A J P R D

Asian Journal of Pharmaceutical Research and Development
Open Access to Pharmaceutical and Medical Research



Original Article

# *In Vitro* Comparative Study of Different Brands of Pantoprazole Sodium Enteric Coated Tablets Marketed In Addis Ababa, Ethiopia

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## ABSTRACT

Pantoprazole is a substituted benzimidazole proton pump inhibitor used for the treatment of acid-related diseases. This study aimed with comparative *in vitro* evaluation of different brands of pantoprazole sodium tablets available in different retail outlets in Addis Ababa, Ethiopia. All brands were evaluated using established procedures to assess the pharmaceutical quality characteristics. The measured thickness of studied brand tablets ranged from 2.79 to 3.49 mm. Brand E (175.4 ± 3.73 N) exhibited maximum hardness while brand C (110.2 ± 6.43 N) had the lowest hardness. When the mean weights of the sample brands are compared, brand C had maximum weight (151.22 mg) and brand D weighed the least (79.18 mg).The disintegration time test indicated that any of the pantoprazole sodium tablet brands did not disintegrate in 0.1N HCl acidic medium for 2 hrs but all disintegrated in the time range of 12.43 min to 24.42 min in phosphate buffer. The *in vitro* drug release study depicted that all brands of pantoprazole sodium tablets released not more than 10% of the labeled amount within 2 hrs under 0.1N HCl medium but showed similar drug release in the buffer medium ranging between 89 and 92% within 45 minutes. Therefore, this study results revealed that all of the tested brands of the pantoprazole sodium enteric coated tablet fulfilled the criteria set in the official monograph for *in vitro* quality control tests.

**Key words**: Brands, Disintegration time, *In vitro* release, Pantoprazole sodium

ARTICLE INFO: **Received:** 26 Dec. 2018; **Review Completed**: 31 Jan.2019; **Accepted:** 09 Feb .2019; **Available online**: 15 Feb. 2019

**Cite this article as:**
Foziya Mohammed , Muluken Nigatu *, Abrham Temesgen, *In Vitro* Comparative Study of Different Brands of Pantoprazole Sodium Enteric Coated Tablets Marketed In Addis Ababa, Ethiopia, Asian Journal of Pharmaceutical Research and Development**. 2019; 7(1):13-18**
**DOI: http://dx.doi.org/10.22270/ajprd.v7i1.467**
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## INTRODUCTION

Proton pump inhibitors (PPIs) are drugs of choice for treatment of acid-related diseases (peptic ulcer disease, gastroesophageal reflux disease (GERD), and Zollinger-Ellison syndrome, Helicobacter pylori (*H. pylori*) infections are among other indications). PPIs suppress gastric acid secretion by blocking the gastric acid pump, H(+)/K(+)-adenosine triphosphatase (ATPase) [1–4]. Enteric coated tablets are prepared to protect the drug from acidic environment of stomach and prevents the release of the contents before reaching the small intestine [5].

Pantoprazole is a substituted benzimidazole PPI which is marketed as enteric coated tablets and injectable formulation (Fig. 1). It is easily degraded in the acidic environment of the stomach and therefore must be delivered to the small intestine as intact. Pantoprazole is well absorbed and has an absolute bioavailability of approximately 77% [4 – 9].

Generic drugs share large portion of the marketed medicines in treating diseases. Generic drugs have entered the market soon after the patent granted to the manufacturer of an "originator" drug has expired [10,11.] Generic drugs are a major asset to national projects as they are the economic alternative of the costlier brand name drugs and create true market competition. Consequently, the use of generic drugs has rapidly increased and now dominates the medication landscape for patient use [11 – 13].

Patients and health professionals assume that generic drugs compete with brand drugs, and are manufactured and marketed by companies that compete with brand drugs[14]. The quality control and assurance of pharmaceuticals depend on monitoring some parameters

like the composition and uniformity of the drug during processing as well as in the final product [15]. Some bioavailability studies indicated that similar therapeutic responses were not exhibited from tablets with same drug and drug content. The variation of performance properties of tablets and therapeutic effects are due to some factors like excipients used in the manufacturing of tablets, physical characteristics of the drug and the manufacturing process [5].

