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Influence of Storage Conditions on the Pantoprazole Dissolution Profile for Gastro-Resistant Tablet Formulations

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ABSTRACT

Generic formulations share the same active pharmaceutical ingredient (API), but differences in excipients can impact the quality and efficacy of formulations. In this study, four gastro-resistant pantoprazole tablet formulations were selected from the Serbian drug market to compare their dissolution profiles. The influence of high and low humidity on disintegration and dissolution was examined. The tablets were removed from the primary packaging and packed in plastic boxes, which were then placed in the desiccator with low (30%) and high (75%) humidity conditions for 1 week to simulate storing medicines in weekly pill organizers. Dissolution, disintegration, and uniformity of content were analyzed according to the 10th *European Pharmacopoeia*. Pantoprazole content was determined using UV-Vis spectrophotometry. Dissolution profiles were compared with one-way analysis of variance and similarity factor analysis (f_2). Although a difference was detected in the dissolution profiles of pantoprazole tablets, the overall dissolution rate was satisfactory for all formulations in all conditions tested. After being exposed to high humidity, two formulations failed to meet the requirements for disintegration due to the enteric coating being damaged during the acid stage of the test. This could lead to the absence of therapeutic effect. Therefore, patients should be advised to keep their pantoprazole tablets away from high humidity, preferably in the original packaging.

KEYWORDS: enteric coating, humidity, disintegration, excipients, dissolution

INTRODUCTION

Pantoprazole belongs to the group of proton pump inhibitors, together with omeprazole, lansoprazole, rabeprazole, and esomeprazole (*1*). Pantoprazole irreversibly binds to the proton pump H^+/K^+ ATPase in the parietal cells of the stomach and reduces secretion of gastric acid (*2, 3*). Therapeutic indications for the use of pantoprazole are gastro-oesophageal reflux disease, stomach and duodenal ulcers, and Zollinger Ellison syndrome. It is also used as part of triple therapy for *Helicobacter pylori* eradication (*3, 4*). Orally administered pantoprazole has an absolute bioavailability of 77 %; it is absorbed rapidly and does not accumulate with frequent use. It is metabolized in the liver, the main metabolite being dimethylpantoprazole-

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sulfate. These metabolites are primarily eliminated from the body by the kidneys (*3, 5*). The optimal effective dose of pantoprazole for adults is 40 mg once per day (*4*). The Biopharmaceutical Classification System classifies pantoprazole as a class 3 drug, characterized by good solubility and poor permeability (*6*). In Serbia, pantoprazole is commercially available in the form of gastro-resistant tablets in 20- and 40-mg doses and in powder for solution for injection as a 40-mg dose, according to the Medicines and Medical Devices Agency of Serbia (ALIMS) (*7*). Because it is unstable in anacidic environment, oral dosage forms of pantoprazole are formulated as gastro-resistant dosage forms. Tablets are the most commonly used solid dosage form of pantoprazole. They enable accurate and precise dosing, are easy to use, have high compliance, and are economical (*2, 8*). The enteric film coating protects the API from the acidic environment of the stomach, allowing for modified release (*8*). However, enteric polymers used for formulation of gastro-resistant films can be brittle, which can lead to defects in the enteric coating under specific manufacturing or storage conditions. These defects can cause premature release of the API, which could lead to therapeutic failure (*9*).

Although generic formulations share the same API, differences in efficacy and quality can occur as a consequence of different excipients or formulation methods used (*2, 10, 11*). An important indicator of formulation quality is the dissolution rate of the API. The presence of various excipients leads to variation in the dissolution profile of the API in different formulations. The influence of excipients on the dissolution profile of API can be examined in vitro with a dissolution test (*12*). If in vivo conditions are accurately predicted in vitro, the dissolution test could replace expensive bioequivalence studies (*6*).

