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Research paper

Pharmacokinetics evaluation of soft agglomerates for prompt delivery of enteric pantoprazole-loaded microparticles

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ABSTRACT

Soft agglomerates containing pantoprazole-loaded microparticles were developed with the aim of prompt delivery of gastro-resistant particles. The objective was to evaluate the relative bioavailability in dogs after the oral administration of soft agglomerates. Gastro-resistant pantoprazole-loaded microparticles prepared by spray drying were mixed with mannitol/lecithin spray-dried powder and agglomerated by vibration. One single oral dose (40 mg) was administered to dogs. Each dog received either a reference tablet or hard gelatin capsules containing the agglomerates. The plasma profiles were evaluated by non-compartmental and compartmental approaches, and the pharmacokinetic parameters were determined. The agglomerates presented 100% of drug particle loading and a production yield of 80.5%. The amount of drug absorbed after oral dosing was similar after reference or agglomerate administration, leading to a relative bioavailability of 108%. The absorption lag-time was significantly reduced after agglomerate administration (from 135.5 ± 50.6 to 15.0 ± 2.5 min). The agglomerated gastro-resistant pantoprazole-loaded microparticles reduced time to peak plasma. The agglomerates were equivalent to the reference tablets in terms of extent but not in terms of rate of absorption, showing that this formulation is an alternative to single-unit oral dosing with enteric coating and with the advantage of reducing time to effect.

1. Introduction

An improved antisecretory therapy includes the minimization of individual variability in pharmacokinetics and pharmacodynamics, more rapid onset of action, sustained control of intragastric acidity, improved nocturnal acid control and dosing independent of meals [1]. Since proton-pump inhibitors require proton-pump activation for maximal antisecretory effect, they are best administered before meals, because maximal activation of the parietal cell occurs in the presence of food [1].

The enteric coatings necessary to protect the proton-pump inhibitors from acid degradation in the stomach have the disadvantage of delaying their absorption. In this way, some strategies to circumvent this limitation have already been investigated. Orally disintegrating lansoprazole tablets containing enteric-coated pellets were developed. The oral pharmacokinetics of these lansoprazole tablets was identical to those obtained after the administration of conventional capsules of enteric-coated granules [2,3]. Recently, an immediate-release omeprazole formulation (powder for oral suspension) was launched into the market. The formulation consists of pure omeprazole powder 40 mg or 20 mg per unit, with 1680 mg of sodium bicarbonate to be reconstituted with water. This formulation displayed shorter time to peak plasma concentration (T_{max}) and higher peak plasma concentration (C_{max}) than the delayed release of omeprazole pellets. After the administration of an omeprazole solution without bicarbonate, the area under the plasma concentration–time profile was reduced by a factor of 10 compared to the immediate-release formulation [4]. Studies showed that the immediate-release omeprazole formulation with a bedtime dose significantly improved nocturnal gastric acid control without the need for meal-induced activation of proton pumps, suggesting that immediate-release formulations offer a potential advantage in controlling night-time gastric acidity [1,5,6].

Enteric dosage forms can be formulated as single units or as multiple-unit systems. Most enteric-coated formulations are manufactured as a single unit. More recently, multiple-unit systems have

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been developed due to their rapid dispersion in the gastrointestinal tract, maximization of drug absorption, reduction of peak plasma fluctuations and minimization of potential side effects without lowering drug bioavailability [7]. They also reduce variations in gastric emptying rates and overall transit times and are less susceptible to dose dumping compared to single-unit dosage forms [2,8,9].

Pantoprazole is a proton-pump inhibitor which inactivates the final step of the gastric acid secretion pathway in gastric parietal cells of the stomach. It is indicated in the treatment of digestive ulcers, gastro-esophageal reflux disease and, in association with other drugs, in the eradication of *Helicobacter pylori* [10]. Pantoprazole is more stable than its analogues, omeprazole, lansoprazole and especially rabeprazole, under neutral to moderately acidic conditions [11].

Pantoprazole pharmacokinetics presents a marked interindividual variability in many pharmacokinetic parameters after single or multiple oral dosing. Time to peak plasma concentration (T_{max}), for instance, ranged from 2 to 4 h (median 2.8 h) after dosing, and the absolute bioavailability ranged from 67% to 89% (77% on average) after oral administration of a reference 40 mg tablet (Protonix 40 mg Delayed-Release Granules for Suspension, Wyeth Pharmaceuticals). Drug absorption was also delayed by food intake: T_{max} varied from 2.5 ± 1.0 h in fasting subjects to 6.3 ± 4.0 h in fed subjects for the Brazilian reference tablet [12] while the reference tablet in Spain presented a T_{max} of 7.5 ± 7.5 h [13].