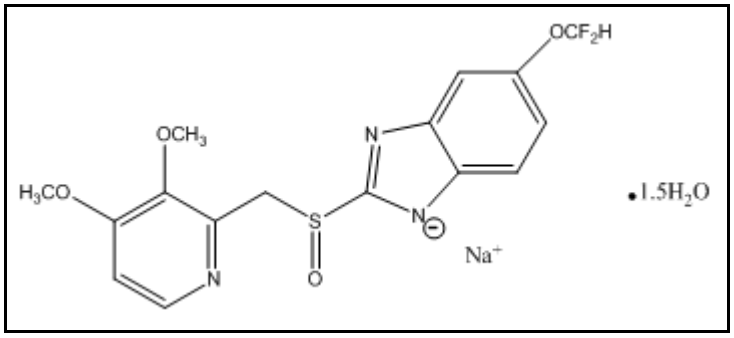


**Figure 1:** Chemical structure of pantoprazole sodium sesquihydrate.

Drug quality is becoming a concern in developing countries. Because of the poor monitoring activities of drug regulatory bodies in these countries, there is high chance of circulation of lower quality drugs in the market which may affect the health and trust of the public [16].

The objective of present study was to undertake comparative *in vitro* evaluation of different brands of pantoprazole sodium tablets available in different retail outlets in Addis Ababa, Ethiopia. All brands were evaluated using established procedures to assess the pharmaceutical quality characteristics.

## MATERIALS AND METHODS

### Materials

Five brands of locally available pantoprazole sodium 20mg enteric-coated tablets (Table 1) were purchased from different retail outlets in Addis Ababa. Pantoprazole sodium reference standard was kindly gifted by Ethiopian Food, Medicine and Healthcare Administration and Control Authority (EFMHACA). Potassium phosphate monobasic (FARMITALIA CAROERBA, Italy), Hydrochloric acid (BDH limited, Poole, England), Sodium hydroxide (BDH limited, Poole, England) and distilled water were used for the study. All chemicals used were analytical grade and used as received.

**Table 1:** Detailed description of pantoprazole sodium 20mg enteric coated tablet products included in the study

| Brand Code | Country of Origin | Batch number | Expiry date |
|---|---|---|---|
| **A** | Germany | 3342 | 02/20 |
| **B** | Turkey | A054467 | 09/19 |
| **C** | India | EPJDE17002 | 05/19 |
| **D** | Saudi Arabia | 7SDO35 | 04/20 |
| **E** | Slovenia | FR5644 | 08/19 |

### Methods

#### *Thickness measurement*

Ten tablets from each brand were taken and sliding caliper scale (Nippon Sokutei, Japan) was used for thickness measurement. Results were expressed as a mean and standard deviation.

#### *Crushing strength*

The hardness tester (Schleuniger, 2E/205, Switzerland) was used for determination of tablets' crushing strengths. After random selection of ten tablets from the sample of each brand, the force was exerted by placing each tablet between two anvils. The force needed to break the tablet was recorded as a crushing strength of that tablet. Results were expressed as a mean and standard deviation.

#### *Weight uniformity of dosage units*

The weight variation test was done by taking twenty tablets from each of the five brands and weighed individually with an analytical balance. The average weights for each brand as well as the standard deviation from the mean value were calculated. Percentage deviation of each individual tablet from the mean was evaluated according to USP/NF (2013).

#### *Disintegration Time*

The test for disintegration time was done as per USP/NF (2013) specification. First, disintegration tester (CALEVA, G.B. Caleva Ltd., UK) was filled with 0.1N HCl and maintained at 37±2°C. Then, it was run for 2 hrs after placing the randomly selected six tablets from

each pantoprazole sodium brand in the disintegration tester. Tablets were examined for a sign of disintegration within 2 hrs running period. By changing the acidic fluid with phosphate buffer of pH 6.8 immediately after 2 hrs, the apparatus was operated for additional 1 hr at 37±2°C and the disintegration time was noted. The tablets were considered completely disintegrated when all the particles are passed through the wire mesh.

