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Research paper

Increasing sodium pantoprazole photostability by microencapsulation: Effect of the polymer and the preparation technique

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Abstract

Pantoprazole sodium is a proton pump inhibitor, used in acid-related disorders, like peptic ulcers and gastroesophageal reflux. This drug is unstable in acid solution and in the presence of salts. The aim of this work was to study the photostability under UVC radiation of pantoprazole and to determine its kinetics. A methanol solution and the solid pantoprazole were evaluated by HPLC within 120 min and 10 days, respectively. The work was also dedicated to evaluate and compare the ability of microencapsulation in stabilizing pantoprazole after UVC radiation. Pantoprazole-loaded microparticles prepared by emulsification/solvent evaporation or spray drying were compared. Pantoprazole was encapsulated using Eudragit S100® or its blend with poly(ε-caprolactone) or HPMC. In methanol solution, pantoprazole was completely degraded after 120 min and presented zero-order kinetics with $t_{1/2}$ of 6.48 min. In the solid form, after 10 days, pantoprazole concentration was reduced to 27% following zero-order kinetic. The microparticles prepared only with Eudragit S100® demonstrated an increase of the drug photostability. After 10 days of irradiation, 56 and 44% of the drug was stable when encapsulated by emulsification/solvent evaporation and spray drying, respectively. The use of polymer blends did not improve the pantoprazole photostability.

Keywords: Pantoprazole; Photostability; HPLC; Microencapsulation; Spray drying; Solvent evaporation

1. Introduction

Pantoprazole, 5-(difluoromethoxy)-2-[(3,4-dimethoxypyridin-2-yl)methylsulfinyl]-3*H*-benzoimidazole, is a substituted benzimidazole derivative that inhibits gastric acid secretion by irreversibly binding the proton pump (H^+/K^+-ATPase) in the gastric parietal cells [1]. It is a prodrug that is activated in the acid environment of the canaliculi of the parietal cells. Pantoprazole binds specifically to a region of the proton pump that is crucial for ATPase activity and acid transport [2]. It is indicated in the treatment of *Helicobacter pylory* infections in a triple therapy consisting in its association with clarithromycin and metronidazole. It is very effective in the management of the gastro-esophageal reflux disease and in the treatment of digestive ulcers, reducing the acid output [3].

Pantoprazole has been successfully microencapsulated by two techniques and using different polymers. The solvent evaporation technique was applied in the preparation of gastro-resistant pantoprazole-loaded microparticles using an O/O emulsion. The *in vivo* activity of the pantoprazole loaded-Eudragit S100® microparticles was carried out in rats and showed that the microparticles were able to protect rat stomachs against ulcer formation, while the drug aqueous solution did not present any activity [4]. Using the same technique, microparticles of poly(ε-caprolactone) (PCL) and of its blend with Eudragit S100® were prepared in order to provide drug controlled release and gastro-resistance [5]. Only the microparticles prepared with the blend were capable to stabilize the drug in the acid

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medium. The spray drying technique was also employed to prepare pantoprazole-loaded microparticles. The Eudragit S100® microparticles presented high encapsulation efficiency and good drug stabilization in acid medium [6]. A blend of Eudragit S100® and HPMC was also tested [7,8]. Microparticles presented acceptable drug loading, encapsulation efficiency, surface area and particle size.

The photodegradation of drug dosage forms in solid state depends on particle size surface area, crystal structure and polymorphism [9]. Only the absorbed radiation participates in photodegradation and the dilution of the drug in the excipient, as well as the coating can affect the photostability [10]. Drugs have already been stabilized in coated tablets, colored gelatin capsules, liposomes, lipospheres and by the complexation with cyclodextrines [9]. Tablets containing nifedipine with particle size of 25 or 220 μm were tested regarding the photostability. The tablets with the smaller particles presented drug loss 5–10% higher [11]. In the same work, two dosages of nifedipine were tested and the photoinstability of nifedipine tablets decreases by increasing the drug content. Lipidic microparticles (lipospheres) were prepared and tested in order to prevent the melatonin photodegradation [12]. Creams containing lipospheres or just melatonin were exposed to light for 2 h. Only the tristearin lipospheres reduced the melatonin loss. In the case of butylmethoxydibenzoylmethane encapsulated in lipospheres of tristearin, the formulations prepared dissolving the drug with ethanol or acetone or dispersing it in the melted lipid were incorporated into a cream and irradiated in solar simulator. All formulations enhanced the drug photostability, but the one avoiding organic solvent was considered the optimum formulation [13].