Stability of the API in pharmaceutical dosage forms depends on different factors such as humidity, temperature, and compatibility with excipients (*10*). Moisture can significantly affect the stability of the pharmaceutical dosage form, altering its appearance and performance. Adequate packaging of medicines is of great importance to maintain the desired physical and chemical characteristics of pharmaceutical dosage forms (*13*). For most medications, storage conditions should be 15–30 °C, well ventilated, and relative humidity no more than 60%, which are ambient conditions as defined by the World Health Organization (*14, 15*). Studies have shown that most patients store medications in the kitchen, bathroom, or bedroom (*15, 16*). A study conducted in New Zealand reported that relative humidity can range from 33–100% in the bathroom and 27.2–85.2% in the kitchen (*16*). Storing medicines outside of their original packaging (for example keeping them in weekly or daily pill organizers) can expose them to higher or lower humidity and potentially compromise their efficacy, leading to therapeutic failure.

The aim of this study was to determine the influence of excipients and humidity on dissolution and disintegration for pantoprazole tablets available on Serbian drug market.

METHODS

Chemicals and Reagents

In this study, four commercial gastro-resistant tablet formulations available on Serbian drug market were tested (Table 1). Each formulation was declared at 40 mg pantoprazole per tablet. Phosphate buffer (0.1 M, pH 6.8) was used as the medium for the disintegration and dissolution test. It was made according to the requirements of the *United States Pharmacopoeia* (USP) (*17*),

using potassium dihydrogen phosphate (Lachner, p.a., Czech Republic) and sodium hydroxide (PanReac, p.a., Spain). Hydrochloric acid (HCl, 0.1 M) was made with 35% HCl (Lachner) and used as media for the disintegration test. Sodium chloride (JTBaker, p.a., USA) and magnesium chloride (JTBaker) were used to make the solutions for setting the conditions of high and low humidity. Information about excipients used in the formulations was extracted from Summaries of Product Characteristics of the selected pantoprazole tablets, which is available online (*7*).

Table 1. Tested Formulations

Formulation	Lot #	Expiry Date	Marketing Authorization Holder
A	126L3G	06/2026	HEMOFARM AD VRŠAC
B	250721	09/2025	ZDRAVLJE AD LESKOVAC
C	516705	07/2024	TAKEDA GMBH PREDSTAVNIŠTVO BEOGRAD (NOVI BEOGRAD)
D	DA1390	05/2026	KRKA-FARMA D.O.O. BEOGRAD

Stability Testing

The tablets were removed from the primary packaging and packed in plastic boxes to simulate storing medicines in weekly pill organizers. A desiccator was used to achieve conditions of high (75 ± 5%) and low (30 ± 5%) humidity at room temperature (25 ± 2 °C). High humidity was achieved with a sodium chloride solution, obtained by dissolving 20 g of sodium chloride in 10 mL of distilled water, while for the condition of reduced humidity (30%) magnesium chloride solution obtained by dissolving 30 g in 3 mL distilled water was used, according to a previously published method (*18*). Twenty-five tablets of each formulation were stored for a week in a plastic box in a desiccator in conditions with high humidity, and another 25 tablets were stored in at low humidity. Conditions were monitored daily using a hydrometer with a thermometer (HTC 288ATH).

UV/Vis Spectrophotometry

UV/Vis spectrophotometer (Agilent Technologies, model 8453, USA) was used for spectrophotometric measurements. Phosphate buffer pH 6.8 was used as a blank. Pantoprazole stock solution in phosphate buffer (0.8 mg/mL) was used to make pantoprazole standard solutions (2.5, 5, 10, 20, 40, and 60 µg/mL), also in phosphate buffer. These standard solutions were used to obtain a calibration curve (Fig. 1). The absorbance was measured at 288 nm, and the concentration of pantoprazole was determined in accordance with a validated UV/Vis spectrophotometric method (*19*). The linearity was confirmed in the tested pantoprazole concentration range (R^2 = 0.9989). This method was used to determine the content of pantoprazole and the dissolution rate in the tested formulations.