***Construction of calibration curve***

Various concentrations of pantoprazole sodium reference standard (10, 14, 18, 22, 26, and 30 µg/ml) in acidic medium of 0.1N HCl and (11, 12, 13, 14, 15, 16, 17 and 18µg/ml) in phosphate buffer of pH 6.8 were prepared. Their absorbances were measured at $\lambda_{max}$ of 305 nm and 288 nm in 0.1N HCl and phosphate buffer, respectively using a UV-Visible spectrophotometer (UV/VIS SPECTROMETER, T92+, UK). The values of absorbance were plotted against the corresponding concentrations.

***In vitro drug release studies***

USP type II dissolution apparatus (ERWEKA, DT600, Germany) operating at 100 rpm was used to study *in vitro* drug release. First, the dissolution was carried out in 0.1N HCl acidic medium for 2 hrs and then changed to phosphate buffer of pH 6.8 (900 ml) for the next 1 hr by maintaining the temperature at 37±0.5 °C. 10 ml samples were withdrawn at prescheduled intervals (0.5, 1, 1.5, 2, 2.25, 2.5, 2.75 and 3 hrs) and replaced with an equal volume of fresh dissolution medium which was kept at a temperature of 37±0.5 °C. Each sample was diluted suitably and analyzed for the drug content at $\lambda_{max}$ of 305 nm for acidic medium and at $\lambda_{max}$ of 288 nm for phosphate buffer using a UV/Visible Spectrophotometer (UV/VIS SPECTROMETER, T92+, UK).

***Statistical analysis***

Origin 7 Software (OriginLab Corporation, MA, and USA) was used to statistically analyze the results. All the data measured and reported are averages of a minimum of triplicate measurements and the values are expressed as mean ± standard deviation.

## RESULTS

All studied brands of pantoprazole sodium 20mg enteric-coated tablets were imported from different countries and they were within the stated use period during the study time (Table.1) Some physical characteristics of the studied pantoprazole sodium tablets are depicted in Table 2. The brand tablets thickness was ranged between 2.79 and 3.49 mm in which brand C is the thickest and brand B is the thinnest of the studied samples.

**Table 2:** Some physical characteristics of the pantoprazole sodium 20 mg enteric-coated tablet samples studied.

| Brand | Thickness (mm) ± SD | Crushing strength (N) ± SD | Average weight (mg) ± SD | Disintegration time in phosphate buffer (min) |
|---|---|---|---|---|
| **A** | 3.13 ± 0.04 | 119.4 ± 5.15 | 92.51 ± 1.07 | 14.15 |
| **B** | 2.79 ± 0.03 | 115.6 ± 6.70 | 97.18 ±1.43 | 20.32 |
| **C** | 3.49 ± 0.02 | 110.2 ± 6.43 | 151.22 ± 1.63 | 17.50 |
| **D** | 2.85 ± 0.03 | 127.5 ± 7.21 | 79.18 ± 0.60 | 12.43 |
| **E** | 3.45 ± 0.04 | 175.4 ± 3.73 | 110.27 ± 1.83 | 24.42 |

From the result of crushing strength, brand E (175.4 ± 3.73 N) exhibited maximum hardness while brand C (110.2 ± 6.43 N) had the lowest hardness.

The mean weights of the sample brand products were ranged between 79.18 mg and 151.22 mg. Brand C had maximum weight (151.22 mg) and brand D weighed the least (79.18 mg). This could be due to the different excipients and formulation techniques adopted by different manufacturers.

As indicated in Table 2, the disintegration time of these five brand products ranged between 12.43 min to 24.42 min in phosphate buffer which is less than 30 min.

The calibration curve was constructed using absorbance readings plotted against concentration (Fig. 2 and 3). The linear regression equations obtained were Y = 0.02617X - 0.06643 ($R^2$ = 0.9997) and Y = 0.04307X - 0.01985 ($R^2$ = 0.9997) in acidic medium of 0.1 N HCl and phosphate buffer of pH 6.8, respectively where Y is absorbance and X is concentration in µg/ml.