There are many reports about the pantoprazole instability in acid medium [1,3,14], as well as in the presence of salts [15,16]. However, there is a lack of information about the stability of pantoprazole under UV–vis radiation. For the other benzimidazoles, omeprazole and lansoprazole, the photodegradation under sunlight simulator has been reported [17]. Both drugs resulted unstable in solution at different pH values when exposed to solar light, which induced significant degradation. The photodegradation kinetic study under UVC light of rabeprazole showed that in methanol solution the degradation was very fast and followed zero-order kinetics [18].

The purpose of this work was to determine the kinetics of photodegradation under UVC radiation of pantoprazole in a methanol solution and in the solid form using an HPLC method. In addition, the work was also dedicated to evaluate and compare the ability of microencapsulation in stabilizing pantoprazole after UVC radiation.

2. Materials and methods

2.1. Materials

Sodium pantoprazole sesquihydrate was obtained from Henrifarma (São Paulo, Brazil). Eudragit S100® was kindly gifted by Almapal® (São Paulo, Brazil, produced by Rohm®, Germany). Methocel F4 M® was provided by Colorcon® (São Paulo, Brazil, produced by Dow Chemical, USA). Poly(ε-caprolactone) was obtained from Aldrich®, (Milwaukee, USA). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. High-performance liquid chromatography

The stability-indicating HPLC method consisted of a Perkin Elmer serie 200 liquid chromatograph equipped with an UV/Vis detector. Detection was made at 290 nm. The stationary phase was a 150 × 3.9 mm NovaPak C_{18} octadecyl silane column (4 μm particle size) (Waters, Ireland). A security guard cartridge C_{18} (4 × 3 mm) (Phenomenex) was used. The mobile phase was prepared by mixing phosphate buffer pH 7.4 and acetonitrile (65:35 v/v). Then, the mobile phase was filtered using a 0.45 μm membrane filter (Milipore, USA). The injection volume was 20 μL and the flow rate was 0.9 mL min^{-1}. The method was validated for specificity, linearity, precision and accuracy [19].

2.2.2. Preparation of the microparticles by emulsification/solvent evaporation

After dissolving the Eudragit S100® in acetone, pantoprazole sodium sesquihydrate (2:1 w/w polymer to drug ratio) was added (MP1). This suspension was emulsified with mineral oil containing sorbitan monooleate (0.4%). The O/O emulsion was mechanically stirred for 2.5 h to remove the acetone. The microparticles were collected by filtration and washed with cyclohexane [4]. Another formulation was prepared by dissolving the PCL in acetone and adding the pantoprazole (ratio 1:1 w/w) prior to the emulsification with mineral oil containing sorbitan monooleate (0.4%) (MP2). After the evaporation of the acetone, a solution of Eudragit S100® in acetone was added to the primary microparticle suspension. The solvent was evaporated and the microparticles collected by filtration and washed with cyclohexane [5].

2.2.3. Preparation of the microparticles by spray drying

Eudragit S100® (MP3) or blended with Methocel F4 M® (MP4) was dissolved in 0.05 M NaOH solution. Pantoprazole was added and the solutions were spray dried (Mini Spray Drier, MSD 1.0, LabMaq, Brazil). The experimental conditions were: 0.8 mm nozzle, inlet temperature of 150 °C and flow rate of 0.44 L h^{-1} [6,8].

2.2.4. Photodegradation kinetics of pantoprazole in solution

For the photodegradation studies, the light source was an UV fluorescent lamp model Ecolume®, 30 W, emitting radiation at 254 nm, fixed to a chamber in a horizontal position. The chamber was internally coated with mirrors in order to distribute the light uniformly. The effect of light was studied exposing the methanol sample solutions in 1 cm quartz cells (duplicates). The temperature was con-

trolled in the chamber (around 25 °C). The photodegradation kinetics of sodium pantoprazole was evaluated in methanol (800 μg mL^{-1}). The samples were placed horizontally to provide maximum area of exposure to the light source. Considering the UV absorption of pantoprazole, the irradiation was carried out at different time intervals (0, 15, 30, 45, 60, 90 and 120 min). After sampling, each solution was diluted with the mobile phase to give the final concentration of 10 μg mL^{-1}. The samples were assayed by HPLC. The mathematical modeling of the pantoprazole degradation profiles was performed using Micromath Scientist® software to fit a zero-order (1), a first order (2) or second order (3) kinetics. The best model was chosen based on the highest regression coefficient and the model selection criteria as well as the best graphic adjustment.

