DESIGN, IN VITRO EVALUATION AND IN VIVO STUDIES OF NOVEL DELAYED RELEASE TABLETS OF PANTOPRAZOLE

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Abstract

In an effort to reduce production costs, a simple, direct compression delayed release formulation consisting of pantoprazole was investigated. Pantoprazole is a proton pump inhibitor belongs to group of benzimidazole. It is very efficient for the treatment of gastric and duodenum ulcers. Even in solid state pantoprazole is sensitive to heat, humidity, light and especially to substances containing an acidic group. For such types of drugs, enteric coating added to the formulation tends to avoid the stomach's acidic exposure, delivering them instead to a basic pH environment where they do not degrade, and give their desired action. Subcoating is desirable to protect the enteric coating. Opadry and Acryl-EZE systems have been utilized for subcoating and enteric coating respectively. Delayed-release tablets with good physical, mechanical and technological properties were obtained with use of different combinations of diluents, binders, superdisintegrants and lubricants. A comparative kinetic study of the present tablets and commercial tablets was established. The value for the similarity factor ($f2$ = 71.6) suggested that the dissolution profile of the present two delayed-release oral dosage forms are similar. Hixon–Crowell (erosion) kinetic profiles were achieved.

Keywords: Pantoprazole**,** delayed release, subcoating, enteric coating, acid uptake, stability, pharmacokinetic, bioequivalence.

1. Introduction

Pantoprazole is a selective and irreversible proton pump inhibitor (PPI) used in medicine as an antiulcerative agent. In low pH values, pantoprazole turns into a cationic sulfenamide, which is its active form [2,4]. Among the various PPIs, it has several important properties that differentiate it from the earlier agents. Its pharmacokinetic parameters increase linearly with dose. The bioavailability of pantoprazole is high and unaffected by food intake. It is more stable than other PPIs at slightly acidic and neutral pH. This drug accumulates in the highly acidic environment of the parietal-cell canalicular lumen and it is activated. The active form, a tetracyclic cationic sulfenamide, reacts with thiol group of cysteines 813 and 822 of the transmembranal H+/K+ATPase [1,5]. This conversion must occur inside the gastric parietal cells, so pantoprazole must be absorbed intact by gastrointestinal tract [2]. Pantoprazole has several advantages compared to its analogues (e.g., omeprazole and lansoprazole) such as specific site of binding, greater stability in neutral pH environment, and longer duration of action [6]. Besides, it presents no potential to induce or inhibit the CYP 450 [1,2,7]. It is a more selective inhibitor of acid secretion than other proton pump inhibitors [8].

Due to the necessity to pass intact through the stomach for reaching the duodenum for absorption, pantoprazole is formulated as solution for intravenous administration (lyophilized powder for reconstitution) or as gastric-resistant tablets (oral delayed-release dosage form). In the case of oral administration, the enteric coating prevents pantoprazole from degradation in the gastric juice (at pH 1–2, pantoprazole degrades in few minutes) [9].

Tablets can be manufactured by wet granulation, dry granulation, or direct compression. Most of the pharmaceutical manufacturers are opting for direct compression tableting, as it requires fewer processing steps, simplified validation, elimination of heat and moisture, economy, and improved drug stability compared with wet granulation technique. Dry granulation requires control of more processing variables than the direct compression. Reproducibility of the product is difficult to achieve in dry granulation. Hence, the current trend in the pharmaceutical industry is to adopt direct compression

technology. Although simple in terms of unit process involved, the direct compression process is highly influenced by powder characteristics such flowability, compressibility and dilution potential.

Up to now, no delayed release tablet of pantoprazole containing granular form of pantoprazole has been developed. The agglomerated pantoprazole has been utilized for preparation of direct compressible tablet. Due to the rapid drug degradation that occurs in acidic gastric fluids, enteric coating is required. To prevent the dissolution of enteric coating because of the presence of alkaline substances in the core, intermediate layer (subcoating) is required between core tablet and enteric layer. In order to overcome the problems associated with the conventional coating systems novel aqueous coating technology has been utilized in the present study both for subcoating and enteric coating.

Taking all the above into account, this study concerns with design and evaluation of delayed release tablet of pantoprazole by utilizing simple, inexpensive direct compression method. Pantoprazole does not possess excellent fluidity, flow and directly compressible properties, so granular form of pantoprazole has been used. Pantoprazole is known to be sensitive to heat and unstable in an acidic environment as well as in the presence of moisture and organic solvents. The present formulation has been designed to protect the drug from moisture and acidic conditions.

2. Materials and Methods

2.1 Materials: Pantoprazole sodium sesquihydrate was obtained from Ranbaxy Laboratories Ltd. (Dewas, India). Opadry II and Acryl EZE were kindly given by Colorcon (Goa, India). Microcrystalline cellulose, pearlitol, lactose, pregelatinized starch, crosspovidone, sodium starch glycolate, crosscaremellose sodium, magnesium stearate, calcium searate, povidone, talc and aeosil were obtained from Ranbaxy Laboratories Ltd. (Dewas, India). Potassium dihydrogen orthophosphate was obtained from (CDH, Mumbai). Acetonitrile, HPLC grade, was obtained from Fisher

Chemicals (CDH, Mumbai). All other chemicals were of analytical grade.