In order to obtain a gastro-resistant formulation presenting fast release, pantoprazole-loaded microparticles were prepared by spray drying using Eudragit S100 as enteric polymer [14]. These microparticles had adequate physico-chemical characteristics for oral delivery, caused a prompt dissolution of the drug in pH 7.4 and showed less than 10% pantoprazole degradation after acid exposure for 1 h. Subsequently, the process parameters and the scale up of these microparticles were evaluated and successfully produced [14]. Pantoprazole-loaded microparticles were stable for 6 months (40 °C and 75% RH) [15]. In the *in vivo* anti-ulcer evaluation, the microparticles significantly reduced ulcer formation compared to the pantoprazole aqueous solution. Because pantoprazole is a photolabile drug, the stability under UVC radiation was also studied [16]. Solid pantoprazole presented a degradation half-life under UVC light of 6.5 days. Microencapsulation increased the stability of the pantoprazole, resulting in a degradation half-life of 8.4 days.

Despite the results above, these microparticles did not present adequate technological characteristics to produce tablets, due to their poor flow and high compressibility index [14]. Additionally, after compression, the microparticles were damaged, and the gastro-resistance property was affected [17]. To overcome these drawbacks, soft agglomerates containing the pantoprazole-gastro-resistant microparticles held together by the addition of mannitol and lecithin spray-dried microparticles were designed [17]. These agglomerates showed immediate disintegration and fast release in enteric conditions, without reducing the gastro-resistance or delaying the release of pantoprazole from the microparticles.

Taking into account these findings, the aim of this study was to determine the pharmacokinetic parameters of the agglomerates containing pantoprazole-loaded enteric microparticles in dogs and to compare them with the pharmacokinetic parameters of a commercial pantoprazole tablet.

2. Materials and methods

2.1. Materials

Sesquihydrate sodium pantoprazole was purchased from Henrifarma (São Paulo, Brazil). Lansoprazole was obtained from Sigma (St. Louis, USA). Methacrylic acid copolymer (Eudragit® S100) was kindly given by Almapal (São Paulo, Brazil). Mannitol (Ph. Eur.) was a gift of Lisapharma (Como, Italy), and lecithin (Lipoid S75) was supplied by Lipoid AG (Ludwigshafen, Germany). Pantozol® tablets were produced by Altana Pharma (São Paulo, Brazil). All other chemicals were of analytical grade.

2.2. Methods

2.2.1. Preparation of the agglomerates containing pantoprazole-loaded microparticles

Pantoprazole-loaded microparticles were prepared in a pilot scale spray dryer (Model PSD 52 APV Anhydro, Soeborg, Denmark) using a centrifugal atomizer at 30,000 rpm, inlet temperature of 180 °C, outlet temperature of 65 °C and feed rate of 2 l/h. The sprayed solution was prepared by dissolving Eudragit® S100 (48 g) and pantoprazole (12 g) in NaOH aqueous solution (6 g/l) (final volume of 1 l).

Mannitol and lecithin spray-dried powder was used as the excipient for the agglomeration [17]. This powder was prepared by dissolving mannitol in 90 ml of water, and lecithin in 10 ml of ethanol at 40 °C. Mannitol and lecithin solutions were mixed at the proportion of 87.5:12.5 w/w (mannitol and lecithin, respectively) giving opalescent mixtures. The final solid concentration was 4% (w/v), and the batch volume was 500 ml. Two replicates were spray dried using a Buchi Mini Spray Dryer B-190 (Buchi Laboratoriums-Tecnik, Flawil, Switzerland) with the following conditions: inlet temperature 90 °C, outlet temperature 38–40 °C, feed rate 5.0 ml/min, nozzle diameter 0.7 mm and drying N_2 flow 300 l/h.

The pantoprazole-loaded microparticles and the mannitol/lecithin spray-dried powder were mixed at 1:1 (w/w) ratio in a 300 ml PET container rotating at 40 rpm for 120 min. The mixtures (15 g each) were placed on the top of a stack of two sieves with nominal apertures of 106 and 850 μm, respectively (25 cm diameter sieves, Granutest, Brazil), which were vibrated for 5 min on a sieve shaker (amplitude 1–2; Bertel, Brazil). Agglomerates between 106 and 850 μm were collected. The reprocess of the non-agglomerated powder was repeated five times by crushing the larger agglomerates and vibrating them again [17].

