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Formulation and evaluation of enteric coated tablet of Ilaprazole

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ABSTRACT
The present study was an attempt to formulate and evaluate enteric coated tablets for Ilaprazole to reduce the gastrointestinal tract side effects. Four formulations of core tablets were prepared and one who shows rapid disintegration (near around three minutes) was selected for enteric coating. Ilaprazole which have an irritant effect on the stomach can be coated with a substance that will only dissolve in the small intestine. Enteric coat was optimized using two different polymers such as HPMCP 50 and Eudragit L 100 in different concentrations. The prepared tablets were evaluated in terms of their pre-compression parameters, physical characteristics and in-vitro release study. 2.5% seal coating on core tablets was optimized and 9% enteric coating on seal coated tablets was performed using HPMC P 50 (60%), triethyl citrate (10%) and IPA:DCM (60:40) which gives the highest dissolution release profile and f_2 value.

***Key Words*:** Ilaprazole, HPMC P 50, Eudragit L 100, delayed release, enteric coated.

INTRODUCTION

Ilaprazole is a substituted benzimidazole which is anti-ulcerous compound known for decreasing gastric acid secretion. This compound, also known as proton pump inhibitor (PPI) is commonly indicated for the treatment of gastric ulcer, peptic ulcer, duodenal ulcers, erosive or ulcerative GERD (Gastro esophageal reflux disease), symptomatic GERD, pathological hypersecretory conditions (Zollinger-Ellison) (Goodman and Gilman, 2001). Ilaprazole is practically insoluble in water, more soluble in alkaline medium as compared to acidic medium. The stability of Ilaprazole is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. Therefore exposure of Ilaprazole to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability (Wilde and McTavish, 1994; McTavish *et al.*, 1991). Delayed release dosage forms (Cole, 1998) are the best formulations which are used for drugs that are destroyed in the gastric fluids, or cause gastric irritation, or are absorbed preferentially in the intestine. Such preparations contain an alkaline core material comprising the active substance, a separating layer and enteric coating layer (Ansel and Poppovich, 1995; Libermen and Lachman, 1989; Lachman *et al.*, 2009). Enteric coatings are usually formulated with synthetic polymers that contain ionizable functional groups that render the polymer water soluble at a higher pH value. Commonly-used enteric coatings may be made from: methacrylic acid copolymers, cellulose acetate (and its succinate and phthalate version), polymethacrylic acid/acrylic acid copolymer, hydroxypropyl methyl cellulose phthalate, polyvinyl acetate phthalate, hydroxyethyl ethyl cellulose phthalate, cellulose acetate tetrahydrophtalate, acrylic resin (Bruce *et al.*, 2003).

The aim of present work was to prepare delayed release i.e., enteric coated tablets of Ilaprazole by using HPMC P 50 and Eudragit L 100 in side vented perforated coating pan to prevent degradation in the stomach due to the acidic environment or gastric enzymes and to study the factors affecting the film coating of tablets performed in a perforated pan coater and further optimization of enteric coating formula is done which implicate more significant effects on dissolution profile of tablet.

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MATERIALS AND METHODS

Ilaprazole was generous gift sample from Cadila healthcare Ltd. Hydroxy Propyl Methyl Cellulose Pthalate 50 (HPMC P 50) and Eudragit L 100 was of Colorcorn Ltd., Ahmedabad, India. All other ingredients used were of analytical grade.

Formulation development of core tablet of Ilaprazole

Ilaprazole core tablets were formulated by using wet granulation method. The formula of wet granulation batches is shown in table 1. The weighed quantity of Ilaprazole and lactose was sieved through #40 size. The above sifted materials were mixed using planetary mixture for 10min. Then, sodium starch glycolatetype A (SSG type A) was passed through #40 and mixed with former blend. Prepare binder solution by dissolving polyvinylpyrrolidone K-30 (PVP K-30) in purified water under stirring. Blend was charged in rapid mixing granulator (RMG) and mass was granulated using binder solution and additional purified water or isopropyl alcohol (IPA) if required until dough mass obtained. The prepared granules were then dried in fluidized bed drier (FBD) at 48°C to 55°C till loss on drying (LOD) was obtained less than 2%. Dried granules were sifted through the #20 screen of oscillator granulator. Then seized granules were mixed with extragranular materials for 10 minutes. This blend was further lubricated with magnesium stearate for 3 minutes. All blends were compressed into tablets using 9/32" round shallow concave punch on multipunch rotary tablet machine. The prepared tablets were stored in tightly closed glass container and evaluated for various parameters.

