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**Original Research Article**

# Formulation and Characterization of Sustained Release Matrix Tablet of Pantoprazole

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**Abstract:** Pantoprazole is a proton pump inhibitor prodrug used in the treatment of gastric, duodenal ulcers and gastro esophageal reflux disease (GERD), Zollinger- Ellison syndrome. This is the most popular drug used in cure and maintenance therapy of peptic ulcer along with antibiotics. It suppresses the acid production by inhibiting the $H^+$ $K^+$ ATPase. Pantoprazole must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric delivery systems are required. The purpose of this study was to prepare matrix tablet using eudragit Rs 100, eudragit S100, and HPMC. On the basis of above result the formulation showed satisfactory result as it has the maximum release i.e. F5 66.50%in 10 hrs. Result of our study suggest that the matrix tablet containing pantoprazole may be suitable for the anti ulcer drug.

**Keywords:** Pantoprazole, matrix tablet, eudragit Rs 100, eudragit S100, and HPMC.



## INTRODUCTION

Gastric acid is a digestive fluid, formed in the stomach and composed of hydrochloric acid. The acid plays a key role in digestion of proteins. Gastric acid is produced by parietal cells (Oxyntic cells). These cells are part of epithelial fundic glands in the gastric mucosa. The pH of gastric acid is 1.5 to 3.5 in the human stomach lumen, the acidity being maintained by the proton pump H+/K+ ATPase. The parietal cell releases bicarbonateinto the blood stream in the process, which causes a temporary rise of pH in the blood, known as alkaline tide. When there is an increase in gastric acid secretion it leads to disease state as Gastro esophageal reflux disease. There are various treatments available now to protect from the disease as proton pump inhibitors (40% effective), Antacids (10% effective) and Sucralfate which have similar effect as PPI's but it should be taken multiple times a day. This limits the use of sucralfate [1]. A substituted benzimidazole derivative called pantoprazole is a PPI that reduces the amount of acid that the stomach parietal cells secrete. More than 80 nations throughout the world currently have access to IV pantoprazole, which is intended for the treatment of Zollinger-Ellison syndrome, gastric and duodenal ulcers, and gastroesophageal reflux disease (GERD). In numerous nations, IV pantoprazole is now recommended for the prophylaxis of acute bleeding stress ulcers as well as the treatment of bleeding peptic ulcers and the prevention of rebleeding. In this study, the evidence for the use of IV pantoprazole in the treatment of PUB, prophylaxis against acute bleeding stress ulcers, and prevention of rebleeding is rigorously analyzed [2].

**DRUG PROFILE- PANTOPRAZOLE [3]**

| | |
|---|---|
| **IUPAC** | -5(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-3H-benzoimidazole. |
| **MOLECULAR FORMULA** | $C_{16}H_{14}F_2N_3NaO_4S$. |
| **MOLECULAR WEIGHT** | 383.371 |
| **BIOAVAILABILITY** | 77% |
| **METABOLISM** | Hepatic (CYP2C19, CYP3A4) |
| **ELIMINATION HALF LIFE** | 1hours |
| **$T_{max}$** | 2.5 hours |

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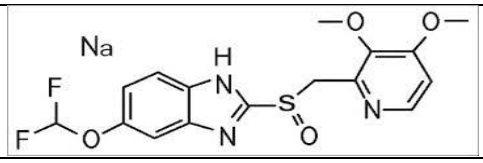
| | |
|---|---|
| **EXCRETION RENAL** | 71% as metabolites |
| **PROPRIETARY NAME** | PROTONIX |
| **ROUTE OF ADMINISTRATION** | Oral, IV |
| **CHEMICAL STRUCTURE** |  |

Pantoprazole sodium sesquihydrate is a white to off- white crystalline powder and is racemic. Pantoprazole has weakly basic and acidic properties. Pantoprazole sodium is freely soluble in phosphate buffer at pH 6.8 and partially soluble in water and practically soluble in n-hexane. The stability of the compound in aqueous solution is pH dependent. The rate of degradation increases with decreasing pH. At ambient temperature, the degradation half-life is approximately 2.8 hours at pH 5.0 and approximately 220 hours at pH 7.8 [4].