2.2 Compatiability Studies: Study of drug–excipient compatibility is an important process in the development of a stable solid dosage form. Drug–excipient compatibility testing at an early stage helps in the selection of excipients that increases the probability of developing a stable dosage form [10]. Compatibility studies of drug with excipients were performed under different storage conditions for one month. Binary powder mixtures prepared by triturating the API with the individual excipients were sealed in vials. Sealed vials were stored at 0°C, 25°C and 40°C. Samples were analyzed after 1st week, 2nd week and at the end of 3rd week.

2.2.1 Preparation of Pantoprazole Core Tablet: Tablets were manufactured using an instrumented 20 station rotary tablet press (Cadmach, Ahmedabad), fitted 5.75 mm standard concave tooling.

Series of formulations were designed for optimization of core tablets. Six batches from P1 – P6, were designed using different diluents, binders, superdisintegrants and lubricating agents. For solving the problem faced in the above batches dummy batch (without API) was compressed. Further five batches P8 – P12 were compressed with the following changes: P8 with addition of talc as antiadherent, P9 with increased concentration of diluent and batches P10 – P12 with both the addition of talc and increased diluent concentration. Four batches from P13 - P16 were further compressed utilizing granular form of pantoprazole. All the compressed tablet batches were evaluated for thickness, hardness, friability, and disintegration time.

2.2.2 Preparation of pantoprazole granules: Accurately weighed 28 gms of sodium carbonate was added to 100 ml distilled water to prepare the sodium carbonate solution. Weighed amount of pantoprazole (304 gms) was transferred to granulator and wetted while mixing with the prepared sodium carbonate solution. The wet mass was transferred to fluidized bed dryer and dried. After drying the granulate was sieved through 36# sieve. The residual moisture of dried granulate was 1.20% as determined by halogen moisture analyzer. The prepared pantoprazole granules were utilized for the preparation of core tablet by direct compression. Remaining sodium carbonate was sifted through sieve # 36. Pantoprazole was mixed with sodium carbonate geometrically. Filler and aerosil were mixed and and sifted through sieve # 30. Blend of API with sodium carbonate was mixed with blend of filler and aerosol. Binder and disintegrant was separately sifted through sieve # 30 and were mixed with the above blend Lubricant was sifted through #44 or #60 and blend was lubricated. The blend was characterized for particle size distribution, angle of repose, bulk density and compressibility indexes.

2.3 Evaluation of the bulk: Prior to compression, bulk was evaluated for their characteristic parameters. Moisture content was determined using halogen moisture. Particle size distribution was performed on random samples of batches using Alpine Airjet Particle Size Analyzer **[11].** The percentage weight of agglomerates retained on each sieve was noted. Angle of repose was determined by funnel method **[12].**

Bulk density and tapped density were determined by cylinder method [13], and Carr's index (CI) was calculated using the following equation.

Carr's index (%) = [(Bulk density – Tapped density) * 100] /Bulk density (1)

Hausner ratio is unsettled volume (V_o) divided by the tapped volume (V_f).

Hausner ratio = V_o/V_f (2)

2.4 Characterization of Tablets: Uncoated tablets were examined using traditional analytical techniques to determine common attributes, such as breaking force, friability and disintegration time. The thickness of the tablet was determined using a thickness gauge (Mitutoyo). Ten tablets from each batch were used & average values were calculated. Hardness was measured using Scheulinger Hardness Tester.

Friability was determined using Roche friability[14] testing apparatus using following equation:-

$$\% \text{ friability} = \frac{(\text{initial weight} - \text{final weight}) \times 100}{\text{Initial weight}}$$

Disintegration test for enteric-coated Tablets **[15]** was performed as per the USP procedure.

2.5 In Vitro Drug Release Studies **[16]:** Drug release was measured in a USP compliant dissolution bath using apparatus I (basket method) at 100 rpm.

Acid Phase - Six tablets were subjected to two hours in 0.1N HCl followed by immediate transfer to a dissolution bath containing phosphate buffer, pH 6.8. The criteria for drug release were not more than 10 percent drug loss after 2 hours in 0.1N HCl.

Buffer Phase - Samples were withdrawn from the dissolution vessels at 5, 10, 15, 20, 25, 30 and 35 minute intervals. The percent drug release was quantified using UV spectrophotometer (Shimadzu) at wavelength of 290 nm. The release studies were conducted in triplicate.

2.6 Assay of pantoprazole in tablets **[17]:** Five randomly chosen tablets from each formulation were accurately weighed and 0 were crushed to a fine powder. An amount equivalent to 10 mg of pantoprazole sodium was added into 10 ml volumetric flasks and volume was made up with acetonitrile. The sample was filtered through a 0.45-µm-membrane filter; different dilutions were made from this stock solution and samples were injected for HPLC analysis. Corresponding concentrations were calculated from the standard curve.

2.6.1 Coating of Pantoprazole Core Tablets [18]: The seal layer (Opadry II) was applied at a theoretical weight gain of 4%. Following application of the seal layer a 12% weight gain of Acryl-EZE was applied as the enteric layer. The 12% weight gain samples were then submitted for disintegration and dissolution analysis.

