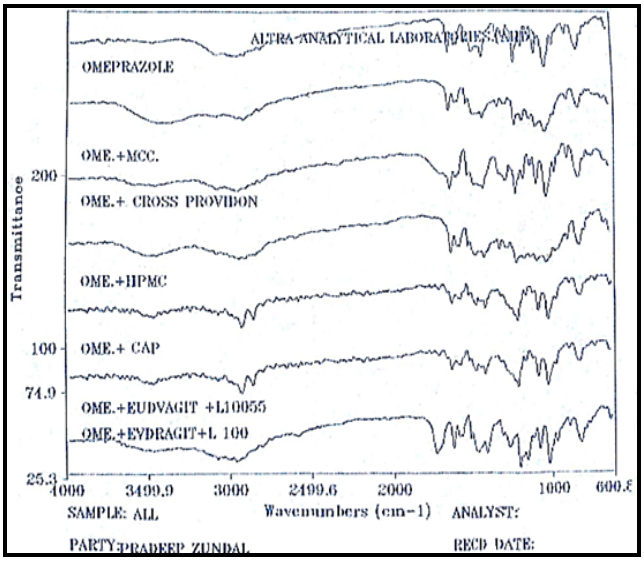

Figure 3: FT-IR spectra of Drug with Excipients

Evaluation of Enteric Coated Tablets

Pre-Compression Evaluations

The preliminary batches was formulated by taking different concentration of crospovidone (1% to 5%) and pre-compression parameters of the preliminary batches was carried out including parameters like bulk and tapped density, angle of repose etc. The results were shown in table 10. The preliminary batches P1 to P5 showed the angle of repose 27.45±0.08 to 29.43±0.02 and Hausner's ratio between 1.18±0.03 to 1.22±0.08, which indicates good flow property and compressibility of all the preliminary batches.

Post-Compression Evaluations

The shape and size of the all the batches were found to be within limit (Table 11). The average weight, hardness and friability test were also found within limit. Among all the preliminary batches of core tablet batch P4 was taken as on optimized batch for core tablet, because batch P4 has shown less friability (0.14%), good hardness (5.0±0.20 kg/cm^2) and less disintegration time (3.16±1min.). So, it was considered as the optimized core tablet for further experiment.

Table 10: Pre-compression evaluations of batch P1 to P5

Parameter	P1	P2	P3	P4	P5
Bulk density (gm/cm^2)	0.48±0.01	0.49±0.01	0.48±0.01	0.51±0.03	0.48±0.08
Tapped density(gm/cm^2)	0.58±0.05	0.60±0.02	0.57±0.07	0.62±0.01	0.59±0.03
Compressibility Index	17±0.01	18.12±0.09	15.25±0.04	17.39±0.07	18.53±0.05
Hausner's ratio	1.20±0.01	1.22±0.07	1.18±0.03	1.21±0.04	1.22±0.08
Angle of repose	28.48±0.01	27.45±0.08	28.62±0.05	29.43±0.02	29.37±0.01
Porosity	0.17±0.02	0.18±0.05	0.15±0.03	0.17±0.09	0.18±0.08

All values are expressed as mean ± SD (n=3)

Table 11: Post-compression evaluation of batch P1 to P5

Parameters	P1	P2	P3	P4	P5
Thickness (mm)	2.0±0.01	2.1±0.03	2.1±0.01	2.0±0.02	2.1±0.04
Diameter (mm)	8	6	8	8	8
Average Weight (mg)	201.1	200.9	202.3	200.3	201.6
Friability test [n=5]	0.3%	0.35%	0.42%	0.14%	0.51%
Hardness (kg/cm2)	5.0±0.14	4.5±0.18	4.5±0.04	5.0±0.20	4.0±0.09
Drug Content	98.2±0.24	98±0.19	100.25±0.09	99.55±0.18	99.15±0.20
Disintegration Time (min.)	7.51±1	6.24±1	4.25±2	3.16±1	3.15±1

All values are expressed as mean ± SD (n=3)

***Physical Properties of Enteric Coated Formulations (F1 to F12*)**

The evaluations of enteric coated tablet of Omeprazole formulation of batches F1 to F3 (enteric coating with Eudragit L100), F4 to F6 (enteric coating with Eudragit L100 55) and F7 to F9 (enteric coating with cellulose acetate phthalate) and also the F8 to F12 (7% weight gain of above enteric polymers) batches were carried out for physical parameters like hardness, friability, weight variation test and disintegration test (Table 12). All the batches (F1 to F12) showed no significant differences in the weight variation test, appearance. But batches like F2 and F3 (8% and 10% weight gain of Eudragit L100), F5, F6 and F11 (8%, 10% and 7% weight gain of Eudragit L100 55) and F8, F9 (8% and 10% weight gain of CAP) were only the batches that were readily passed the disintegration test in 0.1 N HCl. The difference in disintegration time may be due to the differ concentration of enteric coating polymer.