## MATERIAL AND METHODS

**Drug:** Jubilant Life Sciences, Noida, Uttar Pradesh. (India).

**Polymer:** Hydroxypropylmethylcellulose (HPMC) provided by R.V. Northland Institute Chithera, dadri (G.B. Nagar).

**Polymer:** Eudragit RS 100 and Eudragit S 100 purchased from Dequssa Ltd, Mumbai, India

**Solvent:** Distilled water and buffer solution.

**Other reagents:** Di sodium hydrogen phosphate and Potassium di hydrogen phosphate are of Laboratory grade.

**Preparation of sustained release matrix tablet of pantoprazole**

Pantoprazole tablets were prepared by the direct compression method. Specified quantity of pantoprazole, hydroxyl propylmethylcellulose (HPMC), Eudragit S100, Eudragit RS 100, microcrystalline cellulose were weighed according to the formula given in table 2.2 and transferred into a mortar with pestle and mixed thoroughly. The prepared granules powder was dried at $40^0$C for 4 hrs. After that required quantities of magnesium stearate and talc were finally added and mixed thoroughly. The mixture was directly punched into tablets weighing about 200 mg (containing 40 mg of pantoprazole), using a rotary tablet machine with 8 mm diameter concave punches. The different batches of pantoprazole tablets were collected and stored in airtight containers [5].

**Physical characterization of Tablets**

Pantoprazole was physically characterized on the basis of appearance, taste, shape, size, and diameter. All these physical parameters were recorded.

**Determination of weight variation and average weight of the tablets**

A sample of 20 tablets is taken from any batch. Each tablet is weighed singly and the average for 20 tablets found from the data. No tablet should deviate from the average by more than 15% of the average and the relative standard deviation should be less than or equal to 6 And average mass carried out using a digital weighing machine (0.189 to 0.208) and expressed in gm. And result shown in Table 2.

**Determination of hardness and friability of tablets**

The tablets were subjected to a hardness test. It was carried out by using a hardness tester (3.85 to 8.69) and expressed in kg $cm^{-2}$. Friability test is performed by using Roche friabilator. The weight of 39 tablets ($W_1$) are noted initially and placed in the friabalator for four minute which is operated at 25 rpm. The tablets are reweighted and note as ($W_2$). And the result was shown in Table 3. The difference in the weight is noted and expressed as:

$$\% \text{ Friability} = \frac{\text{initial weight} - \text{final weight}}{Initial\ weight} \times 100$$

**Drug content uniformity**

The drug was extracted completely from the tablets in pH 6.8 phosphate buffer and the solution was filtered. Filtrate (1ml) was diluted with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured with a UV- visible spectrophotometer UV-1700 (Shimadzu, Japan) at 289 nm.

***In-vitro* drug release**

A USP dissolution apparatus type SVAM pda 65was employed to study the *in-vitro* drug release from various batches. The dissolution medium used was 900 ml of phosphate buffer of pH 6.8 for 10 hours. The temperature was maintained at $37^0$C and the stirring rate was 100 rpm. Samples (5ml) were withdrawn at regular time intervals and the same volume was replaced with fresh dissolution medium. The samples were measured for drug content at 289 nm (pH 6.8) against blank. The result was shown in Table 4.

**Release Kinetics Evaluation**

Release data were fitted to different mathematical methods to reveal the release mechanism from micro beads. Zero order, first order and Higuchi release models were used for this purpose. The zero order plots was constructed by plotting log (cumulative percentage release) versus time and Higuchi plot was constructed by plotting cumulative percentage release versus square root of time. The release kinetics evaluation results are shown in Table 4.

**Drug Content Uniformity**

The drug was extracted completely from the tablets in pH 6.8 phosphate buffer and the solution was filtered. Filtrate (1ml) was diluted with pH 6.8 phosphate buffer. Absorbance of the resulting solution was measured with a UV- Visible spectrophotometer UV-1700 (Shimadzu, Japan) at 289nm.

**Stability Studies**

The tablets were subjected for short term stability studies the one tablet from each formulation (F1, F4, F8, and F13) were placed at different vials and kept at $45^0$C and 75% relative humidity conditions for 90 days as shown. The sample from different vials was periodically evaluated for physical and chemical stability at the interval of 15 days. The stability studies are shown in Table 5.