2.6.2 Percent Acid Uptake for Enteric Coated Tablets [19]: Accurately weighed 6 tablets (Wo) and exposed to acidic media (0.1 N HCl) for 2 hrs at 37°C in disintegration test apparatus. Excess of moisture was removed and tablets were reweighed (Wt). From the difference in weights before and after exposure to acidic media, the % of acid uptake can be calculated.

$$\textbf{\% Acid uptake} = \frac{Wt - Wo}{Wo} \times 100 \quad (3)$$

2.6.3 Kinetic Analysis of Dissolution Data **[20- 24]:** To analyze the *in-vitro* release data various kinetic models were used. The zero order rate Eq. (1) describes the systems where the drug release rate is independent of its concentration. The first order Eq. (2) describes the release from system where release rate is concentration dependent**.** Higuchi described the release of drugs from insoluble matrix as a square root of time dependent process based on Fickian diffusion Eq. (3). The Hixson-Crowell cube root law Eq. (4) describes the release from systems where there is a change in surface area and diameter of particles or tablets.

$$Qt = k_0 t \quad (4)$$

Where, K_0 is zero-order rate constant expressed in units of concentration/time and t is the time.

$$\text{Log}Q = \text{Log}Q_0 kt/2.303 \quad (5)$$

Where, C_0 is the initial concentration of drug and K is first order constant.

$$Qt = Kt^{1/2} \quad (6)$$

Where, K is the constant reflecting the design variables of the system.

$$Q_0\hat{}1/3 - Qt\hat{}1/3 = K_{hc}t^n \quad (7)$$

Where, Qt is the amount of drug released in time t, Q_0 is the initial amount of the drug in tablet and K_{hc} is the rate constant for Hixson-Crowell rate equation.

The following plots were made: cumulative % drug release vs. time (zero order kinetic model); log cumulative of % drug remaining vs. time (first order kinetic model); cumulative % drug release vs. square root of time (higuchi model)

log cumulative % drug release vs. log time (korsmeyer model) and cube root of drug % remaining in matrix vs. time (hixson-crowell cube root law).

To find out the mechanism of drug release, first 60% drug release data was fitted in Korsmeyer–Peppas model: n

$$Qt/Q\infty = Kt^n \quad (8)$$

Where Qt/Q∞ is fraction of drug released at time t, k is the rate constant and n is the release exponent.

2.7 Stability Studies [25]**:** Physical parameters such as hardness, disintegration and dissolution are routinely evaluated within the framework of a stability programme for a solid dosage form The physical stability of enteric-coated pantoprazole tablets was investigated over 12 weeks at 2-8ºC, 25ºC and 40ºC. The stability batches were analyzed for hardness, disintegration time and drug content after three months.

2.8 In Vivo Evaluation: The study was carried out under the guidelines compiled by CPCSEA (Committee for the Purpose of Control and Supervision of Experiments on animals), Ministry of culture, Government of India and all the study Protocols were approved by local institutional animal ethics committee. [CTCA-465, College of Pharmacy, IPS]

Rabbits (2-3 kg) were divided into 2 groups, each consisting of three animals. First group received formulated tablets of pantoprazole. Second group received the marketed tablets of pantoprazole. Selected white albino rabbits weighing were fasted overnight and only water was given during fasting. Rabbits were orally treated with pantoprazole delayed release tablet. The tablets were introduced directly into the oesophagus using oral feeding tube with 5 ml of distilled water in order to avoid possible damage caused by chewing.

The timing of blood collection was planned according to the previously reported value of time to reach peak serum concentration (*T*max) and serum elimination half-life (*t*1/2). Blood samples were collected before and at 1, 2, 2.33, 2.66, 3, 3.33, 3.66, 4, 4.5, 5, 5.5, 6, 7 and 8 hours after drug administration from marginal ear veins of rabbit. The blood samples were collected in coded, evacuated tubes, kept for 1 hour in incubator (37°C), and centrifuged at room temperature

at 2000 rpm for 10 minutes[26] (Cooling Micocentrifuge, Remi).The serum was collected in coded Eppendorf tubes and serum protein was separated by precipitation with twice volume of acetonitrile, followed by centrifugation at 10,000 rpm for 5 minutes. The serum was collected and stored at -20°C until analyzed.

2.9 HPLC Assay[17]**:** The quantitative determination of drug in plasma was performed by HPLC assay using acetonitrile: phosphate buffer (70:30 vol/vol) mixture as mobile phase delivered at 1.0 mL/min. Twenty microliters of injection volume was eluted in C-18 column (Phenomenex) at room temperature. The column eluant was monitored at 289 nm using diode array UV detector.

2.10 Statistical Analysis: The data was subjected to ANOVA followed by studentized range test for analyzing the statistical difference using the software Graphpad InStat. A confidence limit of $P < .05$ was fixed for interpretation of the results.

3. Results and Discussion

Compatibility Studies work conducted at conditions of 0°C, 25°C, 40°C for a period of 1 month. No color change or difference in color in the stress samples and control samples was observed **(Table 2)** during or after a 3-week storage period, indicating the absence of any incompatibility between the mixture components. Hence all the excipients used with pantoprazole were compatible with it.