***In vitro* Drug Release**

In vitro dissolution studies were performed for all the formulations using USP apparatus 2 tablet dissolution tester by using paddle type at 100 rpm using 750 ml of 0.1N HCl and 1000 ml phosphate buffer 6.8 pH as dissolution medium. The drug release was evaluated using UV spectroscopy.

Table 12: Physical evaluation of batches F1 to F12

Batch	Appearance	Surface	Average Weight (mg)	Disintegration Test in 0.1 N HCl (min.)	Disintegration Test in phosphate buffer pH 6.8 (min.)	Drug content (%)
F1	Pink color	Smooth	218	100.41±2	-	98.62±0.17
F2	Pink color	Smooth	222	Passed	13.54±1	99.78±0.09
F3	Pink color	Smooth	231	Passed	36.22±2	100.06±0.03
F4	Pink color	Smooth	221	109.12±1	-	100.11±0.14
F5	Pink color	Smooth	224	Passed	15.32±3	100.76±0.19
F6	Pink color	Smooth	226	Passed	38.24±2	99.19±0.23
F7	Pink color	Smooth	219	104.55±2	-	100.87±0.20
F8	Pink color	Smooth	224	Passed	14.43±1	98.15±0.07
F9	Pink color	Smooth	225	Passed	39.57±3	98.67±0.18
F10	Pink color	Smooth	220	110.25±1	-	99.54±0.24
F11	Pink color	Smooth	221	Passed	13.41±2	99.35±0.19
F12	Pink color	Smooth	221	108.34±2	-	99.92±0.21

All values are expressed as mean ± SD (n=3)

Table 13: *In vitro* dissolution profile of batches F1 to F6

Medium	Time (min.)	F1	F2	F3	F4	F5	F6
0.1 N HCl	0	0	0	0	0	0	0
	30	5.14±7.85	0.28±4.74	0.48±6.82	0.18±5.97	0.28±5.96	0.62±4.81
	60	7.37±6.49	1.10±6.61	0.65±7.73	7.64±6.70	1.22±6.83	0.95±6.99
	90	15.99±3.84	1.53±5.78	1.07±4.75	16.11±4.86	1.70±4.67	1.26±4.88
Phosphate Buffre pH 6.8	120	52.34±6.79	2.00±5.96	1.41±7.74	41.41±8.95	3.18±7.55	1.80±7.73
	130	68.28±7.99	29.05±6.90	3.52±6.82	71.45±7.47	25.23±8.80	3.76±6.54
	140	82.59±6.72	63.25±4.83	23.26±4.76	81.90±6.62	51.75±5.74	9.10±7.68
	150	84.33±6.76	87.98±6.69	56.06±5.81	84.29±5.59	75.10±7.44	36.74±6.65
	160	85.02±8.86	95.31±7.66	84.31±4.26	85.35±3.78	89.74±4.39	64.01±8.49
	170	85.43±4.68	96.75±6.74	94.15±7.94	88.47±4.52	97.55±6.73	89.68±6.84
	180	86.97±8.85	97.32±5.80	96.96±6.59	90.78±7.60	98.00±7.94	93.90±4.17

All values are expressed as mean ± SD (n=3)

Table 14: *In vitro* dissolution profile of batches F7 to F12

Medium	Time (min.)	F7	F8	F9	F10	F11	F12
0.1 N HCl	0	0	0	0	0	0	0
	30	4.36±7.74	0.55±7.87	0.65±4.19	3.71±4.87	0.14±5.57	0.87±6.68
	60	6.80±5.67	1.05±6.99	0.75±5.48	5.34±3.58	1.12±4.18	2.47±5.47
	90	19.95±6.92	1.27±7.74	0.97±6.40	8.10±5.34	1.48±6.49	9.33±6.66
Phosphate Buffre pH 6.8	120	58.96±4.22	1.67±7.16	1.31±7.55	35.73±5.51	3.60±4.76	31.43±7.20
	130	75.47±5.48	23.38±7.70	2.53±7.65	60.47±4.90	34.11±5.77	56.13±6.62
	140	84.52±7.61	58.36±6.43	8.79±4.79	75.45±6.44	65.57±3.53	69.50±7.59
	150	86.37±6.98	81.76±5.29	52.49±8.38	87.55±7.67	90.91±4.52	83.09±8.48
	160	88.13±3.76	92.29±7.47	79.86±6.59	89.20±5.56	94.64±4.22	89.23±4.37
	170	89.76±4.85	96.53±5.88	92.62±7.29	90.55±4.69	96.71±8.83	90.52±6.29
	180	91.66±7.73	98.10±6.43	98.13±8.52	92.19±6.77	98.74±4.75	92.07±7.79