Evaluation of powder blend

Angle of repose

The angle of repose of powder blend was determined by the funnel method. The accurately weighed powder blends were taken in the funnel. The height of the funnel

Table 1: Formula of wet granulation preliminary batches.

Ingredients	Quantity per tablet (in mg)			
	F1	F2	F3	F4
Intragranular				
Drug-X	10.0	10.0	10.0	10.0
Micro crystalline cellulose 101	46.0	42.0	46.0	42.0
Lactose monohydrate	26.0	26.0	26.0	26.0
Sodium starch glycolate	6.0	6.0	6.0	6.0
Poly vinyl pyrollidone K 30	4.0	8.0	4.0	8.0
Lubrication				
Micro crystalline cellulose 102	46.0	46.0	46.0	46.0
Sodium starch glycolate	4.0	4.0	4.0	4.0
Colloidal silicone dioxide	2.86	2.86	2.86	2.86
Talc	0.18	0.18	0.18	0.18
Magnesium stearate	3.34	3.34	3.34	3.34
Total Avg. Weight (mg)	150.0	150.0	150.0	150.0

was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation **(**Cooper and Gun, 1986).

$$\tan\theta = \frac{h}{r}$$

Where, h and r are the height and radius of the powder cone respectively.

Bulk density and tapped density

A quantity of 2gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced into 10ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5cm at second intervals. Tapping was continued until no further change in volume was noted. Bulk density (ρ_B) and tapped density (ρ_T) were calculated using the following equations (Aulton and Wells, 1998):

ρ_B= Weight of the powder blend/Untapped Volume of the packing

ρ_T=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index

The Compressibility Index of the powder blend was determined by Carr's compressibility index using the formula (Martin, 2001).

$$\text{Carr's index (\%)} = \frac{\rho T - \rho B}{\rho T} \times 100$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material. The ratio of tapped density to bulk density of the powders is called the Hausner's ratio. It is calculated by the following equation (Martin, 2001).

$$\text{H} = \frac{\rho T}{\rho B}$$

Evaluation parameters of core tablets

Appearance

Twenty tablets of each formulation were taken to check any discoloration or degradation of drug in the tablets by visual method. If any discoloration or black spots appears, it shows the degradation or decomposition of the drug in the tablet formulation (Jain *et al.*, 2007; Dietrich and Ney, 2006; Aoki, 2005).

Table 2: Formula for Optimization of enteric coating polymer.

Ingredients (%)	EC1	EC2	EC3	EC4	EC5	EC6
Eudragit L 100	50	60	70	-	-	-
HPMCP 50	-	-	-	50	60	70
Triethyl citrate	10	10	10	10	10	10
Talc	40	30	20	40	30	20
Ferric oxide yellow	0.3	0.3	0.3	0.3	0.3	0.3
IPA : DCM	60:40	60:40	60:40	60:40	60:40	60:40

Weight variation test

To study weight variation, twenty tablets of the formulation were weighed using a Sartorius electronic balance and the test was performed according to the official method.

Hardness

The hardness of five tablets was determined using the dial type hardness tester and the average values were calculated.

Thickness and diameter

The thickness and diameter of the tables was determined by using vernier calipers. Five tablets were used, and average values were calculated.

Friability

The friability of ten tablets was measured by Roche friabilator and average values were calculated.

Content uniformity

The enteric coated tablets of Ilaprazole were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 20mg of Ilaprazole were accurately weighed and transferred to a 100ml of volumetric flask. The flask was filled with phosphate buffer pH 8.0 and mixed thoroughly. Volume was made up to mark with phosphate buffer pH 8.0 and filtered. The absorbance of the resulting solution was measured at the 240nm using a UV/Vis double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was used for the estimation of Ilaprazole in the tablet formulations.

Disintegration time

Disintegration testing of core tablets was carried out in the six tablet basket rack USP disintegration apparatus. One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing disintegration media maintained at 37±2°C.

In vitro dissolution studies

The *in vitro* dissolution study of uncoated tablets of Ilaprazole was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900ml of 8.0 pH phosphate buffer, at 37±0.5°C and 100rpm. A sample (10ml) of the solution was withdrawn from the dissolution apparatus at regular interval for 60 minutes, and the samples were replaced with fresh dissolution medium. The samples were filtered through a 0.45µm membrane filter and absorbance of these solutions was measured at 240nm using UV/Vis double beam spectrophotometer (Shimadzu-1700). Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Table 3: Micromeritic properties of powder blends of batches F1-F4.