The blend containing API and excipients were compressed to prepare the core tablets. The results for bulk characteristics (P1 –P6) are given in **Table 3 and 4**. Tablets obtained were analyzed for weight variation, friability, hardness, thickness and disintegration time. Initially six batches were designed for the direct compression (i.e. Batch No. P1 - P6) using different diluents, binders, lubricants and disintegrants.

In all the batches sticking problem was observed during compression. As per the API requirement, relative humidity was maintained at less than 50%, but then also sticking problem was observed on both lower and upper punches.

To deal with the problem, it was necessary to know whether problem lies with API or any of the excipients of formulation. Therefore dummy tablets (Batch No. P-7) were compressed. Dummy tablets were compressed without any difficulty implying the problem lies with pantoprazole. It was further decided to eliminate carbopol as the binder from the formulation, because it possesses weakly acidic properties which affected the highly sensitive API. A minor color change was observed in tablets formulated using carbopol.

Three strategies were developed for solving the problem, addition of talc as antiadherent, increase in the diluent concentration and if both the above

approaches fail, increase in the diluent concentration along with addition of talc.

Batch no. P8 comprising of talc as antiadherent was compressed, still the sticking problem persisted.

In P9 the diluent concentration was increased, humidity was maintained at 47% (<50% RH).Tablets of this batch were compressed without any difficulty. Tablet weight was increased from 75 mg to 110 mg. B. No. P9 was compressed at different thickness and further evaluation was done. The results are shown in **Table 5**. B. No. P-10 containing talc as antiadherent and increased diluent concentration was compressed without any difficulty. With the positive results obtained above, similar changes were made in all the other batches and compression was tried. In batches P-11 and P-12 still the sticking problem persisted. To verify the results, the compression of batches P-9 and P-10 was again done. In both the bathes sticking was observed especially on lower punch. It was concluded that with increase in diluent concentration and addition of talc as antiadherent, problem with fluidity and flowability of pantoprazole can be eliminated to some extent only. It was found that pantoprazole is highly sensitive to heat, light and moisture which causes difficulty in direct compression of API.

A new approach was designed for the preparation of directly compressible tablets of pantoprazole in which granular form of pantoprazole was utilized.

Blend of all four formulations (B. No. P13- P16) were individually compressed, without any problem, by direct compression method. As evaluated from the study, pantoprazole does not possess excellent fluidity, flow and directly compressible properties, so granulation of pantoprazole was done. Water was used as the granulating agent. Since pantoprazole is very acid labile, therefore it is necessary to process it in the form of alkaline salts or together with alkaline salts. $1/4^{th}$ of sodium carbonate was added to water. The sodium carbonate solution took less drying time as compared with the previously used mannitol solution for granulation. The agglomerated drug can be used in the preparation of tablet cores by direct compression.

The results for the bulk characteristics (P13 – P16) are listed in **table 6 £ 7**. The particle size distribution (PSD**)** of a powder is a list of values that defines the relative amounts of particles present, sorted according to size. 85-90% of particles were found to be greater than 85 mesh. Optimum particle size distribution was obtained in all the four batches, which resulted in good flow properties and compression.

The two parameters compressibility index and hausner's ratio are influenced by variables such as particle size and shape, and cohesivity, since they essentially reflect the impact of tapping on the particle packing. The value of Carr's index between 5-15% and 15-20% indicates excellent and good flowability, respectively. The results indicate good flow properties of all the four batches. The compressed batches were characterized for friability, hardness, thickness and disintegration time. Properties of core tablets are summarized in **Table 8, 9 and 10.**

The formulations had good flow resulting in low weight variation. All tablets were of high quality and complied with pharmaceutical standards. All the tablets from each formulation passed weight variation test, as the % weight variation was within the pharmacopoeial limits of ±5% of the weight. The assay for drug content was found to be uniform among different batches of tablets and ranged from 95 % to 105%. The hardness of all formulations was in the range, 3.5- 5 Kg/cm^2. Tablets with mechanical strength (breaking force) suitable for additional coating unit operations were manufactured. Percentage weight loss in the friability test was found to be less than 0.4% in all the cases. All the batches of tablets prepared were of good quality with regard to hardness, friability and drug content.

The various directly compressible diluents like pregelatinized starch, microcrystalline cellulose, lactose and pearlitol have been utilized in the preparation of pantoprazole core tablets. Diluents for direct compression application should possess both flowability and compressibility. The spray-dried lactose monohydrate grades exhibit increased compressibility due to the nature of the aggregates and the presence of amorphous material. Microcrystalline cellulose is partially depolymerized cellulose consisting of bundles of needle-like microcrystals and is highly compressible. It is also being frequently used as a dry binder in direct compression applications. Microcrystalline cellulose is often used with lactose monohydrate because it has been shown to improve the compressibility of the formulation. The pearlitol SD 200 offers a unique blend of exceptional physical and chemical stability, with great organoleptic and non-carcinogenic properties. Pregelatinized starch, a modified starch is used in oral capsule and tablet formulations as a binder, diluent, and disintegrant.

Magnesium stearate, calcium stearate and stearic acid can be used as lubricants in pantoprazole formulations. Stearic acid is generally the preferred lubricant with pregelatinized starch because of higher magnesium stearate concentrations may have adverse effects on tablet strength and dissolution.

