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Article

Development of microparticles and microparticulated tablets containing piperine

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Piper nigrum (black pepper) is used in Indian traditional medicine and its main alkaloid, Piperine (PIP), presents antioxidant, antitumor and neuroprotective pharmacological properties. This substance is insoluble in aqueous media and can irritate the gastrointestinal tract. Aiming to avoid these inconvenient characteristics and enable PIP oral administration, this study suggested the PIP microencapsulation through the emulsion-solvent evaporation method and the preparation of microparticulated tablets by direct compression. An UV-spectroscopy method was validated to quantify PIP. Microparticles and microparticulated tablets were successfully obtained and the microparticles exhibited excellent flow. The scanning electron microscopy images showed that PIP microparticles were intact after compression. The *in vitro* release showed a controlled release of PIP from microparticles and PIP microparticles from tablets in comparison to PIP and PIP tablets. The release profiles of PIP microparticles and the microparticulated tablets were similar. Therefore, tablets containing PIP microparticles are promising multiparticulated dosage forms because a tablet allows microparticles administration and the intact ones promote a controlled release, decreasing its irritating potential on the mucosa.

Keywords: Ethylcellulose. *Piper nigrum.* Compression. Microencapsulation. Polacrilin potassium.

INTRODUCTION

Piperine (PIP) is found in plants of the *Piper* genus, mainly *Piper nigrum* L., the popular black pepper. Besides its use as a spice, its seeds are used for gastric and respiratory disorders, fevers and obesity (Ahmad *et al*., 2012). Being this species major alkaloid, PIP has been the object of many researches, which found several pharmacological activities in this compound, such as antioxidant (Umar *et al*., 2013; Dey *et al*., 2020), antitumor (Greenshields *et al*., 2015; Yaffe *et al*., 2015) and neuroprotective properties (Wang *et al*., 2019; Liu *et al*., 2020). In addition, PIP has the ability to increase other drugs bioavailability (Bi *et al*., 2019; Izgelov Domb, Hoffman, 2020).

A recent study, sponsored by the International Organization of the Flavor Industry, was conducted to evaluate PIP safety when used as a flavoring substance (Bastaki *et al*., 2018). A 90-day toxicological study was performed in Sprague-Dawley rats with doses of 5, 15 e 50 mg/kg/day. No significant toxicity clinical signs were observed in any of the doses tested and, in conclusion, the NOAEL (No Observed Adverse Effect Level) of PIP was determined at the amount of 50 mg/kg/day. However, this substance is insoluble in water and when orally administered causes irritation throughout its gastrointestinal pass due to its pungency (Rentmeister-Bryant, Green, 1997; Dessirier *et al*., 1999; Butt *et al*., 2013).

Controlled release systems favor the administration of irritant and low water-soluble agents, such as PIP. Considering this, polymeric microparticles are drug release systems presenting sizes ranging from 1 to 1000 μm and prepared using synthetic or natural polymers.

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Considering morphological characteristics, they can be vesicular and matrix systems where the drug can be molecularly dispersed or physically retained (Brown, 2004). These drug carriers are able to provide important advantages to encapsulated drugs, such as taste masking, drug release control and enhance powder flow properties (Ghosh, 2006; Lam, Gambari, 2014).

There are some PIP microparticles described in the literature. Bonepally (2008) developed PCL microparticles containing PIP by O/W emulsion evaporation method. Different batches were prepared with different drugs using polymer proportions and with or without polysorbate 80 in aqueous phase. Pengpong *et al*. (2014) used modified chitosan as polymers to prepare PIP microparticles with 1 to 5% PIP by electrospray ionization.

Zhu *et al.* (2020) developed fast disintegrating tablets containing PIP matrix pellets, aiming to have a sustained *in* vitro release and an improved *in vivo* bioavailability. The pellets were based on a PIP solid dispersion and hydroxypropylmethyl cellulose and were prepared by the extrusion spheronization method. Granules were prepared with lactose, microcrystalline cellulose, low-substitution hydroxypropyl cellulose and carboxymethyl starch sodium by wet granulation and then they were mixed with PIP pellets and compressed to form the fast disintegrating tablets.

