COMPARATIVE IN VITRO EVALUATION OF COMMERCIALLY AVAILABLE PANTOPRAZOLE DELAYED RELEASE TABLETS

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ABSTRACT

Pantoprazole is a substituted benzimidazole derivative that belongs to the category of proton pump inhibitors (PPI’s) and is used as an anti ulcerant. The main aim of the present investigation was to study some physicochemical properties such as weight variation, thickness, diameter, hardness, percent acid uptake, in vitro drug release studies and percent assay of different commercially available formulations of pantoprazole. For study purpose, the various brands were encoded as PNTZ-1, PNTZ-2 and PNTZ-3 respectively. All the products met the requirements as per specifications of Indian pharmacopoeia for tablet formulation. Assay value was also found to be within the limit of 90% to 110% of drug content. The study on dissolution profile revealed that the brand PNTZ-1 had faster dissolution rate while PNTZ-2 had the slowest dissolution rate. The drug release rate followed first order release kinetics. These comparative in vitro evaluation studies of various brands indicate the usefulness, effectiveness and idealness of any commercial product. The data obtained may be useful for further formulation development studies.

KEYWORDS:
Pantoprazole sodium, comparative studies, physicochemical parameters, marketed brands.

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INTRODUCTION:
Ulcers are crater-like sores which form the lining of the stomach (called gastric ulcers), just below the stomach at the beginning of the small intestine in the duodenum (called duodenal ulcers) or less commonly in the esophagus (called esophageal ulcers). In general, ulcers in the stomach and duodenum are referred to as peptic ulcers.\[1\]
Proton pump inhibitors (PPIs) suppress gastric acid secretion by specific inhibition of the H+/K+-ATPase in the gastric parietal cell. This process starts with absorption of the PPI in the parietal cell. PPIs are weak bases, so protonation takes place in the acidic region of the secretory canaliculus of the parietal cell. In the secretory canaliculus, the methylsulfinyl group shifts to a highly reactive sulfenamide. The final step is covalent binding of the reactive sulfenamide to 2 cysteine moieties of the catalytic subunit of the H+/K+-ATPase of the proton pump. This results in inhibition of the acid secretion, followed by elevation of the intragastric pH.\[2\]
Pantoprazole is a proton pump inhibitor, belongs to the group of benzimidazole, used for the treatment of gastric and duodenal ulcers. Pantoprazole undergoes degradation in acid medium of the stomach and therefore is coated with enteric coating polymer that will safely deliver the drug in the small intestine.\[3\]
Quality of pharmaceutical product is the most important factor for efficacy and safety of the product. There are number of commercial brands of pantoprazole sodium tablets available in the Indian market. Even though they contain identical active ingredients, additives (which are not disclosed on the label), the process of manufacturing may however differ. Tablets with same active ingredients may vary in their therapeutic responses due to variations in their observed drug release profiles.\[4,5\]
The present study has been undertaken to evaluate and compare various quality control parameters along with in vitro dissolution profile of three available marketed pantoprazole tablets.

MATERIALS AND METHODS
Materials:
Pantoprazole sodium sesquihydrate standard was obtained as a gift sample from Elder Pharmaceuticals Pvt. Ltd, Mumbai. The commercial brands of pantoprazole 20mg tablets were procured from local retail pharmacy (Mumbai, Maharashtra). All the chemicals and reagents used were of analytical grade and were procured commercially.
 Equipments:
UV Visible spectrophotometer (UV-630 Shimadzu) with 1 cm matched quartz cells. Digital Vernier calliper (Digimatic), Hardness tester (Monsanto type), USP disintegrating apparatus, USP dissolution type-II apparatus, high precision balance and pH meter.

Evaluation of Physicochemical Parameters\(^{[6-10]}\):

1. Uniformity of weight:
The test was carried out by weighing individually twenty tablets and their average weight was calculated. The percent deviation of each tablets weight against the average weight was calculated. The test requirements are met if not more than two tablets deviate from the average weight by 5% and none deviates more than 10%.