Superdisintegrants are added to oral solid dosage formulations to facilitate disintegration. Commonly used superdisintegrants such as crospovidone, croscarmellose sodium, and sodium starch glycolate were utilized. No significant differences were observed in the disintegration times of the tablets with the use of various superdisintegrants probably because pantoprazole possess good aqueous solubility.

The results of dissolution of core tablet in phosphate buffer (pH- 6.8) are shown in **Table 11.**

The dissolution profile of the four batches was compared with the dissolution profile of marketed tablets of Marketed I and Marketed II (coated tablets).

Good release pattern were obtained in all the four batches. Better release profiles were obtained in B. No. P13 and P14 as compared with the marketed formulation, therefore both the batches were selected for further processing (Coating).

The parameters for subcoating and enteric coating are given in **Table 12**. Subcoating was done using Opadry II (white). Opadry II product range consists of fully formulated dry blend systems for aqueous film coating of solid dosage forms. Opadry systems reduced processing times as compared with the conventional coating systems provides superior product in all the respects along with reduction in cost.

Since the substances suitable for enteric coating contain free carboxyl group, problem arises when enteric coating is partly or completely dissolved from inside because of alkaline medium in the interior, and the free carboxyl group promote the decomposition of API. It is therefore necessary to provide sealing intermediate layer between enteric coating and alkaline tablet core. Hence, in the present investigation Opadry II has been used for subcoating.

Acryl-EZE is a world-first film coating product: an optimized, one-step, pigmented, aqueous acrylic system for the application of an enteric film coating for oral solid dosage forms. Acryl-EZE combines the benefits and performance of a globally accepted enteric polymer (Eudragit® L100-55) with a fully formulated coating system, providing significant time savings in both development and production. Acryl-EZE has advantage over conventional enteric coating systems. The conventional enteric coating solution use organic solvents which suffer with many disadvantages. Problem associated with organic solvents are pollution of the atmosphere, safety and hygiene problems of workers, danger of fire and explosion and expensive equipment requirements.

Pantoprazole is known to be unstable in an acidic environment. The coating with Acryl-EZE will protect pantoprazole against acid media as coating solubilizes at pH 5.5.

Percentage of acid uptake by enteric coated tablets is shown in **Figure 1**. Lower the % if acid uptake, more effective the enteric coating will be in protection of drug in the core. Values less than 10 percent acid uptake have shown to correlate to acceptable dissolution performance. % Acid uptake was found to be less than 10% in both P-13 and P-14 batches. Visual observation of the tablets after 2 hours in gastric media (0.1 N HCl) yielded no signs of disintegration, cracking, softening, or degradation.

The drug release in the acidic medium was found to be negligible. Less than 0.5 % of drug was released within 2 hours in 0.1N HCl. and more than 80% released in phosphate buffer.

Drug release in both the formulated batches **(Figure 2)** was found to be higher and more consistent as compared with the marketed formulations**.** Even the percent acid uptake was less in case of formulated batches as compared with marketed formulation. No signs of disintegration, cracking or softening were observed in 0.1 N HCl for 2 hours which showed the intactness of enteric coating.

From the data, it is concluded that the fabricated tablets followed Hixon Crowell release kinetics **(Figure 3. and Table 13)**. Further, to understand the drug release mechanism, the data were fitted to Peppas exponential equation. Based on various mathematical models, the magnitude of the release exponent "*n*" indicates the release mechanism (Fickian diffusion, case II transport or anomalous transport). In the present study the limits considered were $n = 0.45$ (indicates a classical Fickian diffusion-controlled drug release) and $n = 0.89$ (indicates a case II relaxation release transport; non-Fickian, zero-order release). Values of *n* between 0.45 and 0.89 can be regarded as an indicator of both phenomena (drug diffusion in the hydrated matrix and the polymer relaxation) commonly called anomalous transport. From the release exponent in the Korsmeyer-Peppas model ($n = 0.712$) it could be suggested that the mechanism that led to

the release of pantoprazole sodium was an anomalous transport, which indicates the drug release through diffusion and relaxation.

The optimized formulations were charged for stability studies at different temperature conditions: 2-8ºC, 25ºC and 40ºC. The stability batches were analyzed for hardness, disintegration time and drug content after three months.

No change in hardness and disintegration time was noted after three months. Drug content was also found to be within range (95-105%) with negligible change as compared to initial state. Thus formulations are more stable at all the temperature storage conditions.

The mean (± SD) plasma concentration time profile of the 2 formulations, shown in **Figure 4**, was similar and superimposable. Pharmacokinetic parameters for both formulations are shown in **Table 14**. C_{max} was found to be 1520 ng/mL for the manufactured (test) product and 1498 ng/mL for the marketed product. T_{max} (hr) was found to be 2.66 hrs and 3 hrs for formulated and marketed pantoprazole tablet respectively. The area under the plasma concentration v/s time curves ($AUC_{0-\infty}$) for the formulated and marketed tablet was 3317 ng.hr/ml and 3174.8 ng.hr/ml respectively which were not significantly different. Thus, the two formulations can be considered bioequivalent in regard to the rate and extent of absorption.

4. Conclusion

In the present study, delayed release tablet of pantoprazole was developed by change in the manufacturing process with adequate shelf life. Series of formulations were prepared to get the optimized formulation. In all the initial batches prepared sticking problem was observed on both upper and lower punches. The problem could not be solved by including the talc as antiadherent and increasing the diluent concentration.