In this way, this study aimed to develop ethylcellulose microparticles containing PIP. Ethylcellulose (EC) is a nontoxic, nonallergenic and nonirritating long-chain polymer obtained from cellulose ethoxylation widely used in oral formulations (Rowe, Sheskey, Quinn, 2009; Murtaza, 2012). Its coatings are commonly used to modify the release of the associated active and mask unpleasant tastes (Rowe, Sheskey, Quinn, 2009). Despite their potential, microparticles are rarely employed as dosage forms and for this reason; the compression of microparticles in tablets was an objective in this study as well. This dosage form is the most used for oral administration, presenting some advantages as good patient acceptability and cost-effectiveness relation, besides less concern about sterility (Krishnaiah, 2010).

MATERIAL AND METHODS

Material

PIP (Fagron, Brazil – 98% w/w, from China; CAS number 94-62-2) was used; Tween® 80 (Polysorbate 80) from Vetec (Rio de Janeiro, Brazil); Ethocel® 10 (ethylcellulose) was kindly donated from Colorcon (São Paulo, Brazil), Kyron® T-314 (Polacrilin potassium) was kindly donated by Almapal (São Paulo, Brazil); Pullulan was kindly donated by Corn Products (São Paulo, Brazil). Absolute ethanol and methanol were purchased from Dinâmica (São Paulo, Brazil), dichloromethane from Neon (São Paulo, Brazil); Ultrapure water was purified by the Synergy UV Millipore apparatus (Porto Alegre, Brazil).

PIP-loaded microparticles preparation

Ethylcellulose microparticles containing PIP (PIP-MP) were prepared in triplicate by O/W emulsion and solvent evaporation method. An organic phase (EC – 1 g, ethanol – 12 mL, dichloromethane – 8 mL, and PIP – 0.5084 g), in which PIP was dissolved, was injected using mechanical stirring (IKA, Germany) in an aqueous phase (polysorbate 80 – 0.4 g and ultrapure water – 80 mL). This emulsion remained being stirred for two hours to evaporate the solvents, and then it was filtered (8 μm) and washed with purified water for surfactant removal. In sequence, the powder was placed in the oven at 30 ºC for 15 hours and after the microparticles were collected and kept in a desiccator for further characterization. Blank microparticles (B-MP), without PIP, were also prepared for comparison purposes.

Analytical method validation

For samples preparation, methanol was the chosen solvent. Analyses were performed at 343 nm in a UV Spectrophotometer (UV 1800, Shimadzu Corporation), using methanol as blank. The method was tested for its specificity, linearity, precision (repeatability and intermediate precision), accuracy (spike recovery method) and robustness (varying wavelength and methanol supplier), according to ICH Guidelines (2005).

Before samples analysis, 15.1 mg of PIP-MP, equivalent to 5 mg of PIP, were diluted in 25 mL of methanol and stirred at 1100 rpm for 10 minutes. After, an aliquot of 1 mL of this solution was diluted in 20 mL of methanol, obtaining a concentration of 10 µg/mL.

Microparticles characterization

The microparticles were evaluated regarding organoleptic characteristics, process yield, particle size distribution, encapsulation efficiency, drug loading, bulked and tapped densities, Carr index, Hausner factor and morphology.