Powder blend	Angle of Repose (°)	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio
F1	24±1.576	0.527±0.028	0.603±0.039	12.60	1.14±0.031
F2	23±1.328	0.418±0.025	0.521±0.016	19.77	1.25±0.032
F3	22±0.914	0.436±0.027	0.526±0.026	17.11	1.21±0.039
F4	26±1.004	0.432±0.023	0.51±0.023	15.29	1.18±0.028

Coating of tablets

Coating of tablets was done using a side-vented, perforated pan coating apparatus machine. First fixed quantity (1kg) tablets were put in the pan which was pre adjusted at 50°C temperature for 5-10 minutes and actual weight of tablet was determined. Then the tube was put in the coating solution. After that the various parameters like spray rate (8 to 25gm/min), inlet air temperature (20 to 50°C), atomizing air pressure (1 to 3 bar), rotating speed of pan (5 to 20rpm), and % solid content (8 to 20%) were adjusted and optimized. After finishing the coating tablets were kept in the pan at 40° C and 2 rpm for curing. Then tablets were removed from the pan and evaluated for various parameters.

Core tablets were seal coated with 2%, 2.5% and 3% seal coating polymer and evaluated for tablet coating property. Enteric Coating of seal coated tablet was performed using two different polymers, Eudragit L 100 and HPMCP 50 using three different concentrations 7%, 9% and 11%, by trial and error method. Effect of these two polymers was compared. Enteric coating was performed on core tablet of 2.5% seal coated tablets. Solvent ratio of isopropyl alcohol (IPA): dicloro methane (DCM) (60:40) was optimized based on its coating effectiveness. Enteric coating solution was applied to 9% weight gain of avg. wt. of seal coated tablet. Formula for enteric coating solution is shown in table 2. Seal coated tablets were enteric coated using formula of batch no. EC5.

Evaluation parameters of enteric coated tablet

Weight variation test, thickness and diameter, hardness, friability and content uniformity

All these evaluation parameters are same as described in the evaluation parameters of core tablets.

Loss on drying

Pre-weighed glass stoppered bottle was dried for 30 minutes at 60°C in vacuum. 1 gm of the finely powdered tablets was placed in the bottles. By gentle, sidewise shaking, the sample was distributed evenly. The loaded bottle was placed in the oven, removes the stopper and leaved it also in the oven. The sample was dried at 60°C in vacuum for 3 hours. Upon opening the oven, the bottle was close promptly and allowed it to come to room temperature in desiccators before weighing. It was calculated by following formula:

$$\%\text{LOD} = \left(\frac{Loss\ in\ weight\ of\ the\ sample}{Weight\ of\ sample}\right) \times 100$$

Table 4: Evaluation parameters of core tablet of Ilaprazole.

Parameters	F1	F2	F3	F4
Appearance	Black spots	-	-	-
Wt. variation (mg)	150±0.54	150±1.52	150±0.94	150±0.73
Thickness (mm)	3.92±0.02	3.94±0.01	3.92±0.01	3.93±0.04
Hardness (kp)	6.1±0.133	7.4±0.125	7.4±0.095	6.7±0.109
Friability (%)	0.48±0.042	0.45±0.039	0.33±0.055	0.39±0.046
Content uniformity (%)	92.13	96.37	96.74	93.88
Disintegration time (min)	4-5	3-4	3-4	3-4

Percentage weight gain

% Weight gain defined by difference between weight of tablets after coating (W_{ta}) and weight of tablets before coating (W_{tb}) divided by weight of tablets before coating. It was calculated by following equation.

$$\%\text{Weightgain} = \frac{(Wta - Wtb)}{Wtb} \times 100$$

Disintegration Time

Disintegration testing of coated dosage forms was carried out in the six tablet basket rack USP disintegration apparatus. One tablet was introduced into each tube of the basket rack assembly of the disintegration apparatus without disc. The assembly was positioned in the beaker containing 0.1N HCl (pH 1.2) maintained at 37±2°C and operated the apparatus for 2 hours. After 2 hours 0.1N HCl was replaced with phosphate buffer 8.0 pH. A disc was added to each tube and operated for further 60 minutes. The disintegration time of each tablet was recorded.

In-vitro drug release studies

Drug release studies were carried out using a USP type II dissolution test apparatus at 100 rpm for 2 hr in 0.1 N HCl (900 ml) maintained at 37±0.5°C. 10 ml of sample was taken and sample was analyzed using UV spectrophotometer at 240 nm. Then the dissolution medium was replaced with pH 8.0 phosphate buffer (900 ml) and tested for drug release for 1 hr at same temperature and same rotation speed. After 10, 20, 30, 45 and 60 minutes, 10 ml of the samples were taken out and 10 ml volume of fresh phosphate buffer pH 8.0 was added to keep the volume of dissolution medium constant and sample was analyzed using UV spectrophotometer at 240 nm (USP 27, NF 22, 2004).