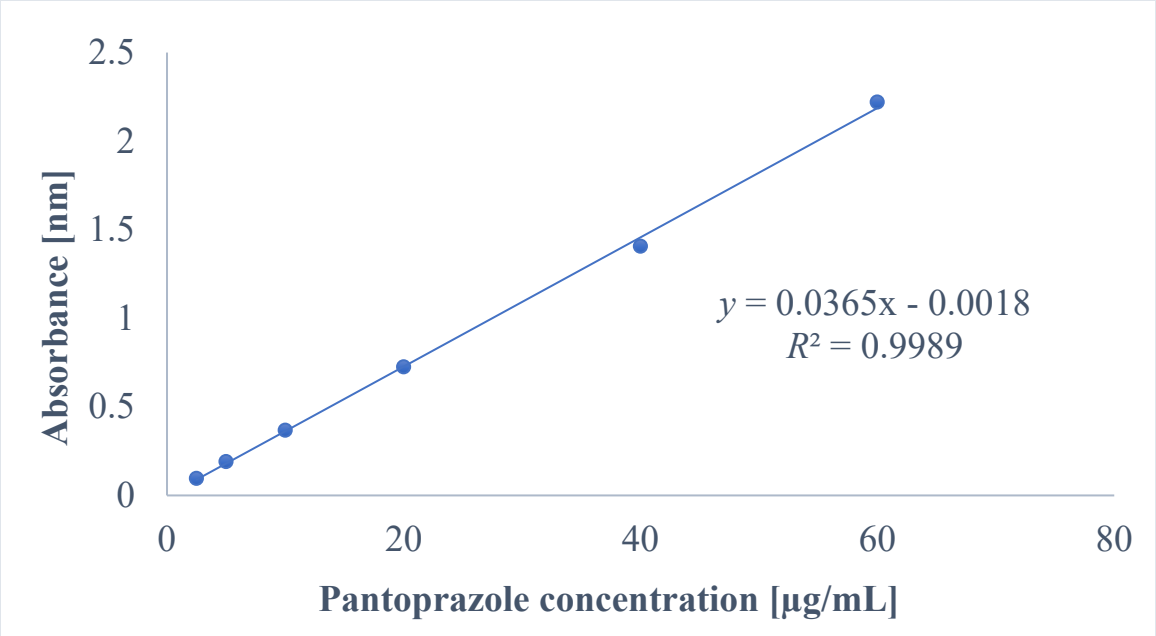


Figure 1. Pantoprazole calibration curve.

Uniformity of Content

From each formulation, the test was performed on 10 tablets from the original packaging, 10 tablets stored at high humidity (75%), and 10 tablets stored at low humidity (30%). Each tablet was dusted in a mortar with a pestle. It was transferred to a flat-bottomed flask (100 mL), and the flask was filled to the line with phosphate buffer pH 6.8. The prepared samples were placed in an ultrasonic bath (Clifton, UK) for 15 min to accelerate pantoprazole dissolution. The samples were then diluted 20 times, their absorbance was measured with the UV/Vis spectrophotometer, and the concentration was determined. From the individual measurements, the mean value was calculated for each formulation stored under the initial conditions and stored at high and low humidity conditions. According to 10th *European Pharmacopoeia* (*EP*), the content of individual tablet may deviate ± 15% of the calculated average content (*20*).

Disintegration Test

The disintegration test was performed in accordance with the *EP*. The test was performed with six tablets of each formulation from the original packaging, six tablets stored at high humidity, and six tablets stored at low humidity. A Erweka disintegration tester (model ZT54, Germany) was used. The tablets were immersed in a 1-L beaker (placed in water bath at 37 °C) filled with 0.1 M HCl and later phosphate buffer. According to the *EP*, no tablet should disintegrate within 2–3 h in acidic medium, and all tablets should disintegrate within 1 h in the phosphate buffer (*20*).