The process yield was calculated by the ratio between the weight of microparticles obtained and the sum of PIP weight and EC used in the preparation (equation 1):

$$Y = \frac{\text{Weight of MP obtained}}{\text{Weight of PIP + EC}} \times 100 \quad (1)$$

The particle size distribution was determined by laser diffraction (Mastersizer 3000E, Malvern Instruments, UK) after previous dispersion of the sample in water (1:10) with two drops of polysorbate 80. PIP encapsulation efficiency (EE) in the microparticles was determined, in triplicate, by UV Spectrophotometry with the validated method described for the treatment of samples in the "Analytical method validation" section. EE was expressed as a percentage, relating sample and standard solution concentration. Drug loading (DL) was determined from the EE obtained and the theoretical drug loading (331.5 mg PIP/g MP) (equation 2):

$$DL = \frac{EE \times \text{Theoretical DL}}{100} \quad (2)$$

The bulk volume was the volume occupied by approximately 1 g of PIP-MP in a 10 mL graduated cylinder. The bulk density was calculated by the ratio between the exact weight and the bulk volume (equation 3):

$$d_B = \frac{\text{PIP-MP weight}}{\text{bulk volume}} \quad (3)$$

The tapped volume was the volume occupied by PIP-MP after 1250 taps (PharmaTest, Brazil) and tapped density was determined by the ratio between the weight of the microparticles and tapped volume (equation 4):

$$d_T = \frac{\text{PIP-MP weight}}{\text{tapped volume}} \quad (4)$$

Carr's index and Hausner ratio were calculated by equations 5 and 6, respectively:

$$CI = \frac{d_T - d_B}{d_T} \times 100 \quad (5)$$

$$HR = \frac{d_T}{d_B} \quad (6)$$

For the morphological analysis, the microparticles were previously gold-coated (Desk II Gold Sputter, Denton Vacuum, USA) and analyzed by scanning electron microscopy (SEM) with an accelerating voltage of 10 kV (Scanning microscope JSM-6360, Jeol, Japan).

Process yield, mean particle size and size distribution, bulk density, tapped density, Carr's index, and Hausner ratio, as well as SEM microphotographs were performed with B-MP for comparison purposes.

PIP *in vitro* release from microparticles

PIP *In vitro* release was performed in a dissolution test equipment (PharmaTest, Brazil) with apparatus 1 (basket). The release medium chosen was 0.1 M hydrochloric acid containing 2% sodium dodecyl sulfate (SDS), which enabled almost total solubilization of PIP in the tablet during the experiment and maintained sink conditions. An amount of PIP microparticles (equivalent to 20 mg PIP, n=3) was weighed inside the baskets, which were put in 900 mL of the selected release medium, under 37 ºC and 100 rpm. The equipment was protected from the light. The assay was carried out for 24 hours and at predetermined times 5 mL of the medium were collected and the same volume was replaced with fresh medium kept at 37 ºC. The sample was filtered through a 28 µm filter and the PIP content was quantified by the validated UV-spectroscopy method. The test was performed with free PIP (20 mg, n=3) in the same conditions for comparison. After, data was analyzed according to zero (%PIP release *versus* time) and first order (ln %PIP release *versus* ln time) equations (by Microsoft Excel).

Preparation of tablets containing PIP-loaded microparticles

PIP-loaded microparticles (equivalent to 20 mg PIP) were mixed in a glass mortar with dissolution improver polacrilin potassium Kyron® T-314 (6%, w/w) and the diluent Pullulan in enough quantity to produce tablets with theoretical mean weight of 100 mg. After, this mixture was compressed by direct compression in a single punch machine (Farmacista Equipamentos Farmaceuticos Ltda, Porto Alegre, Brazil), in manual mode.

Characterization of tablets containing PIP-loaded microparticles

The tablets were characterized according to assays described in FB 5 (2010). Weight determination was performed by weighing of 20 tablets (Metler-Toledo, Brazil); hardness assay of 10 tablets using a portable hardness tester (Ethik Technology, Brazil); friability of 20 tablets submitted to 100 rpm (25 rpm for 4 minutes) in a friabilometer (Ethik Technology, Brazil); thickness of 10 tablets using a caliper (Mitutoyo, Brazil).