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to

Table 5: Evaluation outcome of enteric coated tablet of Ilaprazole.

Parameters	Optimized batch EC5
Weight variation (mg)	172.0 ±1.02
Thickness (mm)	4.02±.02
Hardness (kp)	10.2±0.095
Friability (%)	0.38±0.041
% LOD	1.10±0.2
Content uniformity (%)	99.24
Disintegration time (min)	
in 0.1N HCl	Intact tablets
in phosphate buffer pH 8.0	12.5 min.

Table 6: Accelerated stability study of optimized batch.

Parameters	Storage condition: 40±2°C / 75±5% RH			
	Initial	1 month	2 month	3 month
Weight variation (mg)	172±1.02	172±1.05	172±1.25	172±1.20
Thickness (mm)	4.02±0.02	4.02±0.03	4.02±0.021	4.02±0.031
Hardness (kp)	10.2±0.085	10.3±0.088	10.2±0.088	10.4±0.092
Friability (%)	0.38±0.041	0.41±0.039	0.39±0.044	0.38±0.043
% LOD	1.10±0.2	1.16±0.4	1.22±0.5	1.29±0.6
Content uniformity (%)	99.24	99.28	99.53	99.21
Disintegration time*	12.5	12.3	13	12.8

*- Conducted in phosphate buffer pH 8.0

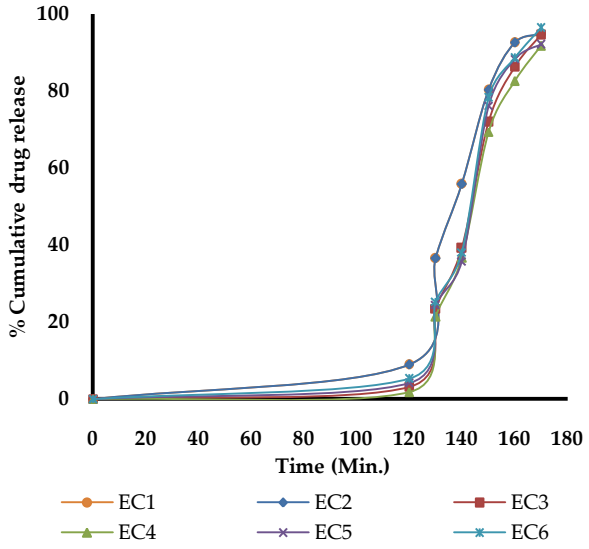

Figure 1: In-vitro drug release profile of formulations EC1 to EC6 of Ilaprazole enteric coated tablets.

compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100. A value of 100% for the similarity factor suggests that the test and reference profiles are identical. This similarity factor was calculated by following formula:

$$f_2 = 50X\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} X100\right\}$$

Where, n is the number of dissolution time and R_t and T_t are the reference and test dissolution values at time t.

Accelerated Stability study of the optimized batch

In order to determine the change in evaluation parameters and in-vitro release profile on storage, stability study of optimized batch was carried out at accelerated storage condition at temperature 40±2°C and 75±5% RH in a humidity chamber for 3 months. Sample were withdrawn after one week interval and evaluated for change in in-vitro drug release pattern, physical appearance thickness, hardness and disintegration time. The similarity factor (f_2) was applied to study the effect of storage on formulation (ICH Stability testing, 1996).

RESULTS AND DISCUSSION

The results of evaluation of powder blend formulations F1 to F4 mentioned in table 3, suggests that it has fair to passable compression property and moderate flow property (Damodaran *et al.*, 2010). The core tablets were evaluated for various parameters and their result are mentioned in table 4. All the batches of core tablet were good in appearance and devoid of any visual deformity except formulation F1 which show some black spots. Weight variation data of all trial batches indicated that they were in range of official standards and no significant difference between individual weights of tablets from the average value. Hardness of all the tablets was kept between 6-8 kp. Friability test for both wet granulation and direct compression was in the range of less than 1%. All the batches pass in content uniformity test as per official requirement. The assay results showed that the

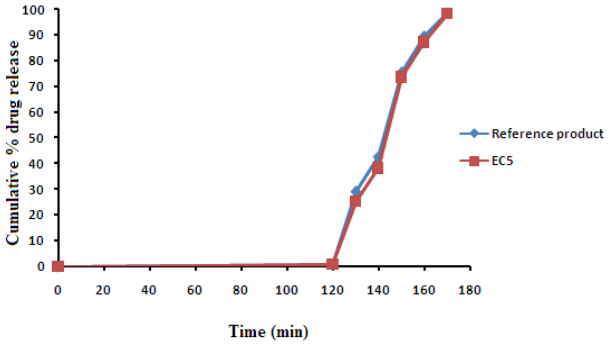

Figure 2: *In vitro* drug release profile of optimized formulation of Ilaprazole and its marketed preparation.

percentage drug content was found to be in the range of 92.13% to 96.74% for all the four formulations, which is acceptable as per the limits prescribed in I.P. (Singh *et al.*, 2009).