## RESULT AND DISCUSSION

Post compression parameters such as hardness, mass variation drug content uniformity of pantoprazole tablets are given in table 2. Tablet should have sufficient hardness to withstand handling without breaking or crumbling. Hardness plays a vital role for drug release in the case of sustained release tablets. Average hardness was found in the range of 3.85 to 8.69 kg $cm^{-2}$. Drug content uniformity ranged from 91.6 to 99.6%. Friability % ranged from 0.189 ± 0.05. The drug release studies were performed on pantoprazole tablets using a paddle type dissolution apparatus. The *in-vitro* release of pantoprazole tablets was studied in phosphate buffer pH 6.8 for 10 hrs at $37^0$C. A set time, samples were collected, filtered and the amount of drug released was assayed by proper analytical technique. The release patterns using different mathematical model are shown in fig.(1-4) and $R^2$ values of different model are shown in table 3. By analyzing the release kinetics it is found that for all formulations, the correlation coefficient is high in case of Higuchi kinetics. Therefore it can be said that the release follows Higuchi kinetics. Moreover the $R^2$ value of zero order kinetics higher than the first order kinetics and it is near to that of Higuchi kinetics. The prepared pantoprazole matrix tablets were divided at different parts and were placed at different vials at different temperature and humidity chamber for 60 days. The sample from different container was periodically evaluated for physical and chemical stability. From the above table of stability data it clear that, tablet granules are not stable at this stability condition. There is no further change in the formulation F4 and F13 for agglomeration, but F1and F8 agglomerate after a definite period of time and finally damage, which shows that they are unstable. Dug content and drug release also decreases, after a definite period of time for all selected formulations. Based on the stability data the proposed shelf-life and storage conditions as defined in the SPC are acceptable. In summary the stability data provided support the proposed shelf-life and storage conditions.

**Table 1: Composition of different formulations**

| S. No. | Formulation code | Amount of drug | Amount of HPMC | Amount of Eudragit S100 | Amount of eudragit rs100 | Amount of microcrystalline cellulose | Amount of talc | Amount of magnesium stearate |
|---|---|---|---|---|---|---|---|---|
| **1** | **F1** | 40 | - | - | - | 154 | 2 | 4 |
| **2** | **F2** | 40 | 20 | - | - | 134 | 2 | 4 |
| **3** | **F3** | 40 | 40 | - | - | 114 | 2 | 4 |
| **4** | **F4** | 40 | 60 | - | - | 94 | 2 | 4 |
| **5** | **F5** | 40 | 80 | - | - | 74 | 2 | 4 |
| **6** | **F6** | 40 | - | 20 | - | 134 | 2 | 4 |
| **7** | **F7** | 40 | - | 40 | - | 114 | 2 | 4 |
| **8** | **F8** | 40 | - | 60 | - | 94 | 2 | 4 |
| **9** | **F9** | 40 | - | 80 | - | 74 | 2 | 4 |
| **10** | **F10** | 40 | - | - | 20 | 134 | 2 | 4 |
| **11** | **F11** | 40 | - | - | 40 | 114 | 2 | 4 |
| **12** | **F12** | 40 | - | - | 60 | 94 | 2 | 4 |
| **13** | **F13** | 40 | - | - | 80 | 74 | 2 | 4 |

**Table 2: Physicochemical evaluation of pantoprazole tablets**

| Batch | Parameters | | | |
|---|---|---|---|---|
| | Hardness (kg $cm^{-2}$)[b] | Friability (%) | Average mass (g)[c] | Content uniformity (%)[a] |
| **F1** | 8.20 ± 0.16 | 0.31±0.15 | 0.203 ± 0.007 | 97.69 ± 0.13 |
| **F2** | 5.66 ± 0.24 | 0.60±0.08 | 0.208 ± 0.015 | 92.56 ± 0.15 |
| **F3** | 3.85 ± 0.09 | 0.76±0.21 | 0.205 ± 0.024 | 95.89 ± 0.25 |
| **F4** | 4.93 ± 0.34 | 0.61±0.11 | 0.199 ± 0015 | 97.64 ± 0.12 |
| **F5** | 4.90 ± 0.17 | 0.63±0.05 | 0.203 ± 0.034 | 93.59 ± 0.16 |
| **F6** | 6.20 ± 0.35 | 0.42±0.09 | 0.206 ± 0.016 | 98.66 ± 0.35 |
| **F7** | 5.80 ± 0.24 | 0.63±0.023 | 0.198 ± 0..006 | 97.58 ± 0.26 |
| **F8** | 8.69 ± 0.21 | 0.27±0.003 | 0.205 ± 0.018 | 99.56 ± 0.14 |
| **F9** | 6.21 ± 0.18 | 0.40±0.36 | 0.207 ± 0.031 | 94.37 ± 0.05 |
| **F10** | 5.83 ± 0.13 | 0.59±0.33 | 0.204 ± 0.120 | 92.96 ±0.41 |
| **F11** | 5.56 ± 0.42 | 0.61±0.17 | 0.208 ± 0.015 | 91.53 ± 0.32 |
| **F12** | 7.66 ± 0.15 | 0.53±0.41 | 0.195 ± 0.018 | 96.32 ± 0.12 |
| **F13** | 8.06 ± 0.02 | 0.34±0.06 | 0.189 ± 0.014 | 98.55 ± 0.49 |