Dissolution Test

The dissolution rate of pantoprazole tablets was tested using a paddle apparatus 2 (Erweka model DT800, Germany) according to the *EP* (*20*). The parameters were set to simulate in vivo conditions: 100 rpm; 37 ± 0.5 °C, 900 mL of phosphate buffer pH 6.8. The dissolution rate was

examined for 60 min, while sampling was performed after 5, 15, 25, 35, 45, and 60 min. Six tablets of each formulation were tested for each storage condition (initial condition and high and low humidity). The dissolution samples obtained were used to determine the concentration of pantoprazole by UV/Vis spectroscopy. According to the USP pantoprazole sodium delayed-release tablets monograph, tested tablets should release at least 75% of the declared content (*21*).

Statistical Analyses

Descriptive statistics were calculated; the mean value and standard deviation were determined. A one-way analysis of variance (ANOVA) test was applied and the differences were considered significant for $p < 0.05$. Statistical tests were performed using SPSS (version 23.0). Similarity factor (f_2) analysis was used to compare dissolution profiles. The U.S. Food and Drug Administration (FDA) guidelines recommend the use of f_2 to compare the dissolution profiles of modified-release tablets (*22*). The tested profiles were considered similar if the value of f_2 is 50–100. Formulation C was used as a reference profile (R_t), because it was the first of the tested formulations to be registered on the Serbian drug market (*7*).

RESULTS AND DISCUSSION

The tablets were examined visually and the appearance of the tested formulations according to the SmPCs is as follows: formulation A – yellow oval tablets; formulation B - dark yellow biconvex coated tablets, ellipsoidal in shape, measuring 5.3 x 10.3 mm; formulation C – yellow, oval, biconvex coated tablets, imprinted on one side with P 40 in brown ink; formulation D - light brownish yellow, slightly biconvex, oval, coated tablets (*7*). After exposure to the storage conditions of decreased and increased humidity, the tablets were examined visually, and it was concluded that they did not change the appearance as stated in the SmPC.

The goal of measuring pantoprazole content was to determine compliance with *EP* requirements. The content of every tablet tested in all conditions was within the range (± 15%) of the calculated average content, which satisfies the requirements of the *EP*.

Disintegration times measured in phosphate buffer are shown in Table 2. Tablets that were not exposed to elevated or reduced humidity and those that were exposed to reduced (30%) humidity satisfied *EP* requirements for all four tested formulations. However, after exposure to 75% humidity, one tablet of formulation A cracked in acidic medium within 30 min, and the tablet core completely disintegrated after 50 min, while parts of the coating remained (Fig. 2A). Excipients in the formation of a gastro-resistant coating were methacrylic acid and ethyl acrylate copolymer 1:1 in formulation A, whereas 30% dispersion was used in formulations B, C, and D. Excipients specific for enteric coating of formulation A are lecithin, an amphiphilic emulator, polyvinyl alcohol, and macrogol 3350. Macrogols in tablet coatings are known to increase water permeability and lower the protection of enteric coating against acidic pH, which could be the reason for the damage to formulation A's enteric coating in the acidic medium after exposure to high humidity conditions (*23*). Also, one tablet of formulation C exposed to 75% humidity leaked in two spots after 30 min, but it did not disintegrate within the prescribed time (Fig. 2B). The plasticizer specific to formulation C is triethyl citrate. A study was conducted to determine the effect of high humidity on methacrylate copolymer film plasticized with triethyl citrate (*9*). It was shown that exposure of films to high humidity (75%) decreased the glass transition temperature

of the films. This reduction of glass transition temperature further led to enteric coating damage, the mechanism of which depended on the storage temperature. At low temperatures (~ 5 °C), brittle fracture of coating occurred, while at higher temperatures (~ 40 °C), mobility of enteric coating increased, causing thinning in some areas (*9*). Further studies are necessary to determine the exact mechanism of formulation C's enteric coating damage in the acidic environment after exposure to high humidity.