For the uniformity of dosage units, the content uniformity was performed as follows: the tablets (n=10) were individually triturated in a glass mortar with a pestle, transferred to a 25 mL volumetric flask and agitated at 1100 rpm for 10 minutes. Then, the volume was completed with methanol to obtain a theoretical concentration of 10 µg/mL. The actual PIP content was determined by the validated UV method and the acceptance value (AV) was calculated, according to equation 7. AV calculated should be below 15, as stated by the Brazilian Pharmacopoeia methodology (FB 5, 2010).

$$AV = |M - X| + k.s \quad (7)$$

X = mean of individual contents (n=10), s = standard deviation, k = acceptability constant (if n = 10, k = 2.4; if n = 30, k = 2.0), M = reference value (if 98.5≤X≤101.5, M=X; if X≤98.5, M=98.5; if X>101.5, M=101.5)

To determine a batch drug loading, 3 tablets were triturated and 25 mg of the powder were transferred to a 25 mL volumetric flask, extracted, diluted and quantified as described for content uniformity (n=3).

PIP *in vitro* release from tablets

PIP *in vitro* release from tablets was performed as described for the microparticles, in the section "PIP *in vitro* release from microparticles". The tablets (n=3) were previously weighed for further adjustment of PIP content and tablets containing free PIP, Pullulan and polacrilin potassium (6%, w/w; n=3) were assayed for comparison purposes observing the same conditions.

RESULTS AND DISCUSSION

Analytical method validation

The analytical method proposed was specific and linear in the range of 0.5 to 20 µg/mL with a correlation coefficient close to the unit (r = 0.9999; y= 0.12381x - 0.00975); significant linear regression (F calculated = 82902.04>F tabulated = 4.75) and no significant linearity deviation (F calculated = 2.67<F tabulated = 3.26). The limit of detection and quantification were 0.05 and 0.16 µg/mL, respectively.

It was also precise with RSD 0.55% for repeatability and 0.64% for intermediate precision, and accurate, with a mean recovery of 99.28 ± 1.00 %. Furthermore, the method was robust, since small variations in wavelength and the solvent from a different supplier did not affect the PIP quantification in the microparticles.

Microparticles characterization

PIP microparticles (PIP-MP) were prepared by O/W emulsion and solvent evaporation method. The powder appeared to be free flowing and presented light yellow color and weak odor, both being PIP characteristics. Microparticles prepared without PIP were also free flowing; however, the powder was white and presented EC odor characteristics.

SEM images of the microparticles showed a spherical surface, more evident for B-MP (Figure 1). In addition, B-MP exhibited an almost porous

surface, which was not so noticeable in PIP-MP. It should be observed that certain porosity is expected for the emulsion evaporation method because of the solvent evaporation step (Morales *et al*., 2010). The micrographs also suggest that the PIP presence modified the microparticles surface.