$$C = C_o - kt \quad (1)$$

$$\ln C = \ln C_o - kt \quad (2)$$

$$1/C = 1/C_o + kt \quad (3)$$

2.2.5. Photostability evaluation of solid pantoprazole and microencapsulated pantoprazole

The microparticles MP1, MP2, MP3 and MP4 and the drug powder were placed in a very thin layer in watch glasses. Two watch glasses were prepared for each time interval for each formulation. The samples were placed inside the mirror chamber and exposed to UV light for a maximum of 10 days. The samples were collected after 1, 2, 4, 6, 8 and 10 days and evaluated for the drug content.

After sampling, the drug content was evaluated in all samples, according to the method previously described for the pantoprazole solution. The microparticles were suspended in a mixture of 0.05 M NaOH and acetonitrile 1:1 (v/v), kept under magnetic stirring for 3 h protected from light, diluted, filtered and quantified by HPLC.

2.2.6. Statistical analysis

A one-way analysis of variance was employed in the comparison of the experimental data. Post-hoc multiple comparisons were performed by Tukey's test for significance at p-values less than 0.05.

3. Results and discussion

3.1. High-performance liquid chromatography

The comparison between the chromatograms obtained for pantoprazole or for pantoprazole in the presence of photodegradation products showed that the method was specific for pantoprazole. Linearity was obtained in range of 0.5 and 15.0 μg mL^{-1}. The method accuracy was determined by investigating the recovery of pantoprazole at three concentrations. Results indicated recoveries from 99.2% to 104.0%. Precision was determined for pantoprazole solutions by performing six replicates of the same concentration on three different days. Precision was adequate (RSD = 0.93%).

3.2. Kinetics of photodegradation of pantoprazole

The methanol solutions developed a yellow color during the experiment, which intensified with time. The concentration of pantoprazole was reduced to 1.7% after 120 min (Fig. 1). The degradation kinetics could be described by zero-order kinetics in the experimental conditions of this study. The correlation coefficient was 0.996 and the MSC was 4.1. The apparent degradation rate constant k was 1.424 min^{-1} and the $t_{1/2}$ was 35.11 min.

Pantoprazole was more photostable than rabeprazole, which degraded 88% in 30 min and presented $t_{1/2}$ of approx. 15 min [18]. Rabeprazole presented zero-order kinetics in methanol solution and UVC light [18].

3.3. Photostability evaluation of solid pantoprazole and microencapsulated pantoprazole

Pantoprazole concentration was reduced much slower than in the methanol solution, but, after 10 days, the drug content was reduced to 27% (Fig. 2). The photodegradation of the solid pantoprazole also followed an apparent zero-order kinetic, with degradation constant rate of 7.710 $days^{-1}$. The $t_{1/2}$ of degradation was 6.5 days.

The drug loading values for microparticle formulations were 220, 160, 173 and 132 mg g^{-1} for MP1, MP2, MP3 and MP4, respectively. The theoretical loading and the encapsulation efficiency of each microparticle formulation are described in Table 1. Higher encapsulation efficiencies (95% and 101%) were observed for the formulations prepared by spray-drying (MP3 and MP4, respectively). Using the solvent evaporation technique the encapsulation effi-

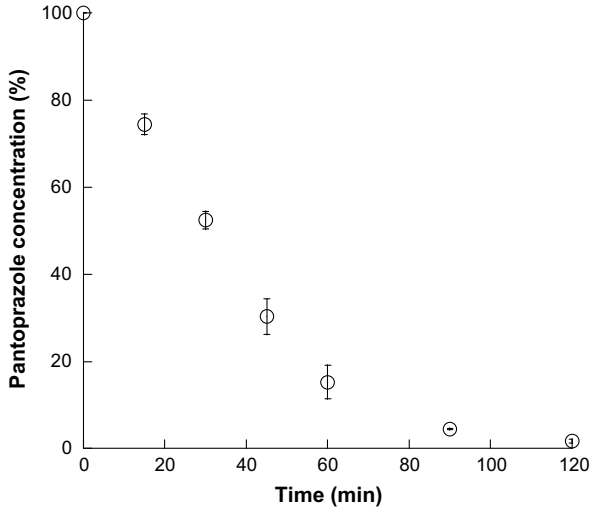

Fig. 1. Pantoprazole concentration in the methanol solution after exposure to UVC light.