2. Thickness and Diameter:
The thickness and diameter of the tablets was determined by using Digital Vernier calipers. Twenty tablets were used, and average values were calculated.

3. Hardness:
The hardness of five tablets was determined using the Monsanto type hardness tester and the average values were calculated and expressed in kg/cm².

4. Loss on drying:
Loss on drying is the loss of weight expressed as percentage w/w resulting from water and volatile matter of any kind that can be driven off under specified conditions. The test is carried out on a well-mixed sample of the substance. If the substance is in the form of large crystals, reduce the size by rapid crushing to a powder.

\[
\%\text{LOD} = \frac{W}{W_t} \times 100
\]

Where, \( W = \) Weight of solvent in sample, \( W_t = \) Total weight of wet sample.

5. Disintegration time:
Disintegration testing of the enteric coated tablets was carried out using USP disintegration apparatus. One tablet was introduced into each tube of the basket rack assembly without disc. The assembly was positioned in the beaker containing 0.1N HCl (pH 1.2) maintained at 37°C ± 2°C and operated for 2 hours. After 2 hours the 0.1N HCl was replaced with phosphate buffer pH 6.8. A disc was added to each tube and operated further for 60 minutes. The disintegration time of each tablet was then recorded.

6. In vitro drug release studies:
USP dissolution apparatus type II was employed to study the in vitro drug release from various formulations prepared. The dissolution medium used
was 1000 ml of acidic buffer of pH 1.2 for 2h at 100 rpm maintained at 37°C followed by 1000 ml of tris-acetate buffer pH 8.5 for 60 min at 75 rpm. The samples were measured at 283 nm and 293 nm respectively using a UV-visible spectrophotometer. The release studies were conducted in triplicate and the mean values were plotted versus time.

7. Assay:

The amount of Pantoprazole sodium present in the tablets was determined. As per the label claim, 10 tablets were crushed and a quantity equivalent to the average weight of the tablets was weighed accurately and transferred to a 100 ml volumetric flask. Around 60 ml of methanol was added to this triturate and the volumetric flask was subjected to sonication for 15 minutes. After sonication, the volume was then made up to the 100 ml mark with methanol. This solution was then filtered using a whatman filter paper 40 and a clear solution was obtained. 1ml of the stock solution was diluted to 10 ml with methanol. Further 5ml of this solution was diluted to 10ml and the absorbance was measured at 289 nm using UV spectrophotometer. The amount of drug present in the tablet was then calculated using the following formula:

\[
\% \text{ Assay} = \frac{\text{Abs spl} \times \frac{\text{Std Wt}}{100} \times \frac{1}{10} \times \frac{5}{10} \times \frac{100}{\text{Spl Wt}} \times \frac{10}{5} \times \frac{10}{100} \times \frac{\text{Potency}}{\text{LC}} \times \frac{\text{Avg Wt}}{\text{Mol Wt P}} \times \frac{\text{Mol Wt PS}}{100}}{\text{Abs std}}
\]

Where; Potency = 99.34, LC = Label Claim
Abs spl = Absorbance of sample, Abs std = Absorbance of standard,
Mol. Wt P = Molecular weight of pantoprazole,
Mol. Wt PS = Molecular weight of pantoprazole sodium sesquihydrate.

8. Percent Acid Uptake\[11\]:

Six tablets were accurately weighed (W_o) and exposed to acidic media (0.1 N HCl) for 2 hours at 37°C in Disintegration test apparatus. Excess of moisture was removed and tablets were reweighed (W_t). From the difference in weights before and after exposure to acidic media, the percent of acid uptake can be calculated.

\[
\% \text{ Acid uptake} = \frac{W_t - W_o}{W_o} \times 100
\]

Drug release kinetics:

To analyse the mechanism of drug release from the selected commercially available brands, the data obtained from in vitro release studies were subjected to zero order model, first
order model, higuchi’s model, korsmeyer’s model and hixon-crowell model. Table 5 shows drug release kinetics of different commercially available brands of pantoprazole tablets.[12]