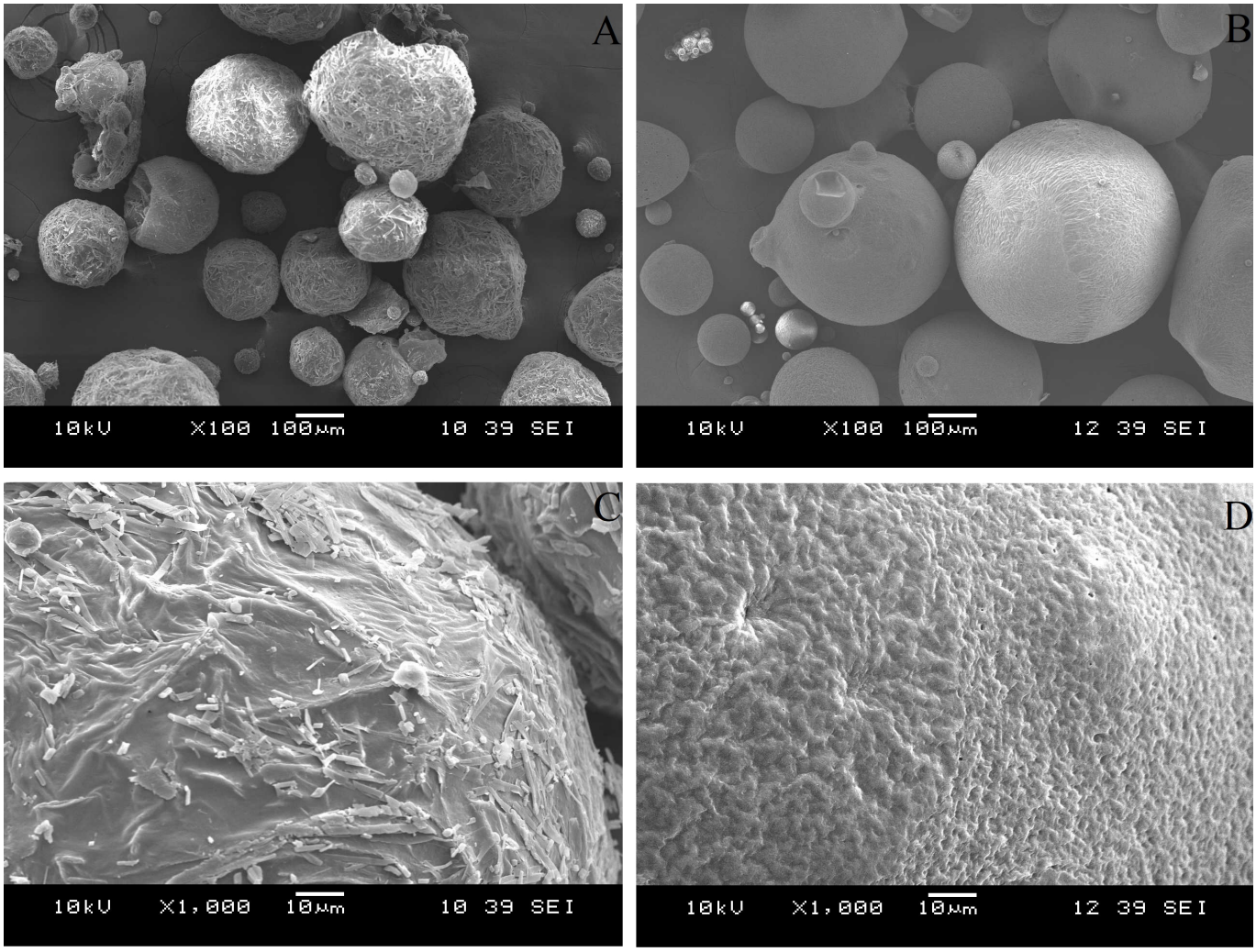

FIGURE 1 – Scanning electron micrographs of PIP-MP (A) and B-MP (B) with magnification of 100x and PIP-MP (C) and B-MP (D) with 1000x.

Regarding the process yield, PIP-MP preparation presented 97.6% yield, which was higher than the preparation of microparticles without PIP ($p<0.05$) as shown by Table I. PIP encapsulation efficiency was 90%, corresponding to a drug loading of approximately 300 mg PIP/g. Bonepally *et al.* (2008) prepared PCL microparticles containing PIP and had an encapsulation efficiency of 50% at maximum. Pengpong *et al.* (2014) prepared chitosan microparticles with PIP using electrospray ionization and obtained 84% of encapsulation efficiency. For this reason, through a relatively simple preparation method it was possible to obtain a good encapsulation efficiency, which can be attributed to the low PIP aqueous solubility in water, which provides a suitable substance entrapment in the microparticles.