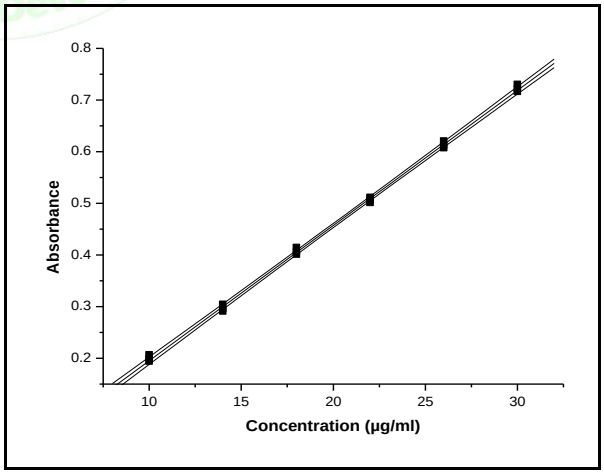


**Figure 2:** Pantoprazole sodium calibration curve at λ max of 305 nm in acidic medium of 0.1N HCl with upper and lower 95% confidence limits.

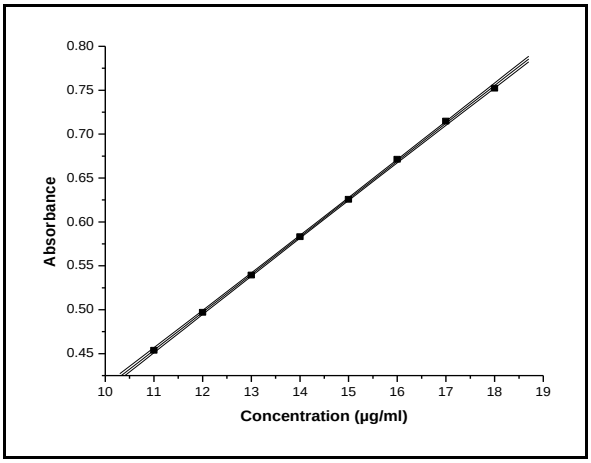


**Figure 3:** Pantoprazole sodium calibration curve at λ max of 288 nm in phosphate buffer of pH 6.8 with upper and lower 95% confidence limits.

In the present study, dissolution test was carried out according to USP by placing the samples in acidic medium of 0.1 N HCl for 2 hrs and then switching the medium to buffer one of pH 6.8 and running for additional 1 hr. The medium and conditions were also maintained according to the pharmacopeia.

Brand B showed higher drug release (8.23%) and brand D revealed lower release (6.61%) within 2 hrs in acidic medium. The dissolution profile in phosphate buffer medium revealed that brand D showed maximum cumulative drug release (92%) while brand E had the minimum cumulative drug release (89%) within 45 min as predicted from the disintegration test result (Fig. 4).

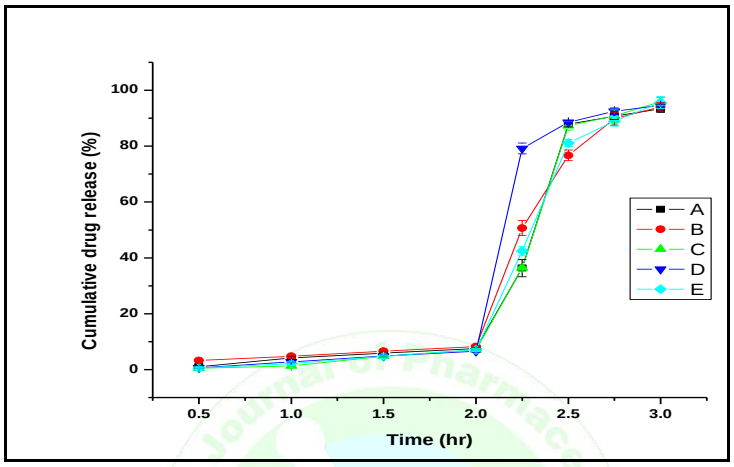


**Figure 4:** *In vitro* release profiles of pantoprazole sodium 20 mg enteric-coated tablets.

## DISCUSSION

The uniformity in thickness of tablets is necessary for consumer requirement and for packaging of the products. According to USP standards, tablets thickness should be controlled within a ±5 % variation. The study indicated that the physical thickness variations were found to be satisfactory as they were within the limit (0.02 to 0.04%).

Hardness test is essential for a tablet because the structural integrity of the tablet should be maintained throughout the whole process starting from manufacturing till the use of medication by the patient. Hardness for the tablet should overcome factors like storage conditions after manufacturing, packaging and shipping. Tablet hardness may affect tablet friability, disintegration time and drug dissolution [17–21].