2.2.2. Characterization of the microparticles and the agglomerates

The spray drying yield was calculated by taking the ratio of the sum of all solids weights to the obtained mass, expressed in percentage. The agglomeration yield was calculated by taking the ratio of the initial mixture weight to the mass of the agglomerated obtained, expressed in percentage. The residual moisture was measured by Karl Fisher titration (DL31, Mettler Toledo). The drug loading was assayed by a validated HPLC method [18]. An amount of pantoprazole-loaded microparticles or agglomerates, equivalent to 10 mg of pantoprazole, was weighed and magnetically stirred with 40 ml of 0.05 M NaOH for 1 h in a volumetric flask. The volume was completed to 50 ml, and the drug concentration was determined after filtration (0.45 μm) by HPLC (Perkin Elmer series 200, USA) using a NovaPak C_{18} column (4 μm particle size) (Waters, Ireland). A security guard cartridge C_{18} (4 × 3 mm) (Phenomenex, USA) was used. The mobile phase consisted of acetonitrile/phosphate buffer pH 7.4 (35:65 v/v), the flow rate was 0.9 ml/min, and the drug was detected at 290 nm.

The particle size distribution was determined by laser diffractometry (Mastersizer 2000, Malvern Instruments, London, UK) after dispersion in *iso*-octane. The mean diameter over the volume distribution $d_{4.3}$ was used. The cohesiveness of the pantoprazole-loaded microparticles and the mannitol/lecithin spray-dried powder, as well as the mixtures in different times of the mixing process was measured in a Powder Characteristics Tester, Model PT-N (Hosokawa Microns, Japan) based on the ability of the powder to

pass through sieves under vibration. More cohesive powders form agglomerates which do not pass through the sieves. The morphology of the agglomerates was determined by optical microscopy (Olympus SZ61 Optical Microscope attached to CoolSnap Pro, Media Cibernetics, digital camera).

2.2.3. Pharmacokinetics study

The protocol was approved by the Federal University of Rio Grande do Sul Ethics in Research Committee (# 2007668).

After an overnight fasting (12 h), a single dose (40 mg) of either formulation, reference Pantozol® – Altana Pharma ($n = 7$) or soft agglomerates containing pantoprazole-loaded microparticles ($n = 6$), was orally administered to female dogs weighing 10–15 kg. The agglomerates were filled into 00 hard gelatin capsules for administration. The dose was given with 50 ml of water. The cephalic vein was cannulated using a 22-gauge catheter, and blood samples (1 ml) were withdrawn at pre-dose and up to 12 h post-dose. Blood samples were immediately centrifuged at 5000 rpm, 4 °C, for 7 min, and the plasma was frozen in liquid nitrogen prior to the HPLC analysis. During all of the time of study, dogs had free access to water and, after 3 h of pantoprazole administration, they received a standard meal (200 g, Royal Canan®).

2.2.4. Analytical method

Cold methanol (300 μl) containing 1 μg/ml lansoprazole acetonitrile solution (internal standard) was added to 300 μl of plasma. The samples were vortexed for 2 min and centrifuged at 12,000 rpm for 15 min. The supernatant was collected and analyzed by HPLC (Perkin Elmer series 200) using a NovaPak C_{18} column (4 μm particle size) (Waters, Ireland). A security guard cartridge C_{18} (4 × 3 mm) (Phenomenex, USA) was used. The mobile phase consisted of acetonitrile/phosphate buffer pH 7.4 (30:70 v/v), the flow rate was 0.9 ml/min, the detector wavelength was set at 290 nm, and the injection volume was 50 μl. The method was validated according to ICH [19] for concentration range between 0.04 and 4.00 μg/ml.

2.2.5. Pharmacokinetic and statistical analysis

Pharmacokinetic parameters were calculated from the individual profiles by non-compartmental approach [20]. The peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were obtained by the visual inspection of the individual profiles. The area under the plasma concentration–time curve ($AUC_{0-\infty}$) was calculated by linear trapezoidal rule (AUC_{0-t}) plus extrapolation of the terminal phase (C_t/ke), where C_t is the concentration of the last sampling time. To calculate the elimination rate constant (ke), regression analyses were performed on the ln of plasma concentration in values versus time at the terminal phase of the plasma profile. The half-life ($t_{1/2}$) was calculated as $\ln 2/ke$.