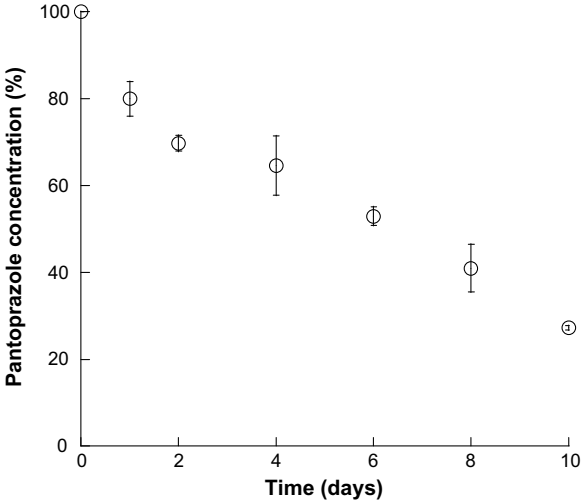

Fig. 2. Pantoprazole concentration after exposure of the solid drug to UVC light.

ciencies were 70% and 48% probably due to the presence of sorbitan monooleate and mineral oil in the powders.

After 10 days of exposure, pantoprazole concentration in MP1 microparticles was $55.7 \pm 1.5\%$ and in MP3 was $44.2 \pm 3.1\%$, while pure pantoprazole showed $27.2 \pm 0.4\%$ (Fig. 3). According to Tukey's test, MP1 and MP3 were statistically different from pure pantoprazole ($p < 0.001$). The microparticles MP1 were able to protect significantly more the drug than the microparticles MP3 ($p = 0.003$). The microencapsulation increased the pantoprazole stabilization in 2 folds.

The microparticles have different particle size, polydispersion and shell thickness. Also, the internal structures are different. The microparticles prepared by emulsification/solvent evaporation are larger (Table 1). The MP1 microparticles are homogeneous and hollow, formed by a solid solution of Eudragit S100® and pantoprazole [4]. On the other hand, the microparticles prepared by spray drying are smaller (less than 10 μm) and the shell is thinner. Furthermore, the spray drying microparticles present blowholes formed by the expansion of the water after the shell rapid solidification [6,7]. The higher pantoprazole content was obtained for the MP1 microparticles (220 mg g^{-1}). The MP3 microparticles had drug loading of 173 mg g^{-1}. In this way, we can presume that both factors (particle size and drug content) affected the microparticles, being in agreement with the literature [9,11]. The MP1 microparticles presented the higher pantoprazole content after irradiation.

When pantoprazole was encapsulated by a polymer blend, different results were obtained. The addition of PCL to the microparticles (MP2) caused a reduction of pantoprazole photostability. The final amount of pantoprazole, after 10 days, was $32.9 \pm 0.3\%$ (Fig. 3). These microparticles did not present an increase of pantoprazole photostability ($p = 0.421$) compared to the pure drug.

Table 1
Drug loading, particle size, surface area and half-life of pantoprazole degradation in the microparticles

Microparticles	Theoretical loading (mg g^{-1})	Encapsulation efficiency (%)	Particle size (μm)	Specific surface area (m^2 g^{-1})	Photodegradation $t_{1/2}$ (days)
MP1	318.2	70 ± 5	56 [4]	41 [4]	10.2
MP2	333.3	48 ± 2	456 [5]	36 [5]	6.5
MP3	181.8	95 ± 3	7 [6]	87 [6]	8.4
MP4	130.4	101 ± 1	7 [7]	70 [7]	2.5