Table 2. Content of Pantoprazole and Disintegration Time in Phosphate Buffer

Formulation	Storage Conditions	Content (%), Mean ± SD	Disintegration Time (min)
A	Initial	43.62 ± 1.67	29
	30% moisture	43.73 ± 1.03	24
	75% moisture	43.51 ± 1.48	31
B	Initial	41.63 ± 0.71	23
	30% moisture	42.62 ± 0.69	22
	75% moisture	41.87 ± 0.16	22
C	Initial	41.74 ± 0.56	25
	30% moisture	41.29 ± 0.41	29
	75% moisture	41.85 ± 1.19	22
D	Initial	41.88 ± 0.81	18
	30% moisture	41.84 ± 1.07	20
	75% moisture	42.90 ± 1.71	19

A **B**

Figure 2. Enteric coating failures of formulation A (***A***) *and formulation C* (***B***).

The dissolution test of gastro-resistant tablet formulations of pantoprazole should show a release of at least 75% of the declared content in the phosphate buffer (*21*). All formulations met this requirement in all three tested conditions (initial, reduced, and elevated humidity); however, there was a noticeable difference in the rate of the API release.

In the initial conditions, formulation A showed the slowest pantoprazole dissolution rate (Fig. 3). The formulation released 58.44% API at 35 mins and 93.47% API at 45 mins. These values statistically differ from formulations B, C, and D, which released 91.98%, 98.32%, and 97.71% API at 35 mins ($p < 0.001$ for all) and 97.62% ($p = 0.023$), 99.39% ($p = 0.003$), and 99.07% API ($p = 0.004$) at 45 mins, respectively. The difference of the dissolution profile of formulation A in relation to the reference formulation C was also confirmed by the model independent method (f_2

= 34.95). Formulation A is the only tested formulation that contains polyvinyl alcohol in the enteric coating, which is defined as a waterproof film-forming agent (*8*). The presence of this polymer is a possible cause of slower penetration of water into the tablet, and thus slower release of the API in all three tested conditions. Also, specific for formulation A is the diluent maltitol, whereas mannitol is used in the other formulations. A study has shown slower release of API (theophylline) in tablets containing maltitol than in tablets containing mannitol (used as a filler) (*24*). The authors attributed this to the fact that during compaction strong bonds are formed between hydroxyl groups of polyols. As maltitol has more hydroxyl groups than mannitol, maltitol forms more bonds and therefore slows down the penetration of water into the tablets and consequently slows the dissolution rate of API (*24*).

Under conditions of high humidity, all formulations have a slightly accelerated dissolution rate compared to the initial conditions (Figs. 3 and 4). This acceleration may be due to swelling and weakening of interparticle bonds due to moisture absorption (*25*). In the core of formulation A, C, and D, we noticed the presence of super-disintegrant crospovidone, which is very hygroscopic and has been shown to accelerate the release of APIs when stored under high humidity (*26*). However, it was observed that only in formulation B there was a statistically significant influence of elevated humidity on the dissolution profile at 25 and 35 mins compared to dissolution of formulation B in the initial conditions at the same times (p = 0.051 and p = 0.031 respectively). This could be attributed to the presence of highly hygroscopic sodium starch-glycolate, a super-disintegrant specific for formulation B, but also PEG 400, a film plasticizer. It was mentioned that macrogols in film coating can lead to higher water permeability, especially liquid grade macrogols, such as PEG 400. This can consequently lead to faster release of pantoprazole from formulation B when exposed to high humidity.

When comparing dissolution profiles of the four tested formulations after being stored in conditions of high humidity, formulation A showed statistically significantly slower release of pantoprazole than formulations B, C, and D (p < 0.001 for all) at 25 mins and at 35 mins (p = 0.019, 0.020, and 0.018, respectively), which was similar to differences in dissolution profiles in the initial conditions. Formulation D at 25 mins showed statistically significantly faster dissolution of pantoprazole than formulations A (p = 0.001), B (p = 0.024), and C (p = 0.014). Differences in the dissolution profiles of formulations A and D compared to C in high humidity conditions was confirmed by f_2 values (f_2 = 32.28 and f_2 = 47.02 respectively). The enteric coating of formulation D contains the synthetic polymer povidone (polyvinylpyrrolidone (PVP). Povidone differs in molecular weight and viscosity in water, which is expressed as the K-value calculated based on the relative viscosity of PVP in water. The value ranges from 10 to 120. Povidones of lower molecular weight, such as K25 in this preparation, are hygroscopic and can be used as excipients for increasing solubility (*23*). The enteric coating of formulation D also contains surfactants sodium lauryl sulfate and polysorbate 80, which are wetting agents that further facilitate penetration of water into the tablet. Specific for formulation D is the presence of macrogol 6000, which has been shown to accelerate release of the API in some formulations (*27*). The core of formulation D also contains hygroscopic excipients, sorbitol, and super-disintegrant crospovidone, which has been shown to accelerate the release of the APIs when stored under high humidity (*26*). Compared to other formulations, we noticed that the composition of formulation D includes the largest number of hygroscopic excipients, which may be the cause of