RESULTS AND DISCUSSION

As per Indian Pharmacopoeia (I.P.), the tablets weighing more than 80 mg but less than 250 mg can have the deviation of maximum 7.5%. All the brands of pantoprazole sodium delayed release tablets were within the range, with the brand PNTZ-1 having the least variation of 1.45 %. Using Monsanto hardness tester, the hardness of the tablets were tested. All the tablets showed good strength, which is necessary for safe transportation. The brand PNTZ-2 had minimum hardness while the brand PNTZ-1 had maximum hardness. All the brands of tablets disintegrated before 15 minutes conforming to the I.P. specifications. The brand PNTZ-1 had the least disintegration time of 6 minutes 46 seconds in the phosphate buffer pH 6.8. Assay value of all the brands were within the range of 90% to 110% of the stated amount of pantoprazole. Dissolution test was carried out using USP type-II dissolution apparatus. Tablets of all the brands remained intact in the acid stage while drug release from the tablets started when the same were exposed to tris-acetate buffer pH 8.5 (buffer stage). The variation in the dissolution profile of the selected marketed brands was observed in the order: PNTZ-1 > PNTZ-3 > PNTZ-2. The data from the in vitro drug release studies were fitted to the various drug release rate kinetic models and it was found that drug release rate from all the brands was that of first order.

CONCLUSION

All the products gave satisfactory results, with respect to uniformity of weight, hardness test, disintegration time and assay. The comparison of dissolution profiles demonstrated that the brand encoded as PNTZ-1 had the best drug release profile as compared to other brands. The drug release rate from all the brands followed first order kinetics. The same brand had better acid resistant property, an important property for enteric coated tablets like pantoprazole. All other physicochemical properties were quite comparable to each other for all the brands.

ACKNOWLEDGEMENT

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REFERENCES

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5. Bushra M. U. Et al; Comparative in vitro evaluation of commercially available rabeprazole tablets; Der Pharmacia Sinica; 2013; 4(6); 28-31.
8. Indian pharmacopoeia; The Indian pharmacopoeia commission, Ghaziabad; 2010, Volume-I; Pg. 178.
TABLES AND FIGURES

TABLES:

Table 1: Limits of weight variation as per I.P.

<table>
<thead>
<tr>
<th>Sr. No.</th>
<th>Average weight of Tablets (mg)</th>
<th>Maximum % difference allowed</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>80 or less</td>
<td>10</td>
</tr>
<tr>
<td>2.</td>
<td>More than 80 but less than 250</td>
<td>7.5</td>
</tr>
<tr>
<td>3.</td>
<td>More than 250</td>
<td>5</td>
</tr>
</tbody>
</table>

Table 2: Physicochemical evaluation of different brands of Pantoprazole tablets

<table>
<thead>
<tr>
<th>Sr. No</th>
<th>Parameters</th>
<th>PNTZ-1 Results</th>
<th>PNTZ-2 Results</th>
<th>PNTZ-3 Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Appearance</td>
<td>Brown, Circular, biconvex enteric coated tablets</td>
<td>Light yellow, Circular, biconvex enteric coated tablets</td>
<td>Yellow, Circular, biconvex enteric coated tablets</td>
</tr>
<tr>
<td>2.</td>
<td>Average weight (mg)</td>
<td>201.17</td>
<td>108.72</td>
<td>119.13</td>
</tr>
<tr>
<td>3.</td>
<td>Weight variation (%)</td>
<td>1.45</td>
<td>2.17</td>
<td>1.47</td>
</tr>
<tr>
<td>4.</td>
<td>Thickness (mm)</td>
<td>3.78-3.88</td>
<td>2.96-3.10</td>
<td>3.16-3.21</td>
</tr>
<tr>
<td>5.</td>
<td>Diameter (mm)</td>
<td>8.38-8.49</td>
<td>6.14-6.24</td>
<td>6.66-6.77</td>
</tr>
<tr>
<td>6.</td>
<td>Hardness (kg/cm²)</td>
<td>7.1 ±0.418</td>
<td>6.0 ±0.5</td>
<td>6.6 ±0.821</td>
</tr>
<tr>
<td>7.</td>
<td>Disintegrating time</td>
<td>2h 6min 46sec</td>
<td>2h 7min 50sec</td>
<td>2h 7min 04sec</td>
</tr>
<tr>
<td>8.</td>
<td>Percent Acid uptake</td>
<td>4.15</td>
<td>5.09</td>
<td>5.91</td>
</tr>
<tr>
<td>9.</td>
<td>Drug content (mg)</td>
<td>19.82</td>
<td>19.05</td>
<td>19.56</td>
</tr>
<tr>
<td>10.</td>
<td>Assay (%)</td>
<td>99.12</td>
<td>95.28</td>
<td>97.82</td>
</tr>
</tbody>
</table>