Seal coating trial was taken on core tablet of F3 batch. In this trial and error method for optimization of seal coat percentage on core tablet, three different percentage of coating solution was applied on core tablets i.e. 2%, 2.5% and 3%. The weight gain was found to be in the range of 3.08 to 4.62mg. Seal coated tablet containing 2% seal coat were devoid of full coating. It was partially coated with seal coating solution. Core tablet containing 2.5% and 3% were fully coated with barrier coating without any kind of coating defect. So, 2.5% seal coating on core tablet was optimized concentration of seal coating (Crotts and Sheth, 2000; Nair *et al.*, 2010). Entric coating was performed using Eudragit L 100 was used in 50%, 60% and 70% w/w in batches EC1, EC2, EC3 respectively and HPMC P 50 was also used in same amount respectively in batches EC4, EC5 and EC6.Solvent IPA:DCM was used in 60:40 ratio to prepare coating solution. 9% enteric coating was performed in all batches.

Enteric coated tablet of all batches pass in weight gain test. Enteric coated tablet of batches EC1 and EC4 failed in official disintegration test, while other batches of tablet passed in this test. The assay result of all the trial batches of enteric coated tablets was within official limit. Enteric coated tablet of EC1 shows less resistance in 0.1N HCl it may be because it contains less amount of Eudragit L 100 also it fail in disintegration test. Dissolution profile of EC2 and EC3 containing 60 and 70% w/w of Eudragit L 100 shows that as polymer amount increases dissolution profile retard and acid resistance increases. EC2 shows better profile than EC3. EC4 batch gave less resistance in 0.1N HCl and release more than 5% drug. EC5 and EC6 gave sufficient protection of core tablet in 0.1N HCl and did not release more than 5% drug. Dissolution profile of EC5 and EC6 were almost same but profile of EC6 was quite different from marketed product. EC5 gives highest dissolution profile and acid resistance than other enteric coated batches. So, enteric coating formula of EC5 was optimized for further study. In vitro drug release profile of formulations EC1 to EC6 of Ilaprazole enteric coated tablets are shown in figure 1.

Enteric coated tablets of optimized batch EC5 were passed in weight variation, hardness, thickness and diameter, friability,% LOD test as per official requirement as depicted in table 5. The % drug content was obtained to be 98.57% which is acceptable under the limits. The cumulative % drug release after 170 minutes was found to

be 98.4%. From the results of comparative study of dissolution profile of final batch with reference product, it was concluded that final formulation EC5 showed good similarity (i.e., more than 50) with reference product.

From the results of the accelerated stability study (table 6) of final formulation EC5 for 3 months, it was concluded that with storage conditions no significant changes were found in final formulation EC5. From the results of similarity factor (f_2) applied in accelerated stability study, it was concluded that final formulation EC5 after 3 months has shown good similarity (i.e., more than 50) with initial formulation. In vitro drug release profile of optimized formulation of Ilaprazole and its reference product are shown in figure 2.

CONCLUSION

Seal coating trial was taken on core tablet of F3 batch. It was concluded that 2.5% seal coating of core tablet was taken as optimize percentage coating of seal coat as compared to 2% and 3%. Enteric coating was performed by two different polymers, HPMCP 50 and Eudragit L 100. It was concluded after study that HPMCP 50 was more effective as enteric coating polymer at same concentration than Eudragit L 100 along with 10% Triethyl citrate and 9% enteric coating on seal coated tablet. As concentration of enteric coating polymer increases in formulation, acid resistance increases. It was concluded that 9% enteric coating on seal coated tablet was optimum to protect core tablet from acidic environment of stomach *in-vivo*. Based on *f*2 value of optimized batch EC5 when compared with reference product, it was concluded that developed formulation of delayed release tablet of Ilaprazole was similar with reference product. From the stability result we have concluded that there was no change in the formulation after 1 month accelerated stability study. So, prepared delayed release tablet of proton pump inhibitor was stable.

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