The relative bioavailability (f_{rel}) was calculated by Eq. (1), where "ref" and "test" correspond to the reference tablet and the agglomerates, respectively.

$$f_{rel} = \left(\frac{AUC_{0-\infty}, test}{AUC_{0-\infty}, ref}\right) * 100 \quad (1)$$

A compartmental analysis was carried out on the individual profiles by adjusting the data to a one compartmental model with lag-time (t_0) using:

$$C_p = D * \frac{F}{V_d} * \left(\frac{ka}{ka - ke}\right) * \left(e^{-ke(t-t_o)} - e^{-ka(t-t_o)}\right) \quad (2)$$

where C_p = plasma concentration, D = dose (40 mg), ka = absorption rate constant, t = time, V_d = volume of distribution and F = bioavailability. For modeling, the term F/V_d was named y, and it was determined as a single value. Curve fitting was performed using Micromath Scientist® software. All data were weighted equally. The suitability of the model to fit the data was evaluated by visual inspection of the plots, correlation coefficient and model selection criteria (MSC) were given by the software.

The Eq. (3) was used to calculate the time to reach peak concentration based on the constants ka and ke and it was called T'(estimation of time to peak). The T' does not take into account the lag-time (t_0):

$$T' = \frac{\text{in}(ka/ke)}{(ka - ke)} \quad (3)$$

Total clearance (CL/F) was estimated by:

$$CL/F = \frac{D}{AUC_{0-\infty}} \quad (4)$$

An analysis of variance (ANOVA) ($\alpha = 0.05$) was performed on the pharmacokinetic parameters. In order to compare standard deviations an F-test was performed by the software StatGraphics® ($\alpha = 0.05$).

3. Results

3.1. Characterization of the soft agglomerates

Pantoprazole-loaded microparticles were obtained by spray drying with the yield of 78%, residual moisture of 2.4%, mean diameter of 28.3 μm, drug loading of 161.1 ± 0.8 mg/g and encapsulation efficiency of 97.9 ± 0.5%. Microparticle cohesiveness was 12% and did not agglomerate per se. These characteristics were consistent with those previously reported, confirming the reproducibility of the process [14,17].

The mannitol/lecithin excipient was prepared with the yield of 57%, residual moisture of 1.3% and mean size of 5.02 μm presenting a high cohesiveness (44%). The agglomeration yield (80%) was similar to the value previously reported (76%) [17]. The agglomerates had a drug loading of 80.3 ± 0.4 mg of pantoprazole per gram of agglomerates. The agglomerates had a spherical shape with rough surface (Fig. 1). The size distribution of the agglomerates after redispersion in *iso*-octane presented two populations, one of 5 μm corresponding to the mannitol/lecithin excipient original size and the other of 30 μm corresponding to the pantoprazole-loaded microparticles original size. No additional peaks were observed.

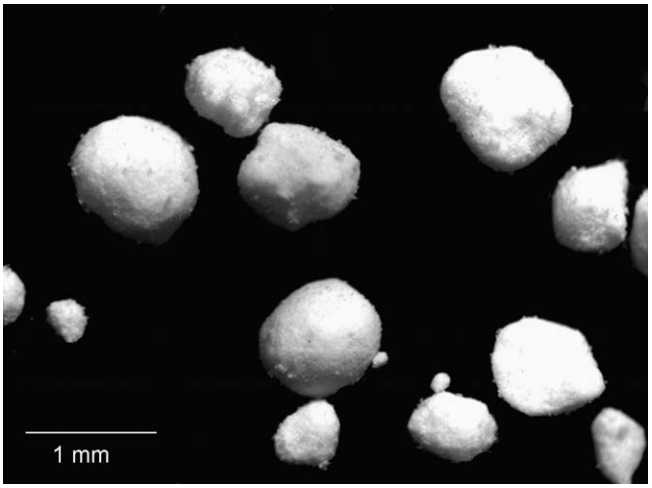

Fig. 1. Optical image of the agglomerates.

3.2. Validation of the analytical method for the determination of pantoprazole in plasma

The analytical method presented a limit of quantification of 0.04 μg/ml and a linear calibration curve from 0.04 to 4.00 μg/ml, with a correlation coefficient of 0.998. Quality control limits of 0.08, 0.40 and 1.80 μg/ml showed standard deviations of 1.28%, 1.34% and 1.73%, respectively. The accuracy values were 106.63 ± 0.02%, 102.44 ± 0.43% and 105.15 ± 1.48%, respectively. Mean plasma recovery was 95%. These results were in accordance with the criteria of ICH for bioanalytical methods [19].