Table 3: Comparative percent drug release in Acid stage (0.1N HCl)

<table>
<thead>
<tr>
<th>Dissolution medium</th>
<th>PNTZ-1</th>
<th>PNTZ-2</th>
<th>PNTZ-3</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1 N HCl pH 1.2</td>
<td>2.81 ±0.2631</td>
<td>4.56 ±0.2946</td>
<td>3.07 ±0.1374</td>
</tr>
</tbody>
</table>

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Table 4: Comparative percent drug release in Buffer stage (tris-acetate buffer pH 8.5)

<table>
<thead>
<tr>
<th>Dissolution medium</th>
<th>Time points (mins)</th>
<th>PNTZ-1 (% drug release)</th>
<th>PNTZ-2 (% drug release)</th>
<th>PNTZ-3 (% drug release)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tris acetate buffer pH 8.5</td>
<td>5</td>
<td>20.34 ±0.0230</td>
<td>21.37 ±1.206</td>
<td>19.35 ±0.005</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>43.0 ±0.566</td>
<td>41.58 ±1.333</td>
<td>39.56 ±1.314</td>
</tr>
<tr>
<td></td>
<td>15</td>
<td>68.23 ±0.011</td>
<td>71.62 ±0.833</td>
<td>65.83 ±0.587</td>
</tr>
<tr>
<td></td>
<td>30</td>
<td>79.41 ±0.681</td>
<td>76.62 ±0.692</td>
<td>79.02 ±0.663</td>
</tr>
<tr>
<td></td>
<td>45</td>
<td>85.68 ±0.832</td>
<td>81.25 ±0.257</td>
<td>82.70 ±0.445</td>
</tr>
<tr>
<td></td>
<td>60</td>
<td>89.77 ±0.304</td>
<td>85.71 ±1.933</td>
<td>88.09 ±0.332</td>
</tr>
</tbody>
</table>

Table 5: Data of drug release rate kinetics of different marketed brands

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Zero order Regression Coefficient ($R^2$)</th>
<th>First order Regression Coefficient ($R^2$)</th>
<th>Higuchi equation Regression Coefficient ($R^2$)</th>
<th>Korsmeyer plots Regression Coefficient ($R^2$)</th>
<th>Hixon-crowell Regression Coefficient ($R^2$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PNTZ-1</td>
<td>0.746</td>
<td>0.924</td>
<td>0.853</td>
<td>0.861</td>
<td>0.853</td>
</tr>
<tr>
<td>PNTZ-2</td>
<td>0.682</td>
<td>0.834</td>
<td>0.793</td>
<td>0.832</td>
<td>0.783</td>
</tr>
<tr>
<td>PNTZ-3</td>
<td>0.749</td>
<td>0.908</td>
<td>0.855</td>
<td>0.868</td>
<td>0.859</td>
</tr>
</tbody>
</table>
FIGURES:

Figure 1: Percent acid uptake by enteric coated tablets of different brands

Figure 2: Comparative Dissolution Profile of different marketed brands