accelerated release of API under conditions of high humidity due to possible moisture absorption.

Statistical analysis showed no significant difference between dissolution profiles of each individual formulation tested in the initial conditions and after exposure to conditions of reduced humidity (Figs. 3 and 4). Model-independent analysis once again indicated a difference in the dissolution profile of formulation A compared to reference formulation C (f_2 = 34.00). The results of the dissolution test show a more pronounced effect of reduced humidity only on formulation D (though not statistically significant), and other formulations did not have large differences in the percentage of release compared to the initial conditions. The release of pantoprazole from formulation D under reduced humidity conditions at 25 mins decreased to 29.97% from the original 68.2% under initial conditions. There was a more noticeable difference between the dissolution profiles of formulations exposed to high humidity compared to low humidity. At 15 mins, there was a statistically significant difference between the amount of released pantoprazole content for formulation B under elevated humidity and reduced humidity (p = 0.008). Formulation D at 75% humidity released 96.73% at 25 mins at 75% humidity, whereas only 29.98% was released at the same time at 30% humidity, which was statistically significant (p = 0.024). These results were not unexpected, because under conditions of reduced humidity, tablets may take longer to swell, which is a key step for further dissolution (*25*).

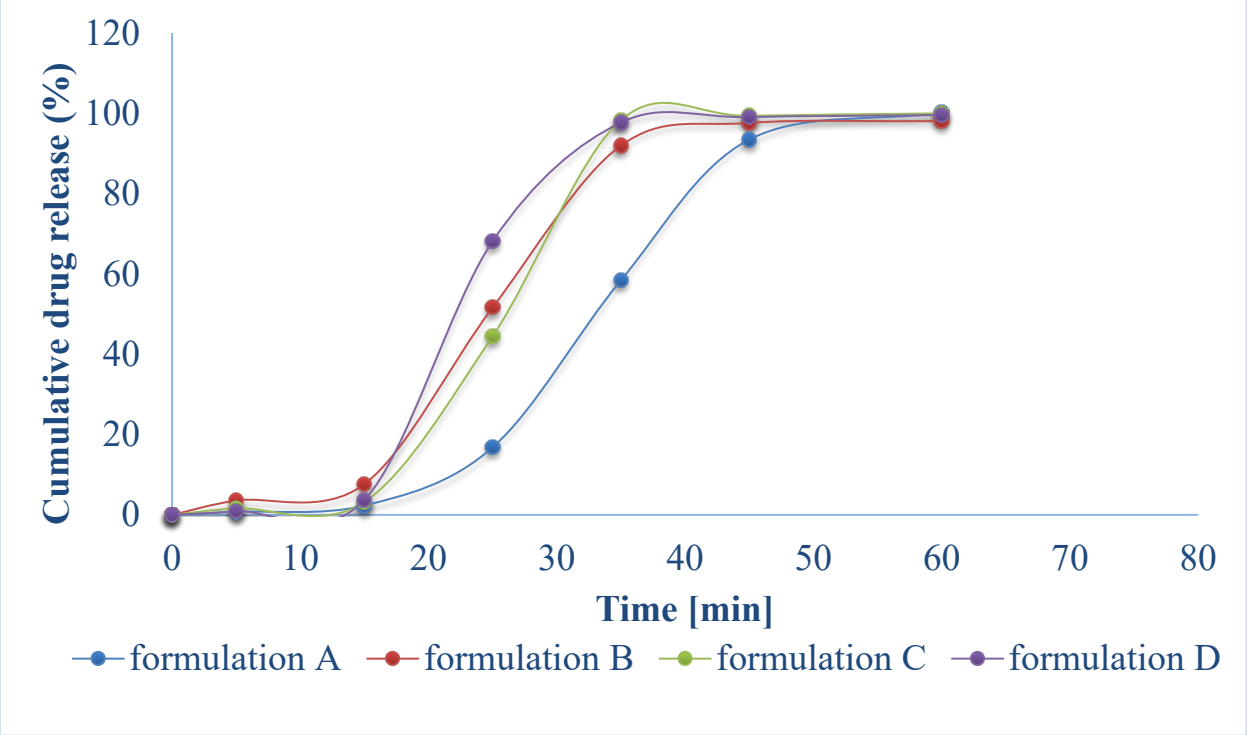
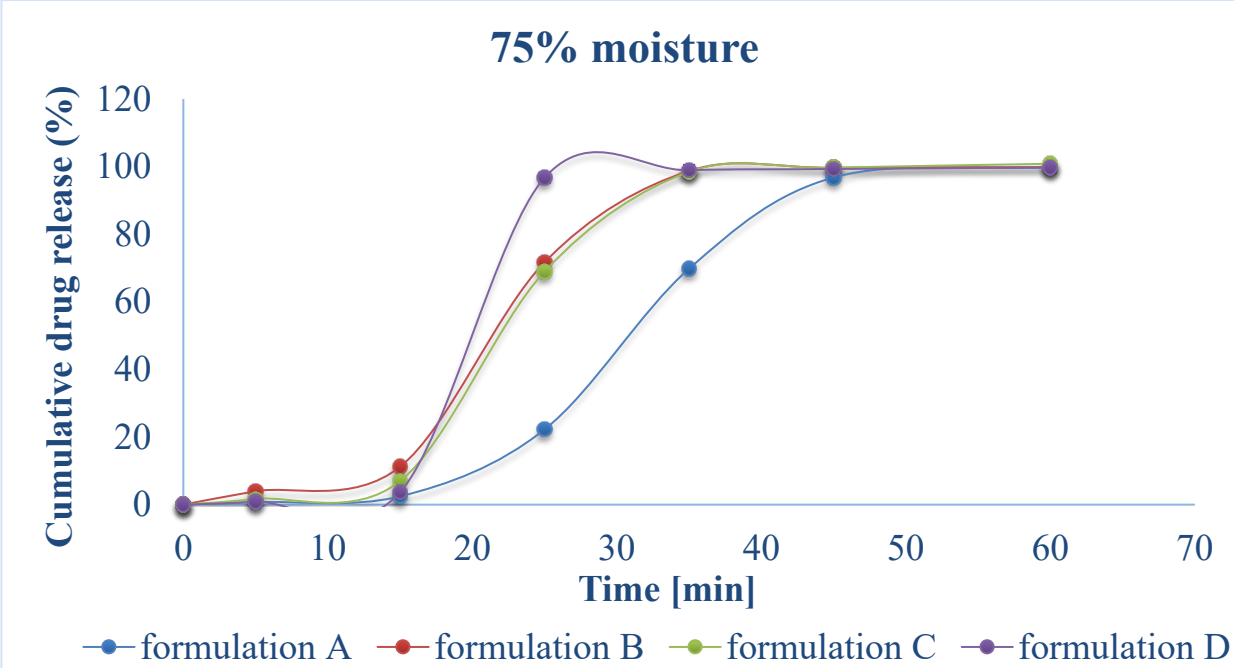


Figure 3. Dissolution profiles of pantoprazole formulations in the initial conditions.