3.3. Pharmacokinetic analysis

The pharmacokinetic parameters estimated by non-compartmental analysis are shown in Table 1. There was no significant difference between the $AUC_{0-\infty}$ of the reference tablets and the agglomerates after oral administration to dogs, with average values of 215 ± 75 and 232 ± 194 μg min/ml, leading to a relative bioavailability of 108%. The microencapsulation and the agglomeration processes did not influence the extent of pantoprazole absorption. There was no difference in the variability (deviations) of the parameter $AUC_{0-\infty}$ between agglomerates and reference tablet. The elimination rate constant, and consequently the half-life, did not show a significant difference between the reference tablets and the agglomerates. The same was true for C_{max}. For the C_{max}, the deviations of the values found for the reference tablet and the agglomerates were not statistically different ($\alpha = 0.05$). After the administration of Pantozol®, a large variability was observed in terms of T_{max} (Fig. 2). This variability was reduced after the administration of the agglomerates (Fig. 2).

On the other hand, the T_{max} was reduced after the agglomerate administration from 180.0 ± 99.5 min to 47.5 ± 11.3 min ($p < 0.0002$) due to the large difference observed in the lag-time (Table 2). Although the agglomerates did not significantly improve the pantoprazole bioavailability, the time to reach the peak plasma was reduced showing an advantage of the multiple-unit systems in comparison with enteric-coated tablets. Furthermore, the agglomerates presented a reduction in the T_{max} variability with *F*-test showing *p*-value of the comparison of the standard deviations of 0.0002.

The individual profiles were fitted to the one compartment model with lag-time. Fig. 3 shows a representative fit for each formulation. The model adequately described the data for both formulations showing correlation coefficients ranging from 0.988 to 0.998 for the reference tablets and from 0.874 to 0.995 for the agglomerates, and MSC ranging from 3.09 to 5.28 for the reference tablets and from 0.96 to 4.05 for the agglomerates. The mean

Table 1
Mean pharmacokinetic parameters of pantoprazole for both reference tablet and agglomerates after oral administration of 40 mg to dogs.

Parameters	Reference tablet	Agglomerates
AUC_{0-t} (μg min/ml)	212 ± 75	230 ± 192
$AUC_{0-\infty}$ (μg min/ml)	215 ± 75	232 ± 194
ke (min^{-1})	0.021 ± 0.007	0.028 ± 0.007
$t_{1/2}$ (min)	36.0 ± 13.5	26.0 ± 6.0
C_{max} (μg/ml)	2.36 ± 0.69	3.16 ± 1.95
T_{max} (min)	180.0 ± 99.5	47.5 ± 11.3[a]
CL/*F* (L/min)	0.21 ± 0.07	0.42 ± 0.17

AUC_{0-t} = area under the plasma concentration–time curve from time 0 to 12 h; $AUC_{0-\infty}$ = area under the plasma concentration–time curve from time zero to infinity; *ke* = elimination rate constant; $t_{1/2}$ = elimination half-life; C_{max} = peak plasma concentration; T_{max} = time to the peak plasma concentration and *CL*/*F* = clearance/bioavailability.
[a] $\alpha = 0.05$.

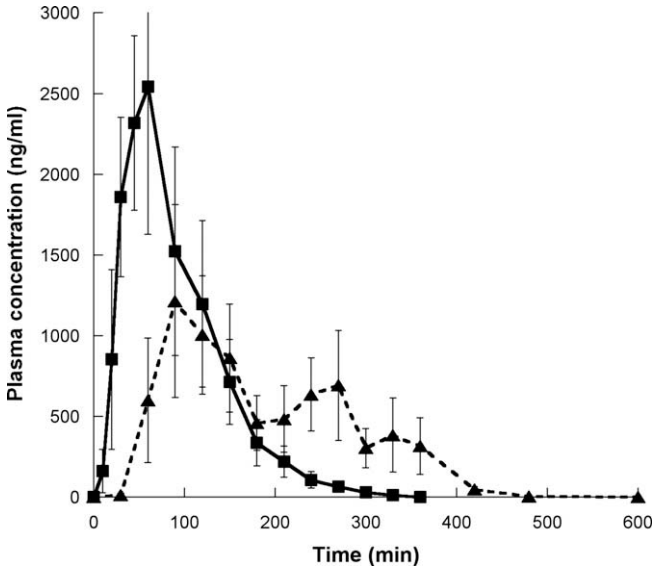

Fig. 2. Mean plasma concentration profiles of animals after administration to dogs with a single dose of 40 mg pantoprazole as one tablet of Pantozol® ($n = 7$) (▲) and as agglomerates (filled in a hard gelatin capsule) ($n = 6$) (■).