**Table 3: In-Vitro drug release profile of pantoprazole**

| Time (hrs) | Cumulative % drug release | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **F1** | **F2** | **F3** | **F4** | **F5** | **F6** | **F7** | **F8** | **F9** | **F10** | **F11** | **F12** | **F13** |
| **1** | 5.63 | 6.21 | 5.71 | 7.66 | 8.53 | 6.76 | 7.31 | 8.52 | 6.92 | 5.35 | 4.45 | 7.68 | 7.53 |
| **2** | 8.17 | 10.36 | 9.33 | 11.65 | 10.11 | 9.45 | 12.19 | 13.69 | 11.12 | 9.30 | 8.63 | 9.86 | 9.69 |
| **3** | 15.62 | 15.25 | 15.06 | 16.01 | 15.98 | 14.22 | 17.51 | 19.33 | 14.69 | 14.15 | 10.52 | 13.66 | 15.23 |
| **4** | 24.19 | 19.18 | 21.17 | 24.71 | 25.33 | 19.59 | 23.49 | 28.63 | 22.33 | 19.68 | 20.33 | 19.23 | 23.22 |
| **5** | 31.69 | 27.16 | 26.35 | 29.57 | 30.69 | 25.33 | 27.17 | 39.33 | 29.64 | 27.19 | 28.65 | 28.69 | 31.33 |
| **6** | 38.92 | 36.62 | 34.33 | 35.78 | 39.89 | 32.45 | 34.50 | 40.68 | 35.66 | 33.09 | 38.45 | 38.65 | 37.64 |
| **7** | 45.66 | 47.50 | 40.69 | 43.33 | 45.66 | 40.59 | 39.51 | 46.34 | 40.05 | 38.59 | 45.60 | 49.92 | 46.49 |
| **8** | 51.02 | 50.67 | 47.58 | 51.60 | 53.33 | 45.56 | 47.00 | 55.01 | 44.50 | 45.63 | 48.96 | 55.60 | 52.22 |
| **9** | 56.44 | 58.90 | 53.22 | 58.89 | 59.21 | 48.98 | 54.61 | 59.89 | 48.71 | 52.00 | 51.67 | 59.23 | 60.66 |
| **10** | 60.38 | 64.65 | 59.26 | 65.33 | 66.50 | 57.41 | 61.39 | 64.56 | 55.98 | 58.11 | 54.99 | 63.72 | 65.23 |

