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Research Article

Optimization and Evaluation of Dexlansoprazole Delayed Release Enteric Coated Tablets

Ayush Garg*, Indrajeet Singhvi

Pacific College of Pharmacy, Udaipur – 313024, Rajasthan, India

***Correspondence:** ayush20.garg@gmail.com (Tel. +918233547528)

Abstract

The present study was an attempt to formulate and evaluate enteric coated tablets for Dexlansoprazole 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. Dexlansoprazole 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 HPMC P 50 and Eudragit L 100 in different concentrations. Enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment (intestinal pH 5.5 and above) where they do not degrade, and give their desired action. This stimulated us to formulate Dexlansoprazole as an enteric coated tablet and the prepared tablets were evaluated in terms of their pre-compression parameters and physical characteristics.

Keywords: Dexlansoprazole, HPMC P 50, Eudragit L 100, delayed release, enteric coated

Introduction

Dexlansoprazole is a substituted benzimidazole. Benzimidazoles are anti-ulcerous compounds known for decreasing gastric acid secretion. These compounds, also known as Proton Pump Inhibitors (PPI), are 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 syndrome) [1]. Dexlansoprazole is practically insoluble in water, more soluble in alkaline medium as compared to acidic medium. The stability of Dexlansoprazole is a function of pH; it is rapidly degraded in acid media, and is more stable under alkaline conditions. Therefore exposure of Dexlansoprazole to the acidic content of the stomach would lead to significant degradation of the drug and hence, reduced bioavailability [2, 3]. Delayed release dosage forms [4] 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 [5-7].

The first aim of present work was to prepare Delayed release i.e., enteric coated tablets of Dexlansoprazole by using Methacrylic acid copolymer (Colorcoat EC4S) 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. The second aim of present work was optimization of enteric coating formula which implicates more significant effects on dissolution profile of tablet.

Enteric coatings are usually formulated with synthetic polymers that contain ionizable functional groups that render the polymer water

Table 1: Formula of wet granulation preliminary batches

Ingredients	Qty/tab.(mg) F1	Qty/tab.(mg) F2	Qty/tab.(mg) F3	Qty/tab.(mg) F4
Intragranular				
Dexlansoprazole	30.0	30.0	30.0	30.0
Micro crystalline cellulose 101	46.0	42.0	46.0	46.0
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
Purified water	q.s.	q.s.	—	—
Isopropyl alcohol	—	—	q.s.	q.s.
Lubrication				
Micro crystalline cellulose 102	47.0	47.0	47.0	47.0
Sodium starch glycolate	4.6	4.6	4.6	4.6
Colloidal silicone dioxide	2.86	2.86	2.86	2.86
Talc	0.20	0.20	0.20	0.20
Magnesium stearate	3.34	3.34	3.34	3.34
Total Avg. Weight (mg)	170.0	170.0	170.0	170.0

soluble at a 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 [8].

Materials and methods

Materials

Dexlansoprazole was generous gift sample from Cadila healthcare Ltd. Hydroxy Propyl Methyl Cellulose Pthalate and Eudragit L 100 was of Colorcon Ltd., Ahmedabad, India. All other ingredients used were of analytical grade.

Methods

Formulation development of core tablet of Dexlansoprazole

Dexlansoprazole core tablets were formulated by using Wet granulation method. The formula of wet granulation batches is shown in Table 1. The weighed quantity of Dexlansoprazole and lactose was sieved through 40# size. The above sifted materials were mixed using planetary mixture for 10min. Then, SSG type A was passed through #40 and mixed with former blend. Prepare binder solution by dissolving 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 IPA if required until dough mass obtained. The prepared granules were then dried in Fluid Bed (FBD) at 48 ºC to 55 ºC till LOD was obtained less than 2%. Dried granules were sifted through the #20 screen of Oscillator granulator (OG). 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

Micromeritic properties of powder blends

Angle of repose

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

$$\tan\theta = h/r$$

Where, h and r are the height and radius of the powder cone respectively [9-11].

Bulk density and tapped density

Both bulk density (BD) and tapped density (TD) was determined. A quantity of 2 gm of API powder from each formula, previously shaken to break any agglomerates formed, was introduced into 10 ml 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 2.5 cm at second intervals [9-11]. Tapping was continued until no further change in volume was noted. LBD and TDB were calculated using the following equations.

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

TD = 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. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TD-BD) \times 100]/TD$$

Hausner's ratio

The Hausner's ratio is a number that is correlated to the flowability of a powder or granular material [9-11]. The ratio of tapped density to bulk density of the powders is called the Hasner's ratio. It is calculated by the following equation.

$$H = \rho T / \rho B$$

Where ρT = tapped density, ρB = bulk density

Blend Uniformity

An accurately weighed amount of Dexlansoprazole powder blend (100 mg) was extracted with 8.0 pH phosphate buffer and the solution was filter through 0.45µ membrane. The absorbance was measured at 240 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer.