Dealing with the sticking problem, it was concluded that pantoprazole is sensitive to heat and moisture which causes problem with the direct compression. So, newer approach was developed in which only granulation of the pantoprazole was done with sodium carbonate solution. The sodium carbonate solution took less drying time as compared with the previously used mannitol solution for granulation which resulted in saving time during the process development. Rest of the excipients were mixed with the granular pantoprazole for the direct compression.

The use of agglomerated pantoprazole resulted in better flow properties as indicated by the flowability indexes (Carr ratio and Hausner index). The tablet hardness and friability were found as per Pharmacopoeial standards.

It can be concluded formulated tablet was better than marketed tablet in the following respects:-

a) Use of direct compression manufacturing method which is easier, simplified and economical method of manufacturing of tablets as compared to wet granulation. Different directly compressible diluents have been analyzed. Good results are obtained in all the formulated batches.

b) Use of fully formulated aqueous polymeric systems for both subcoating and enteric coating. With these systems, there are fewer processing steps involved, and fewer ingredients to inventory and submit to quality control testing compared with a traditional system, thus saving time and money. Reduced processing times can eliminate defects such as edge chipping and erosion by decreasing the overall mechanical stress experienced by the tablets. Ultimately, reduced processing times can improve productivity in manufacturing.

c) Less percent acid uptake as compared to marketed formulation which showed the intactness of enteric coating.

d) More cumulative % drug release and consistent drug release as compared to marketed formulation.

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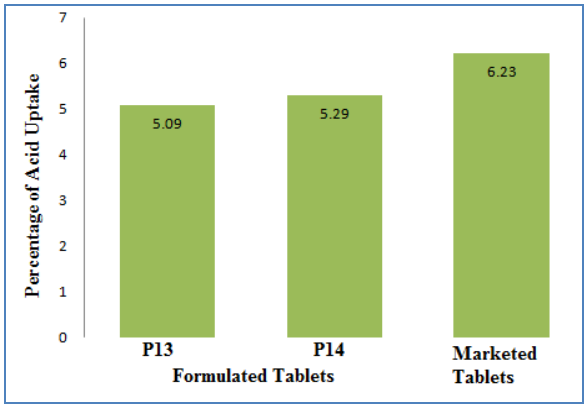

Figure 1. Percentage of Acid uptake by enteric coated tablets

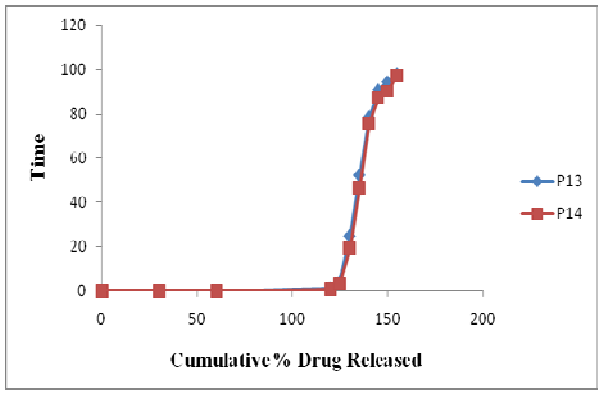

Figure 2. Cumulative % Drug Release from the enteric coated tablets

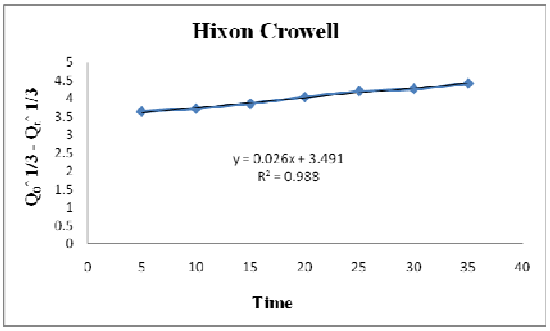

Figure 3. Hixon Crowell plot for batch no. P13

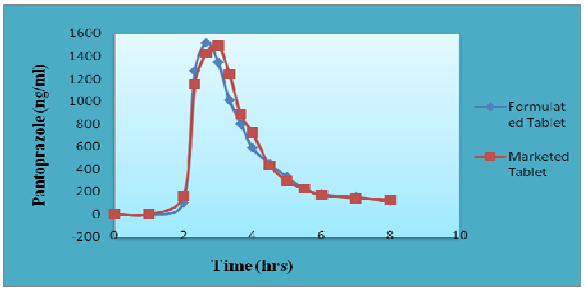

Figure 4. Mean plasma concentrations of pantoprazole at different time intervals after single oral administration of 20-mg tablet of pantoprazole in rabbits.