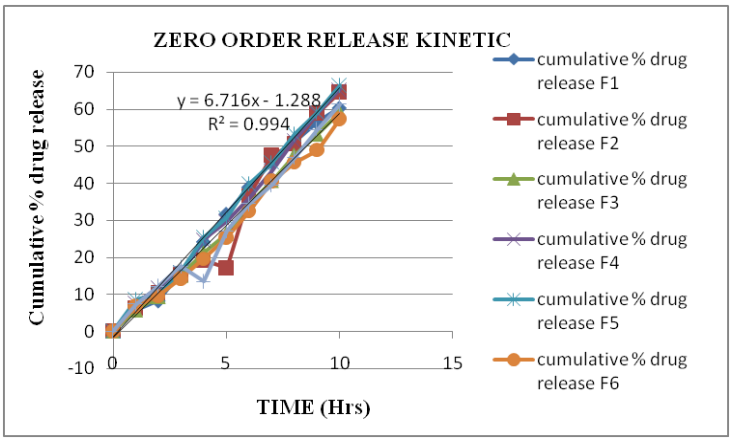



**Figure 1: Zero order release kinetc model**

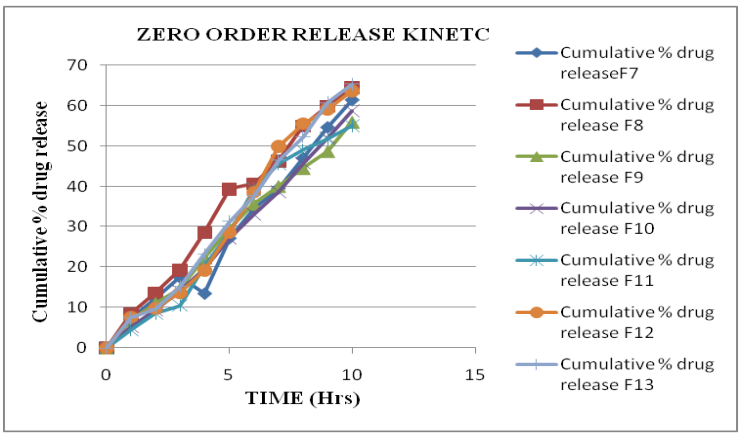



**Figure 2: Zero order release kinetc model**

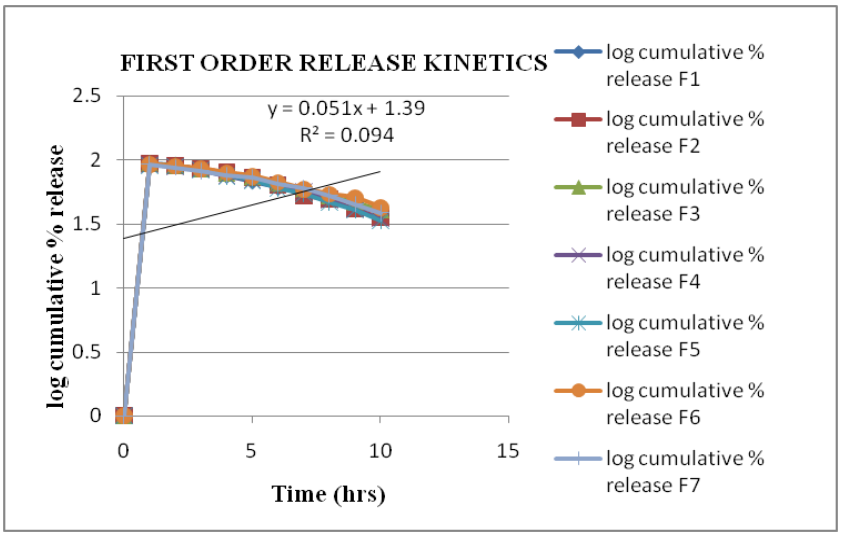



**Figure 3: First order release kinetc model**

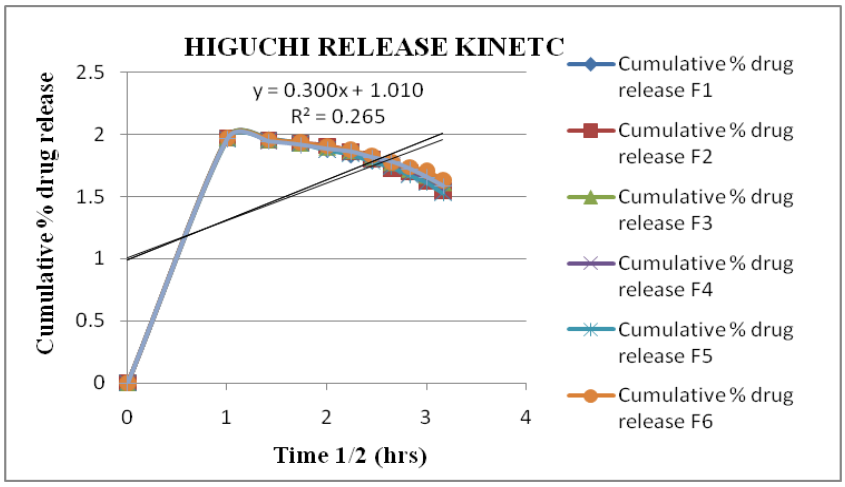



**Figure 4: Higuchi release kinetc model**

**Table 4: Correlation coefficient of different mathematical models**

| FORMULATION CODE | CORRELATION COEFFICIENT ($R^2$) | | |
|---|---|---|---|
| | ZERO ORDER KINETICS | FIRST ORDER KINETICS | HIGUCHI KINETICS |
| **F1** | 0.6418 | 0.7070 | 0.9338 |
| **F2** | 0.6804 | 0.7458 | 0.9299 |
| **F3** | 0.6956 | 0.7620 | 0.9257 |
| **F4** | 0.7074 | 0.7843 | 0.9213 |
| **F5** | 0.6939 | 0.7801 | 0.9254 |
| **F6** | 0.7105 | 0.7801 | 0.9224 |
| **F7** | 0.7137 | 0.7843 | 0.9214 |
| **F8** | 0.9912 | 0.9861 | 0.9243 |
| **F9** | 0.9952 | 0.9872 | 0.9216 |
| **F10** | 0.9957 | 0.9693 | 0.9250 |
| **F11** | 0.9731 | 0.9728 | 0.9387 |
| **F12** | 0.9782 | 0.9591 | 0.9317 |
| **F13** | 0.9934 | 0.9661 | 0.9377 |

**Table 5: Stability data at $45^0$C and 75% relative humidity**

| Action | Agglomeration | | | | Drug content | | | | Drug release at 10 hours | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | F1 | F4 | F8 | F13 | F1 | F4 | F8 | F13 | F1 | F4 | F8 | F13 |
| 15 days | Sticky | No change | No change | No change | 41.54 | 44.11 | 42.31 | 42.33 | 64.23 | 68.23 | 63.50 | 63.85 |
| 30 days | Damage | No change | Sticky | No change | - | 43.28 | 41.55 | 41.21 | - | 65.24 | 61.52 | 62.14 |
| 60 days | Damage | No change | Damage | No change | - | 42.33 | - | 40.44 | - | 63.29 | - | 61.53 |

## CONCLUSION

The digesting liquid known as gastric acid is made of hydrochloric acid and is produced in the stomach. Acid is crucial to the digestion of proteins. Parietal cells create gastric acid (Oxyntic cells). The epithelial fundic glands in the stomach mucosa contain these cells. The proton pump H+/K+ ATPase keeps the pH of gastric acid in the human stomach lumen