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.

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 [12-14].

Hardness

The hardness of five tablets was determined using the Dial type hardness tester and the average values were calculated [12-14].

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 Dexlansoprazole were tested for their drug content. Ten tablets were finely powdered; quantities of the powder equivalent to 20 mg of Dexlansoprazole were accurately weighed and transferred to a 100 ml 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 285 nm using a UV/Vis double beam spectrophotometer. The linearity equation obtained from calibration curve as described previously was used for the estimation of Dexlansoprazole in the tablet formulations [12-14].

Disintegration time

The disintegration time of the six tablets were measured by using USP Disintegration apparatus at 37.5 ºC.

***In vitro* dissolution studies**

The in vitro dissolution study of uncoated tablets of Dexlansoprazole was determined using USP dissolution testing apparatus II (paddle type). The dissolution test was performed using 900 ml of 8.0 pH phosphate buffer, at 37 ± 0.5 °C and 100 rpm. A sample (10 ml) 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 0.45 µ membrane filter and absorbance of these solutions was measured at 285 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

Coating of tablets

Coating of tablets was done using a side-vented, perforated pan coating apparatus Ganscoater GAC 275 machine. First fixed quantity (1 kg) tablets were put in the pan which was pre adjusted at 50° C temperature for 5-10 minutes. Then 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 25 gm/min), inlet air temperature (20 to 50 °C), atomizing air pressure (1 to 3 bars), rotating speed of pan (5 to 20 rpm), and % solid content (8 to 20%) were adjusted and optimized. After finishing of 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.

Optimization of Seal Coating Percentage

To find out the optimum coating concentration of seal coating this helps to separate core tablet from acidic enteric coating layer. Instacoat - Transparant contains HPMC 6cps, PEG, ethyl cellulose, sodium methyl paraben. Concentration of Instacoat - Transparant was optimized via trial and error method. Core tablets were seal coated with 2 %, 2.5 % and 3 % seal coating polymer and evaluated for tablet coating property.

Optimization of Enteric Coating Formula

Enteric Coating of seal coated tablet was performed using two different polymers. Eudragit L 100 and HPMC P 50 were used in enteric coating 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. Optimization of enteric coating was performed in different stage. First, solvent ratio of IPA: DCM was optimized based on its coating effectiveness. Then comparative efficiency of enteric coating polymer HPMCP 50 and Eudragit L 100 was evaluated using three different concentrations. After that enteric coating percentage weight gain optimization performed where, seal coated tablet was enteric coated up to 7%, 9% and 11% and evaluated for tablet coating property.

Optimization of enteric coating polymer by Trial and Error

Enteric coating optimization was performed using three different concentrations of both polymers separately. Formula for enteric coating solution is shown in Table 2. Enteric coating solution was applied to 9% weight gain of avg. wt. of seal coated tablet.

Table 2: Formula for Optimization of enteric coating polymer

Ingredients (%)	EC1	EC2	EC3	EC4	EC5	EC6
Eudragit L 100	50	60	70	–	–	–
HPMC P 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

Optimization of Enteric Coating weight gain on Seal Coated Tablet

Seal coated tablets were enteric coated using formula of batch no. EC5. Enteric coating weight gain were optimized by applying 7%, 9% and 11% of enteric coating solution on seal coated tablet and evaluated.

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

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:

% LOD = (Loss in weight of the sample/Weight of sample) * 100

% Weight gain

% Weight gain defined by difference between weight of tablets after coating (Wta) and weight of tablets before coating (Wtb) divided by weight of tablets before coating. It was calculated by following equation.

%Weight gain = (Wta - Wtb)/ Wtb * 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 °C ± 2 °C and operated the apparatus for 2 h. After 2 h 0.1N HCl was replaced with phosphate buffer 8.0 pH. A disc was added to each tube and operated for further 60 min. 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 h in 0.1 N HCl (900 ml) maintained at 37 °C ± 0.5 °C. 10 ml of sample was taken and sample was analyzed using UV spectrophotometer at 285 nm. Then the dissolution medium was replaced with pH 8.0 phosphate buffer (900 ml) and tested for drug release for 1 h 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 285 nm [15].

Comparison of dissolution profiles with marketed products

The similarity factor (f2) 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 f2 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,

$$f_2 = 50 \mathrm{X} \log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} w_t\left(R_t - T_t\right)^2\right]^{-0.5} \mathrm{X}\, 100\right\}$$

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 (f2) was applied to study the effect of storage on formulation [16].