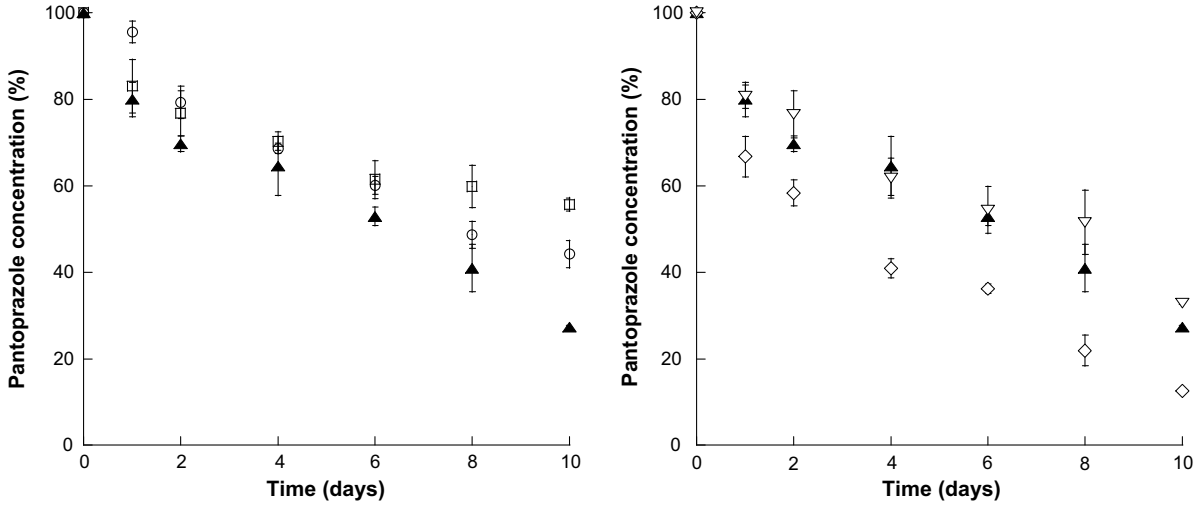

Fig. 3. Pantoprazole concentration after exposure of the pure solid drug (▲), microparticles MP1 (□), MP2 (∇), MP3 (○) and MP4 (◇).

These MP2 microparticles are also hollow, but they are formed of portions of crystalline pantoprazole coated by the two polymers [5]. The addition of HPMC to the microparticles prepared by spray drying caused a reduction of the photostability of pantoprazole ($p < 0.001$). The MP4 microparticles showed that after 10 days of irradiation, only $12.6 \pm 0.3\%$ of the drug was stable (Fig. 3). These microparticles had small particle size (7.5 μm) and high surface area ($70\ m^2\ g^{-1}$). The microparticles containing amorphous pantoprazole and formed by a molecular dispersion of the polymer and the drug stabilized the drug, whereas the microparticles containing crystalline drug did not. Melatonin was encapsulated with tristearin forming a molecular dispersion of the hormone into the lipoparticles [12]. This formulation that presented the slowest release of melatonin among the formulation tested also presented the higher photostabilization of melatonin. In another study, butyl methoxydibenzoylmethane and its complex with hydroxypropyl-β-cyclodextrin were encapsulated in lipospheres of triacetin [20]. The lipospheres containing the sunscreen presented a nearly molecular dispersed state while the complexed drug was amorphous. The lipospheres containing the complex presented higher photostabilization of the sunscreen [20].

Concerning the mathematical modeling of the photodegradation of encapsulated pantoprazole, the microparticles MP1, MP2, MP3 and MP4 followed second order kinetics. The degradation rate constants were 0.00098, 0.00154, 0.00119, 0.00396 $days^{-1}$, respectively and the half-lives of degradation are shown in Table 1.

4. Conclusions

Under UVC light, pantoprazole was demonstrated to be very unstable. In methanol solution, the photodegradation followed zero-order kinetics and was completely degraded after 120 min. In the solid form, pure pantoprazole concentration was reduced to 27% after 10 days of exposure.

The pantoprazole-loaded microparticles showed different effects on the photostability of pantoprazole. The microparticles prepared only with Eudragit S100® demonstrated an increasing of the photostability of the drug. After 10 days of irradiation, 56 and 44% of the drug was stable when encapsulated by emulsification/solvent evaporation and spray drying, respectively. The use of polymer blends did not improve the pantoprazole photostability. The microparticles formed by a solid solution of the polymer and the drug stabilized the drug, whereas the microparticles containing drug crystals did not.

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