between 1.5 and 3.5. Alkaline tide is a transient elevation in blood pH brought on by the parietal cell's release of bicarbonate into the bloodstream. Gastroesophageal reflux disease is a disease state that results from an increase in gastric acid output. Pantoprazole is a proton pump inhibitor prodrug used in the treatment of gastric, duodenal ulcers and gastro esophageal reflux disease (GERD), Zollinger- Ellison syndrome. This is the most popular drug used in cure and maintenance therapy of peptic ulcer along with antibiotics. It suppresses the acid production by inhibiting the $H^+$ $K^+$ ATPase. Pantoprazole must be absorbed in the gastrointestinal tract and because it is unstable under acidic conditions, enteric delivery systems are required. The purpose of this study was to prepare matrix tablet using eudragit Rs 100, eudragit S100, and HPMC. Selective formulations were characterized for entrapment analysis; *In-vitro* drug release study from every formulation was conducted for 10 hrs. The release data were further analyzed to curve fitting into different mathematical models. This shows that drug release kinetics follow Higuchi kinetics mathematical model. Average particle size of selective formulation was shows that particles are smaller in sizes, which provide uniform distribution of drug release in the body. Drug release at 10 hrs was found to be at the range of 54.99% - 66.50% in all formulations. The release data revealed the possibility of prolonged drug release profile. Moreover the release kinetics evaluation revealed that the formulation was following Higuchi kinetics mathematical model. On the basis of above result the formulation showed satisfactory result as it has the maximum release i.e. F5 66.50% in 10 hrs. (required for matrix tablets). Result of our study suggest that the matrix tablet containing pantoprazole may be suitable for the anti-ulcer drug, which are known to cause such side effects as headache, diarrhea and abdominal pain.

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