Results and discussion

The results of micromeritic properties of powder blends F1-F4 shown in Table 3, suggests that it has fair to passable compression property and moderate flow property [17]. 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, as shown in Table 4.

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

Powder blend	Angle of Repose (^{0})	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

Table 4: Evaluation parameters of uncoated tablet of dexlansoprazole

Parameters	F1	F2	F3	F4
Appearance	Black spots	-	-	-
Weight variation (mg)	170±0.54	170±1.52	170±0.94	170±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±0.0555	0.39±0.046
Disintegration time (min)	4-5	3-4	3-4	3-4

The assay results showed that the 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 [18].

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 4.62 mg. Seal coated tablet containing 2 % seal coat were devoid of full coating. It was partially coated with seal coating solution. Weight gain was achieved without any kind of process problem. 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 [19-20].

Optimization of enteric coating formula

IPA: DCM in 60:40 ratios was used because it formed proper spray from coating machine gun and coating was performed satisfactorily on tablet. 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.

Except enteric coating polymer all other excipients were kept constant to evaluate the effect of amount of enteric coating polymer and its protection efficiency in 0.1 N HCl. Solvent IPA: DCM was used in 60:40 ratios 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 increase dissolution profile retard also acid resistance was increased. EC2 shows better profile than EC3 as it was reflected from f2 value.

EC4 batch gave less resistance in 0.1N HCl and release more than 5% drug. Also, enteric coating did not remain intact during disintegration test in 0.1N HCl for 2 h. 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 better f2 value than EC6.

Batch EC1 and EC4 which contains only 50% w/w enteric coating polymer fail in dissolution test as per USP because it release more than 5% drug in acidic medium. EC2 and EC5, both contain 60% w/w Eudragit L 100 and HPMCP 50 respectively. But, this enteric coating polymer EC5 gives better dissolution profile and acid resistance than batch no. EC2 containing Eudragit L 100. So, enteric coating formula of EC5 was optimized for further study.

Evaluation parameters of enteric coated tablet of optimized batch EC5 of dexlansoprazole

Enteric coated tablets of all trial batches were passed in weight variation, hardness, thickness and diameter, friability, % LOD test as per official requirement, as shown in Table 5. The % drug content was obtained to be 98.57% which is acceptable under the limits. The cumulative % drug release after 170 min was found to be 98.4% with f2 value of 85.7. From the results of comparative study of

Table 5: Evaluation parameters of enteric coated tablet of dexlansoprazole

Parameters	Optimized batch EC5
Weight variation (mg)	192.0 ±1.02
Thickness (mm)	4.02±.020
Hardness (kp)	10.2±0.095
Friability (%)	0.38±0.041
% LOD	1.10±0.20
Content uniformity (%)	99.24±0.35
Disintegration Time (min)	In 0.1N HCl: Intact tablets In phosphate buffer pH 8.0: 12.5 min

dissolution profile of final batch with market preparations, it was concluded that final formulation EC5 showed good similarity (i.e., more than 50) with market products, as shown in Figure 1.

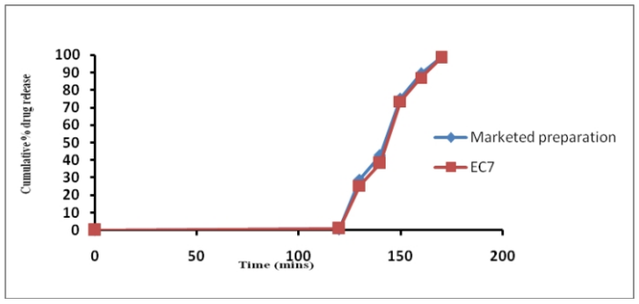

Figure 1: *In vitro* drug release profile of optimized formulation of dexlansoprazole and its marketed preparation

Accelerated stability study of the optimized batch

From the results of the accelerated stability study as shown in 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 (f2) 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, as shown in Table 6.

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 f2 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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Conflict of interest

The authors declare no competing interests.

Table 6: Accelerated stability study of optimized batch

Parameters	Storage condition: 40°C ± 2°C / 75%RH ± 5 % RH			
	Initial	1 month	2 month	3 month
Weight variation (mg)	192±1.02 ±1.02	192±1.05 ±1.02	192±1.25	192±1.20 ±1.02
Thickness (mm)	4.02±0.020	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±0.20	1.16±0.40	1.22±0.50	1.29±0.60
Content uniformity (%)	99.24±0.35	99.28±0.22	99.53±0.17	99.21±0.19
Disintegration time (min) (in phosphate buffer pH 8.0)	12.5	12.3	13	12.8

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