Table 1. Compositions of Different formulations

Ingredients	P1	P2	P3	P4	P5	P6	P8	P9	P10	P11	P12	P13	P14
Pantoprazole	22.77	22.77	22.77	22.77		22.7	22.77	22.77	22.7	25.4	25.4	25.4	25.4
Pearlitol SD 200	28.74		25.46		48.3	25.1	54.67	51.80		11.31			30.9
Pregelatinized starch	11.62							17.05		32			
Microcrystalline Cellulosel	-	33.89	15.5		15.5	15.5	15.5					32	12
Lactose				34.76					36.3		39.3	10.9	
PVP K30		6.2		6.2					6.2		3.6		
Crospovidone	3.1	3.1						4.54		3.2		3.2	
Croscaremellose Sodium				2.23					2.23		3.2		
Sodium Starch Glycolayte			2.235		2.23	2.23	2.6						3.2
Sodium carbonate	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	7.2	6.45	6.45	6.45	6.45
Colloidal Silicon Dioxide	0.775	0.775	0.775	0.775	0.77	0.78	1.1	1.1	1.1	0.8	0.8	0.8	0.8
Stearic acid	0.775							1.136		0.8			
Calcium Stearate		1.05	1.05	1.05	1.05	1.24	1.76		1.76			1.2	1.2
Magnesium Stearate											1.2		
Talc						3.12	4.4	4.4	4.4				
Total	75	75	75	75	75	78	110	110	110	80	80	80	80

Table 2. Compatibility Study Results for Pantoprazole with Various Excipients

S. No.	Active Pharmaceutical Ingredient + Excipients	Station Time								
		0°C			25°C			40°C		
		1wk	2wk	3wk	1wk	2wk	3wk	1wk	2wk	3wk
1	Pantoprazole + Pearlitol SD 200	NC	NC	NC	NC	NC	NC	NC	NC	NC
2	Pantoprazole + Carbopol 934 P	NC	NC	NC	NC	NC	NC	NC	NC	NC
3	Pantoprazole + Carbopol 974 P	NC	NC	NC	NC	NC	NC	NC	NC	NC
4	Pantoprazole +Crospovidone	NC	NC	NC	NC	NC	NC	NC	NC	NC
5	Pantoprazole + Sodium Carbonate	NC	NC	NC	NC	NC	NC	NC	NC	NC
6	Pantoprazole + Sodium starch glycolate	NC	NC	NC	NC	NC	NC	NC	NC	NC
7	Pantoprazole + Aerosil	NC	NC	NC	NC	NC	NC	NC	NC	NC
8	Pantoprazole + Magnesium stearate	NC	NC	NC	NC	NC	NC	NC	NC	NC
9	Pantoprazole + Stearic acid	NC	NC	NC	NC	NC	NC	NC	NC	NC
10	Pantoprazole + Microcystalline cellulose	NC	NC	NC	NC	NC	NC	NC	NC	NC
11	Pantoprazole + Lactose	NC	NC	NC	NC	NC	NC	NC	NC	NC
12	Pantoprazole + Povidone K 30	NC	NC	NC	NC	NC	NC	NC	NC	NC
13	Pantoprazole + Pearlitol SD 200	NC	NC	NC	NC	NC	NC	NC	NC	NC
14	Pantoprazole + Pregelatinized starch	NC	NC	NC	NC	NC	NC	NC	NC	NC
15	Pantoprazole + Talc	NC	NC	NC	NC	NC	NC	NC	NC	NC

wk = week, NC = No change

Table 3. Particle Size Distribution (PSD)

Batch No.	P1	P2	P3	P4	P5	P6
Sieve	% Retained					
150 #	36.74	31.65	28.97	6.32	17.6	28.48
100 #	19.24	16.82	14.89	3.21	8.84	11.52
85 #	10.36	9.65	6.91	2.24	2.92	3.85
60 #	5.57	4.59	3.08	1.2	0.63	1.22
36 #	4.08	2.53	1.29	0	0	0
25#	1.62	1.16	0	-	-	-
18#	-	-	-	-	-	-

Table 4. Characterization of Physical Properties

Batch No. → Parameters ↓	P1	P2	P3	P4	P5	P6
Angle of repose (°)	35.4	34.7	35.6	32.8	35.7	36.5
Bulk density (g/cm^3)	0.31	0.43	0.43	0.57	0.35	0.45
Tapped density (g/cm^3)	0.54	0.74	0.74	0.65	0.65	0.74
Compressibility Index (%)	42.10	40.90	40.90	40	42.10	39.47
Hausner's ratio	1.72	1.72	1.69	1.66	1.72	1.65

Table 5: Physical characteristics of tablets (Batch No. P9a – P9e)

B. No. P9a		B. No. P9b		B. No. P9c		B. No. P9d		B. No. P9e		Friability
Thickness 4.00 mm		Thickness 4.32 mm		Thickness 4.55 mm		Thickness 4.65 mm		Thickness 4.85 mm		
Thickness (mm)	Hardness (kp)	Thickness (mm)	Hardness (kp)	Thickness (mm)	Hardness (kp)	Thickness (mm)	Hardness (kp)	Thickness (mm)	Hardness (kp)	
4 mm	7.0 kp	4.3 mm	4.1 kp	4.55 mm	3.6 kp	4.65 mm	3.2 kp	4.85 mm	1.3 kp	0.4%
3.98 mm	5.6 kp	4.32 mm	5.3 kp	4.54 mm	3.4 kp	4.64 mm	2.6 kp	4.8 mm	1.5 kp	
3.98 mm	6.2 kp	4.32 mm	6.2 kp	4.55 mm	3.6 kp	4.65 mm	2.2 kp	4.82 mm	1.8 kp	0.3%
4 mm	6.2 kp	4.3 mm	4.2 kp	4.5 mm	3.7 kp	4.65 mm	2.7 kp	4.85 mm	2.1 kp	
3.9 mm	5.8 kp	4.34 mm	4.2 kp	4.52 mm	3.7 kp	4.66 mm	3.1kp	4.84 mm	1.3 kp	0.09%
nil		nil								nil