Table 2
Pharmacokinetic parameters estimated by fitting the individual data after oral administration of 40 mg of pantoprazole to a one compartmental model with lag-time.

Parameters	Reference tablet	Agglomerates
ka (min^{-1})	0.035 ± 0.003	0.055 ± 0.014
ke (min^{-1})	0.026 ± 0.006	0.018 ± 0.003
t_0 (min)	135.5 ± 50.6	15.0 ± 2.5[a]
y (1/L)	0.130 ± 0.011	0.125 ± 0.036
T' (min)	35.8 ± 4.7	36.0 ± 6.9

ka = absorption rate constant; *ke* = elimination rate constant; t_0 = lag-time; $y = F/V_d$ = bioavailability/volume of distribution and *T'* = estimated time to peak plasma concentration.
[a] $\alpha = 0.05$.

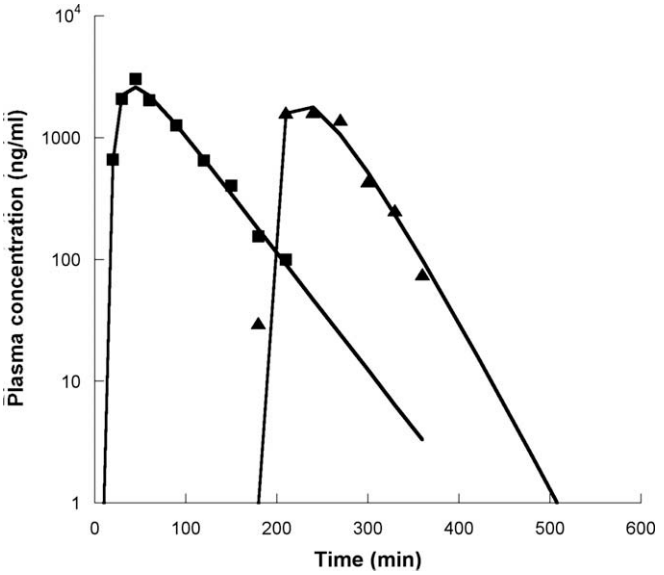

Fig. 3. Representative individual plasma concentration–time profiles after administration to dogs of a single 40 mg dose of pantoprazole as Pantozol® tablets (reference) (▲) or hard gelatin capsules containing agglomerates (■). Lines indicate fit to the one compartmental model with lag-time.

parameters and the standard deviations are shown in Table 2. The absorption rate constant showed no statistical difference: $0.035 \pm 0.003\ min^{-1}$ for the reference tablet and $0.055 \pm 0.014\ min^{-1}$ for the agglomerates. The elimination rate constants obtained by modeling were 0.026 ± 0.006 and $0.018 \pm 0.003\ min^{-1}$, statistically similar as well. The lag-time for the reference plasma profile was 135.5 ± 50.6 min, and it was significantly reduced to 15.0 ± 2.5 min ($p < 0.01$) when the agglomerates were administered. The estimated time to peak plasma (T'), however, was similar for both formulations, 35.8 ± 4.7 and 36.0 ± 6.9 min for the reference tablet and the agglomerates respectively, due to the similarity of *ka* and *ke* for both formulations.

4. Discussion

The cohesiveness was a key parameter in the formation of the agglomerates, and it was achieved by using a population of spray-dried microparticles made of mannitol and lecithin. The increase in cohesiveness during the mixing of these microparticles with the pantoprazole gastro-resistant microparticles was responsible for the high agglomeration yield. The agglomeration did not affect the drug stability and did not change the original size of the pantoprazole-loaded microparticles and the mannitol/lecithin excipients. Compared to our previous work [17], the agglomeration yield was increased. We can presume that the controlled mixing process was responsible for improving the overall process and the production yield.