All values are expressed as mean ± SD (n=3)

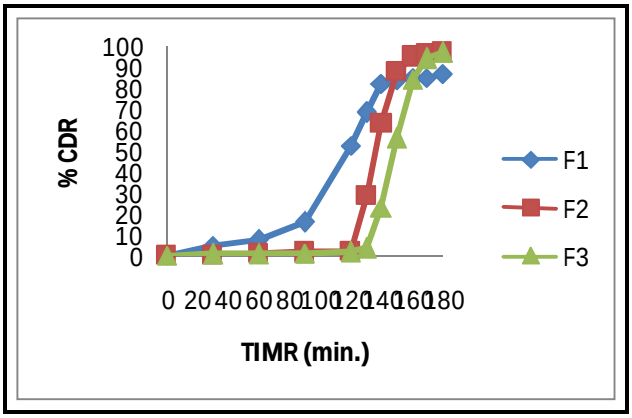

Figure 4: Drug release profile of batches F1 to F3 in 0.1 N HCl and phosphate buffer pH 6.8

The *in vitro* dissolution of batches was studied in 0.1 N HCl for 2 hours and 1 hour in phosphate buffer pH 6.8. Here, batch F2 and F3 has shown physical resistance to the acid medium after 2 hour and the drug release was found to be within specified limits (table 13). F2 and F3 (8% and 10% weight gain) had stable coating in acidic environment and after 2 hours in phosphate buffer batch F2 shown release of Omeprazole (97.32 ± 5.80%) but F3 started release after 10 min in phosphate buffer and showed 96.96 ± 6.59% drug release till 60 min. So, batch F2has shown better results for polymer Eudragit L 100 for enteric coating of Omeprazole.

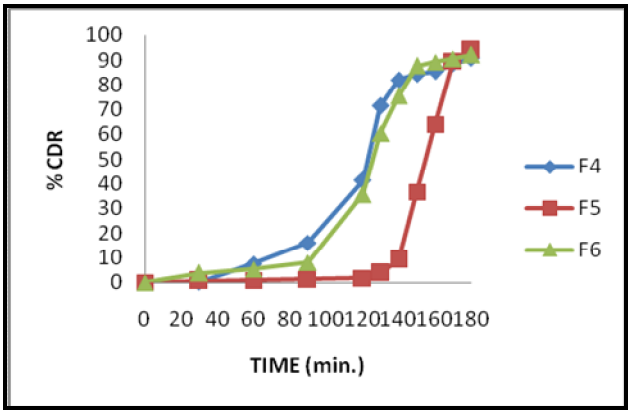

Figure 5: Drug release profile of F4 to F6 batches in 0.1 N HCl and phosphate buffer pH 6.8

Here, batch F5 and F6 could prevent the drug release in acidic condition (table 13). Batch F5 and F6 (8% and 10% weight gain) had stable coating in acidic environment and after 2 hours in phosphate buffer batch F5 shown release (98.00±7.94%) of Omeprazole, but batch F6 started release after 20 min in phosphate buffer and at 60 min showed 93.90 ± 41.17% drug release. So, batch F5 has shown better results for polymer Eudragit L 100-55 for enteric coating of Omeprazole.

Here, batch F8 and F9 could prevent the drug release in acidic condition (table 14). Batch F8 and F9 (8% and 10% weight gain) had stable coating in acidic environment and after 2 hours in phosphate buffer batch F8 shown release 98.10±6.43% of Omeprazole but F9 started release after 10 min in phosphate buffer and showed release up to 98.13±8.52% after 60 min. So, batch F7has shown better results for polymer Cellulose acetate phthalate for enteric coating of Omeprazole.