Tablet hardness of 4 kg is considered to be the minimum for a satisfactory tablet [22]. All the tested brand tablet products showed optimum hardness of above 100N, which is necessary for proper packaging, handling and transportation. It is an important factor for the tablet to resist attrition in the container, owning to partial powdering, chipping, or fragmentation of the tablets during handling and transporting.

Weight variation is an indicative of the proper manufacturing practices followed by the drug manufacturers. Tablets with poor weight variation may be resulted from factors like improper tooling sets and poor granulation flow properties. The weight variation test may also be an indicative of the drug content uniformity of tablets [19,21].

For the limit of weight variation test, the USP states that the individual weights from each sample deviated from the mean weight should be within 10% for tablets with average weight of 130 mg or less and 7.5% when the average weights of tablets are between 130 and 324 mg and 5% when the average weights of tablets are 324 mg and above. Hence, it is revealed from the test that the tablets' weight uniformity is met by all brands of pantoprazole sodium tablet products (brand C lies within 7.5% and the rest sample brand products lie within 10% deviation (Table 2).

Disintegration refers the breaking of a tablet into smaller particles and it is an important process for dissolution. The disintegration test is used to determine the time elapsed for tablets to disintegrate into smaller particles that will pass through a 10 mesh screen. The disintegration time affect drug absorption rate as well as its therapeutic efficacy [19]. The type and amount of excipients used in tablet formulation and the manufacturing process are the possible reasons that affect the disintegration time of tablets.

The present study indicated that all of the pantoprazole sodium tablet brands did not show any signs of disintegration when immersed in acidic medium of 0.1N HCl for 2 hrs. Then after the samples were transferred to phosphate buffers (pH 6.8) which simulate the intestinal

fluid and all brands disintegrated at different times. USP specified the limit for the disintegration time of enteric-coated tablet in phosphate buffer to be 1 hr. All the brands passed the disintegration test as all were completely disintegrated in the buffer medium in less than 30 min. Brand D disintegrated faster (12.43 min) whereas brand E showed relatively delayed disintegration time (24.42 min) compared with other brand products.

The performance of a drug product depends on the release of the active pharmaceutical ingredient from the dosage form. As a result, *in vitro* dissolution/drug release testing has become an increasingly powerful tool in the manufacturing of generic products. It is a common parameter to be evaluated during formulation development as there is relation with the *in vivo* performance of certain products [23 - 25].

The dissolution profile of tablets are determined by sampling the medium containing the dissolved drug at appropriate time points. For delayed-release tablets like pantoprazole sodium, dissolution profile should exhibit that the product is stable in acidic environment and readily release its content in the favorable pH of small intestine.

The *in vitro* dissolution study result depicted that all brands of pantoprazole sodium tablets released not more than 10% of the labeled amount the drug in 2 hrs which is in agreement with the USP specification for enteric-coated tablets (Fig. 4). The USP dissolution test requirement stated that not less than 75 % of the labeled amount of pantoprazole sodium should be dissolved in 45 minutes in the buffer medium. From the dissolution profile, it is clearly seen that all brands met the specified limit that more than 85% drug released in 45 minutes. In the present study, it was found that all brand products were in compliance with the standard limits for dissolution test.

## CONCLUSION

The results showed that all tested brand products were of good pharmaceutical quality. Hardness tests showed that all brands of pantoprazole sodium tablets possess sufficient strength to withstand stress during packaging, transportation and handling of these products.

All brands passed the weight uniformity and disintegration test as they met the official criteria. The i*n vitro* release profile of all brands was found to be in compliance with acceptance limit of USP dissolution test in which none of the brands exhibited more than 10% drug release in acid stage (pH 1.2) in 2 hrs and more than 75% of drug released in 45 minutes under buffer medium (pH 6.8).

Therefore, the present study results revealed that all of the tested brands of the pantoprazole sodium enteric coated tablets fulfilled the criteria set in the official monograph for *in vitro* quality control tests.

## ACKNOWLEDGMENTS

The authors are grateful to Addis Ababa University and CDT-Africa for providing the opportunity to conduct the study and EFMHACA for kindly donating pantoprazole sodium reference standard.

## CONFLICTS OF INTEREST

All authors have declared that no conflicts of interest exist.

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