Table 6. Particle Size Distribution (PSD)

Batch No.	P13	P14	P15	P16
Sieve	% Retained			
150 #	47.66	54.66	31.98	34.62
100 #	29.55	34.94	23.14	29.85
85 #	18.21	21.06	11.52	16.5
60 #	8.85	10.06	7.70	8.45
36 #	nil	nil	Nil	nil

Table 7. Characterization of Physical Properties

Batch No. → Parameters ↓	P13	P14	P15	P16
Angle of repose (°)	21	23.4	21.4	21.65
Bulk density (g/cm^3)	0.54	0.63	0.47	0.57
Tapped density(g/cm^3)	0.625	0.74	0.57	0.65
Compressibility Index (%)	13.51	14.7	18.6	13.5
Hausner's ratio	1.15	1.17	1.22	1.15

Table 8. Hardness of randomly selected 10 tablets

No. of tablets		1	2	3	4	5	6	7	8	9	10	Mean ± sd
P-13	hardnes (kg /cm^2)	5.26	4.31	4.37	3.93	4.88	5.52	5.48	5.0	4.86	4.85	5.82 ± 0.51
P- 14		4.23	4.65	4.61	3.89	4.23	5.44	5.58	4.81	3.54	4.94	4.59 ± 0.64
P- 15		5.28	4.36	3.97	4.84	5.59	3.88	4.55	4.64	4.69	4.38	4.61 ± 0.53
P- 16		4.89	4.99	5.46	4.64	4.88	5.57	5.0	4.83	4.69	5.56	5.05 ± 0.35

Table 9. Thickness of randomly selected 10 tablets

No. of tablets		1	2	3	4	5	6	7	8	9	10	Mean ± sd
P-13	Thickness (mm)	3.23	3.23	3.24	3.28	3.28	3.23	3.24	3.24	3.23	3.24	3.24 ± 0.01
P- 14		3.31	3.28	3.27	3.28	3.32	3.31	3.29	3.32	3.29	3.31	3.29 ± 0.01
P- 15		3.28	3.35	3.29	3.34	3.35	3.28	3.36	3.25	3.28	3.28	3.30 ± 0.03
P- 16		3.28	3.25	3.25	3.23	3.28	3.24	3.32	3.28	3.32	3.24	3.26 ± 0.03

Table 10. Physical Characteristics of Tablets

Formulation	Percent Friability	Disintegration Time (min)	Average Percent Dissolution	Average Percent Assay
Pharmacopeial limits	Not more than 1%	NMT 15 minutes **(pH 6.8)**	Not less than 80%	95-105%
P-13	0.123%	9	99.65%	101.7
P-14	0.122%	8	97.21%	101.68
P-15	0.183%	8.5	95.54%	99.96
P-16	0.36%	7.9	92.38%	102.26

Table 11. Pantoprazole Dissolution Profile from Uncoated Core Tablets (pH 6.8)

Time (min)	P13	P14	P15	P16	Marketed I	Marketed II
	Uncoated tablets				Coated tablets	
	Cumulative % Drug Release					
0	0	0	0	0	0	0
5	50.30%	46.72%	47.28%	32.65%	0.25%	16.4%
10	75.96%	69.59%	77.66%	51.69%	26.135%	55.55%
15	90.39%	87.68%	88.63%	69.21%	48.135%	72.25%
20	96.20%	91.36%	91.45%	82.54%	92.75%	80.64%
25	99.65%	97.21%	95.54%	87.25%	94.95%	95.18%
30	-	-	-	92.38%	95.62%	96.97%

Table 12. Coating Process Parameters for Seal Layer and Enteric Layer

Coating Parameter	Subcoating	Enteric Coating
Solvent	Distilled Water	Distilled water
Solids content (%w/w)	12	20
Theoretical weight gain (%)	4	12
Tablet charge (kg)	1	1
Inlet air temperature (°C)	55-65	50-55
Tablet surface bed temperature (°C)	44	33
Exhaust air temperature (°C)	37-40	32-35
Pan Speed (rpm)	20	20

Table 13. *In-Vitro* Release Kinetics of Pantoprazole Tablets

Batch No.	Peppas Equation			Higuchi		First order		Hixon Crowell		Zero Order	
	K	n	R^2	K	R^2	K	R^2	K	R^2	K	R^2
P13	1.642	0.9222	0.712	27.83	0.9602	-0.059	0.9725	0.0267	0.9885	3.2	0.9119
P14	1.794	0.9318	0.77	27.96	0.9615	-0.04	0.9665	0.0253	0.9795	3.3	0.9251

Table 14. Pharmacokinetic Parameters of Pantoprazole in Rabbit

S. No	Pharmacokinetic Response	Formulated Pantoprazole Tablet	Marketed Pantoprazole Tablet
1	Cmax (ng/ml)	1520	1498
2	Tmax (hr)	2.66	3
3	AUC $_{0\rightarrow\infty}$ (ng. hr/ml)	3317	3174.8