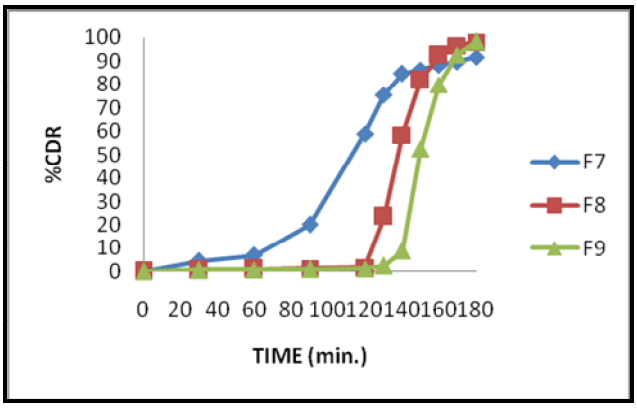

Figure 6: Drug release profile of F7 to F9 batches in 0.1 N HCl and phosphate buffer pH 6.8

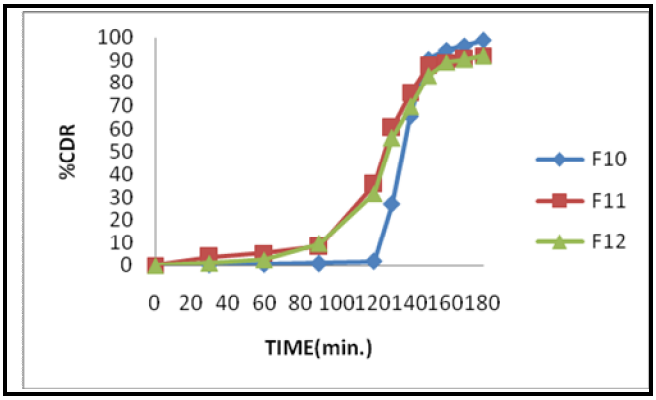

Figure 7: Drug release profile of F10to F12 batches in 0.1 N HCl and phosphate buffer pH 6.8

Here, table 15 showed the cumulative drug release. Batch F11 could prevent the drug

release in acidic condition. Batch F11 (7% weight gain of Eudragit L 100-55) had stable coating in acidic environment and after 2 hours in phosphate buffer F11 showed release 98.74±4.75% of Omeprazole but batch F10 and F12 could not provide stable coating in stomach for 2 hours. So, batch F11 was considered as an optimized batch of polymer Eudragit L 100-55 for enteric coating of Omeprazole. Finally from all above 12 batches F11 was selected as an optimized batch because it has shown better drug release and consumed less concentration of enteric coating polymer (7%) as compared to other batches.

Curve Fitting Analysis

The dissolution data so obtained was fitted to various kinetic models like Zero Order, First order, Higuchi, Korsmeyer-Peppas models. Results were shown in table 15.

Table 15: Different kinetic model applied on batch F11

Model	R^2	r	K	SS	AIC
Zero-order	0.6397	0.8517	0.447	7294.0605	99.8430
First-order	0.5209	0.7818	0.006	9698.0932	102.9765
Higuchi	0.4411	0.7290	4.979	2091.8973	0.4411
Korsmeyer-peppas	0.9035	0.9415	0.000	2357.7484	89.4201
Hixson-Crowell	0.5551	0.8028	0.002	9005.3407	102.1613

The *in vitro* release kinetics was best explained by Korsmeyer-peppas, as the plots showed the highest linearity (r^2 = 0.9035), followed by Zero-order (r^2=0.6397), Hixson Crowell (r^2 = 0.5551), first order equation (r^2 = 0.5209). Hence the drug release kinetics demonstrates that the concentration was nearly independent of drug release. n value of korsmeyer-peppas is 1.003 indicate that drug release observed by diffusion and erosion both mechanism and the model is non fickian (anomalous transport).

Comparison of Developed Formulation with Marketed Product

Optimized formulation was compared with the marketed enteric coated tablets of Omeprazole (OPT TABLETS – 20 mg) having an equivalent dose of 20 mg. The disintegration time and release profile of optimized formulation and the marketed formulation is given in Table 16. From the result, it was concluded that optimized formulation had similar disintegration profile, drug content and % drug release with marketed product.

Similarity and Dissimilarity Study

The f2 value calculated using equation of similarity was found to be 59.906. So, f2 value ensures sameness or equivalence of two curves. The f1 value was found 1.86.