The plasma concentration profiles after the administration of sodium pantoprazole showed a large variability among individuals (Table 1), as previously reported in studies evaluating the bioequivalence of pantoprazole enteric-coated tablets (40 mg) in healthy human subjects [12,21,22]. Campos and co-workers [21] found $AUC_{0-\infty}$ of 6500 ± 4948 ng h/ml and Lou and co-workers [22], values of 10.58 ± 7.80 μg h/ml, for the reference tablets in Brazil and China, respectively. Comparing fasting and fed subjects, Mendes and co-workers [12] found 5348 ± 5793 ng h/ml for the fasting subjects and 4765 ± 2975 ng h/ml for the fed subjects. The large difference among individuals was due to the extensive metabolization of pantoprazole to inactive metabolites in the liver, primarily by cytochrome P450 (CYP) isoforms CYP2C19 and CYP3A4, both highly variable among individuals [22].

The pharmacokinetic parameters for the reference tablets and the agglomerate administration in dogs were similar. No statistical differences were observed concerning the extension of the absorption, clearance, volume of distribution, elimination half-life, absorption and elimination rate constants and the peak plasma concentrations. The agglomerates provided an increase of 8% in extent of bioavailability compared to the enteric tablets, without clinical significance. Corroborating to *in vitro* gastro-resistance tests [17], no significant degradation of pantoprazole occurred in the presence of acid medium when microencapsulated. The agglomerates were able to protect pantoprazole from stomach acid medium to the same extent as conventional enteric-coated tablets.

In humans, T_{max} varied from 2.2 to 3.2 h [21,22]. Similar T_{max} values were found after the administration of the reference tablets to dogs (3.0 ± 1.7 h). For the agglomerates, however, a shorter time to peak was observed (0.8 ± 0.2 h) with a smaller variability. The difference in T_{max} between reference tablets and agglomerates found in dogs can be explained by the gastric emptying time. In the case of a large solid, such as conventional single-unit tablets, the emptying from the stomach appears to be delayed which can be attributed to the influence of peristalsis on gastric emptying and in the gastrointestinal tract. On the other hand, the gastric emptying of pellets with a size lower than 1.4 mm is almost as fast as liquid emptying, occurring within minutes of intake [23].

A previous report compared the pharmacokinetics of pantoprazole enteric-coated tablets and a suspension prepared with crushed tablets dispersed in 0.5 M sodium bicarbonate solution [24]. The relative bioavailability of the suspension was 75%, but with a shorter T_{max} (0.60 ± 0.66 h) compared to the tablets (2.5 ± 0.5 h). This suspension was proposed as an alternative for patients who cannot swallow tablets, however patients with delayed gastric emptying are not indicated to take this formulation because the contact with sodium bicarbonate in the stomach would be too long [24].

In this context, the agglomerates reduced the lag-time to reach plasma levels by a factor of 9, shortening the time to pharmacological response and producing a more uniform time to effect which is advantageous to patients. In the treatment of peptic ulcers, patients need to have the pain suppressed rapidly and efficiently [25], for this there is an advantage to the agglomerates compared to classic single-unit tablets. Although the agglomerates presented only a slightly higher bioavailability than the enteric-coated tablets, the dose can be easily divided in this formulation without losing the gastro-resistance. Furthermore, the agglomerates can be easily administered in different ways: hard gelatin capsules containing agglomerates and direct administration of the agglomerates or dispersion of the agglomerates in water for drinking or feeding via nasogastric tube, allowing the access of all patients to the oral dosing. Based on the benefit of immediate-release omeprazole [1,5,6], the agglomerates have the potential advantages of not needing meal-induced activation and improved control of nocturnal gastric acidity. As far as we know, this is the first report of an enteric drug delivery system with reduced time to effect based on microparticles.

5. Conclusions

The pantoprazole-loaded enteric microparticles were successfully agglomerated by mixing them with spray-dried mannitol/lecithin powder, giving high yield and complete drug microparticle agglomeration. After the redispersion of the agglomerates in water, the primary pantoprazole particle sizes were recovered. There was no significant degradation of pantoprazole levels in the stomach when administered in the form of agglomerates. The agglomerates containing pantoprazole were equivalent to the reference tablets in terms of extent but not in terms of rate of absorption. The time to peak plasma concentration was reduced by a factor of 9 when the agglomerates were administered. The soft agglomerates were shown to be a viable alternative for pantoprazole oral dosing for any kind of patient, being bioequivalent to tablets, but with the advantage of reduced time to effect.

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