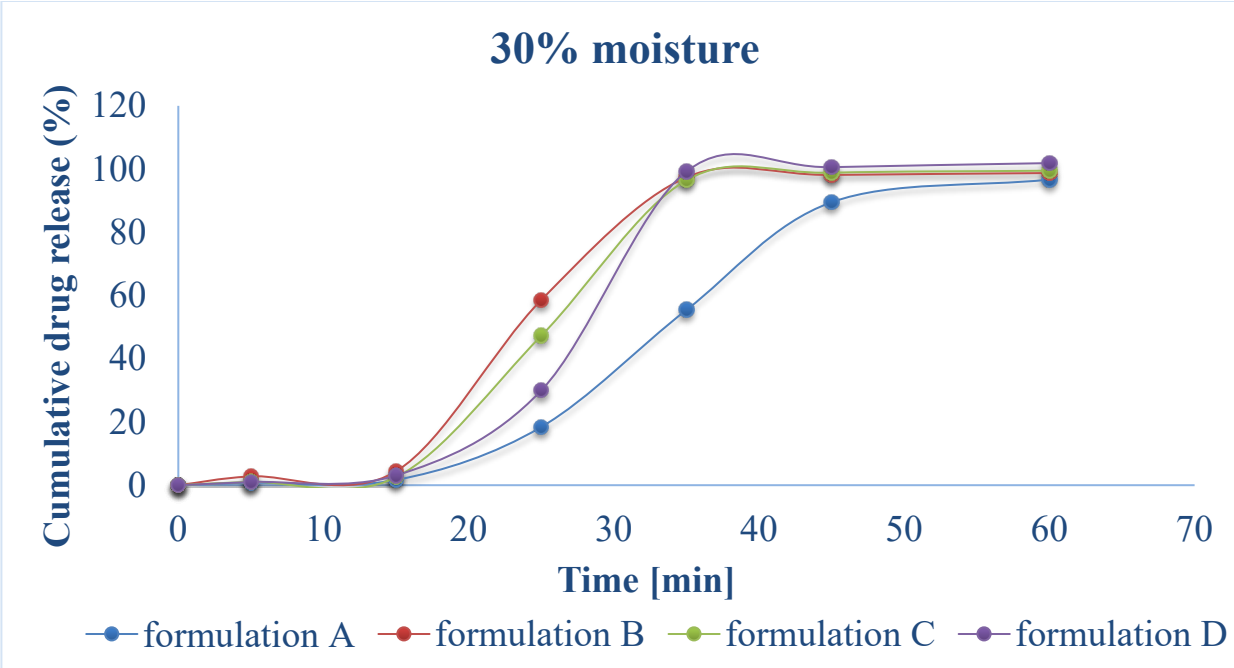


Figure 4. Dissolution profiles of pantoprazole formulations after exposure to high and low humidity conditions.

CONCLUSION

All four tested commercial gastro-resistant pantoprazole tablet formulations showed a satisfactory dissolution rate of API, even after exposure to reduced or elevated humidity conditions. Statistically significant differences were noted in the rate of pantoprazole release from

different formulations due to the presence of different excipients in both the enteric coating and the core of the tested pantoprazole formulations. Nevertheless, all four formulations in all tested conditions met the *EP* requirements in the phosphate buffer. This study has shown that exposure of commercial pantoprazole tablets to the conditions of low humidity had little effect on their disintegration and dissolution profiles.

After being exposed to the conditions of high humidity (75%), two tested formulations failed to meet the requirements for disintegration test. In the acid stage of the test, the enteric coating of one tablet was slightly damaged, but the tablet core did not disintegrate completely, and the coating on the other tablets was so damaged that the core disintegrated completely. Premature release of acid labile API such as pantoprazole from a gastro-resistant formulation due to enteric coating failure can cause absence of therapeutic effect. Therefore, patients should be advised to keep pantoprazole gastro-resistant tablets away from places with high humidity, especially if their preference is keeping medications in pill organizers instead of their original packaging.

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CONFLICT OF INTEREST

The authors disclosed no conflicts of interest related to this article.

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