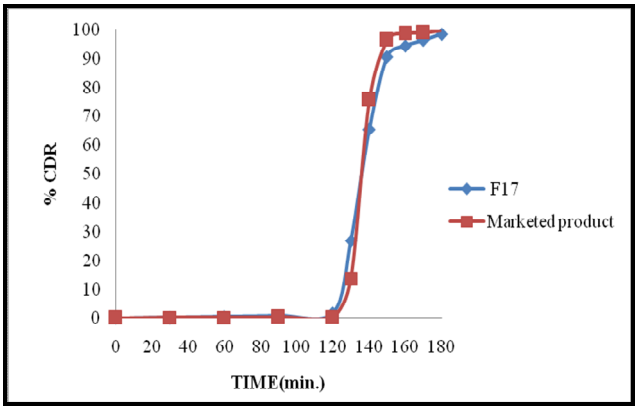

Figure 8: Comparative Release Profile between Marketed Formulation & Optimized Batch F11

Stability Studies of Omeprazole Enteric Coated Tablets

Stability study of enteric coated tablet of Omeprazole was carried out for 4 weeks at specified condition. All data are mentioned in Table17 and 18. The stability studies of the optimized batch F11 of enteric coated tablet of Omeprazole revealed that no significant changes in the physical parameters, disintegration time,

% drug content and % drug release at 180 min in phosphate buffer pH 6.8 when stored at temperature and humidity conditions of 25ºC ± 2ºC / 60% RH ± 5% RH and 40 ± 2ºC/ 75% RH ± 5 % RH. So, it can be concluded that formulation having good stability.

Table 16: Comparison of Omeprazole enteric coated marketed formulation with optimized formulation (F11)

Parameters	F11	Marketed Product
Appearance	Pink color	Yellowish brown
Surface	Smooth	Smooth
Shape	Flat Round	Flat Capsule
Average Weight (mg)	221	217
Disintegration Test in 0.1 N HCl (min.)	Passed	Passed
Disintegration Test in phosphate buffer pH 6.8 (min.)	13.41±2	10.53±1
Drug content (%)	99.75±0.24	100.18±0.13
% CDR	98.74±4.75	100.01±2.41

Table 17: Stability study of optimized batch (F11) carried out at 25ºC ± 2ºC / 60% RH ± 5% RH and 40 ± 2ºC/ 75 ± 5 % RH

No. of weeks	%Drug Content at		% Cumulative Drug Release at	
	25ºC ± 2ºC / 60% RH ± 5% RH	40ºC ± 2ºC / 75% RH ± 5% RH	25ºC ± 2ºC / 60% RH ± 5% RH	40ºC ± 2ºC / 75% RH ± 5% RH
0	99.35±0.19	99.35±0.19	98.74±4.75	98.74±4.75
1	99.01±0.62	98.98±0.62	98.27±6.21	98.06±6.57
2	98. 65±0.35	98.32±0.35	97.86±7.18	97.45±7.44
3	98.50±0.21	98.16±0.21	97.32±6.15	97.17±7.71
4	98.24±1.29	98.07±1.29	96.97±7.26	96.57±8.50

Table 18: Disintegration test for optimized batch F11 kept for stability studies at 25ºC ± 2ºC / 60% RH ± 5% RH and 40 ± 2ºC/ 75 RH ± 5 % RH

No. of weeks	25ºC ± 2ºC / 60% RH ± 5% RH		40ºC ± 2ºC / 75% RH ± 5% RH	
	Disintegration (0.1N HCl) (min.)	Disintegration (phosphate buffer pH 6.8)(min.)	Disintegration (0.1N HCl) (min.)	Disintegration (phosphate buffer pH 6.8) (min.)
0	Passed	13.41±2	Passed	13.41±2
1	Passed	13.50±1	Passed	13. 59±3
2	Passed	14.06±2	Passed	14.19±1
3	Passed	14.22±2	Passed	14.33±1
4	Passed	14.36±3	Passed	14.47±2

CONCLUSION

The present study demonstrates that the omeprazole enteric coated tablets could be successfully intestine targeted by using pH dependent polymer. Omeprazole enteric coated tablets were prepared using enteric coating polymers like Eudragit L 100, Eudragit L 100-55 and cellulose acetate phthalate. Omeprazole and excipients were compatible with each other as indicated by FT-IR and DSC. Among the different formulations prepared in this study, batch F11 containing polymer Eudragit L 100-55 with 7% weight gain of enteric polymer has shown negligible drug release in 0.1 N HCl and after 2 hours in phosphate buffer showed complete drug release in phosphate buffer pH 6.8 within 60 minutes. Korsmeyer-peppas model was found to be the best model followed by first kinetic model. It was concluded that batch F11 was good formulation as it was meeting all specifications. The release profile of omeprazole from enteric coated tablets (F11) has shown a slow release following first order kinetic with non fickian mechanism. The results demonstrated the effective use of omeprazole enteric coated tablets as a delayed release preparation for treatment of duodenal ulcer.

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