TABLE I – Process yield, encapsulation efficiency, drug loading, mean particle size and span of the microparticles containing PIP (PIP-MP) and without PIP (blank microparticles – B-MP) (n=3; mean ± standard deviation)

Formulation	Yield (%)	Encapsulation Efficiency (%)	Drug loading (mg/g)
PIP-MP	97.6 ± 0.3	90.0 ± 0.9	298.3 ± 2.9
B-MP	94.3 ± 0.2	--	--

The PIP-containing microparticles presented a lower size than those without the PIP ($p<0.05$), as shown in Table II. Both PIP-MP and B-MP presented span close to 2 ($p>0.05$), indicating a slight polydispersion in terms of particle size, which can be corroborated by the SEM images. Bonepally *et al.* (2008), using the same preparation method with different polymers, obtained smaller particles than those obtained in this work, which may result in a worse flow, once the size of the microparticles influence on powder flow properties.

TABLE II – Particle sizes and span of the microparticles containing PIP (PIP-MP) and without PIP (blank microparticles – B-MP) (n=3; mean ± standard deviation)

Formulation	Dv (10) (µm)	Dv (50) (µm)	Dv (90) (µm)	D [4,3] (µm)	Span
PIP-MP	53 ± 18	171 ± 15	344 ± 27	190 ± 13	1.698 ± 0.180
B-MP	77 ± 1	329 ± 28	763 ± 24	376 ± 17	2.085 ± 0.110

When analyzing the particles size, it is possible to suggest that PIP exerts a surface activity, once its existence in the microparticles not only reduces their size but also improves the size distribution. Therefore, in the emulsion step of the preparation method, PIP could be located in the interface of the droplets, reducing the system energy and, consequently, the droplets size. As the solvents evaporate and the small droplets generate the microparticles, consolidating them, PIP could act modifying the droplets surface. In the SEM images of PIP-MP and B-MP (Figure 1), it becomes clear that PIP modifies the surface of the microparticles, corroborating the PIP surface activity hypothesis.

The microparticles flow properties study is fundamental to define which excipients are required to compress that powder, mainly when using direct compression (Koo, 2016). Besides, in compressing microparticles, as they will be under stress, it is very important to prevent ruptures so the excipients need to be able to provide mechanical protection (Heng *et al*., 2000).

Bulk density and tapped density values are listed in Table III. PIP-MP bulk density value is higher than the one obtained for B-MP, showing a lower volume occupied by the powder, which is interesting for storage purposes. In addition, as the preparation of tablets is an objective in this study, this enables the obtainment of smaller tablets, which will be easier to swallow.

TABLE III – Densities and flow properties of the microparticles containing PIP (PIP-MP) and without PIP (blank microparticles – B-MP) (n = 3; mean ± standard deviation)

Formulation	Bulk density (g/cm3)	Tapped density (g/cm^3)	Carr Index (%)	Hausner ratio
PIP-MP	0.25 ± 0.05	0.28 ± 0.05	11 ± 2	1.13 ± 0.02
B-MP	0.15 ± 0.03	0.16 ± 0.03	5 ± 1	1.06 ± 0.03

PIP-MP tapped density was 0.28 ± 0.05 g/cm^3 and for B-MP, 0.16 ± 0.03 g/cm^3. The reason for this difference is the size: B-MP is almost twice the size of PIP-MP and, as the compaction of PIP-MP occurs, the particles are settled among each other, showing a smaller volume.

Besides, bulk density and tapped density of MP-PIP and B-MP were used to calculate Carr Index and Hausner ratio (Table III). According to Leturia *et al.* (2014), values of Carr Index below 15 and Hausner ratio below 1.25 indicated an excellent flow, and both PIP-MP and B-MP presented this behavior. Even though the PIP presence increased the Carr index and Hausner ratio ($p<0.05$), they were still in the same range.

PIP *in vitro* release from microparticles

The microencapsulation of drugs using EC as a polymer is mostly explored by its ability to control the release of the drug associated (Rogers, Wallick, 2012; Murtaza, 2012). PIP *in vitro* release from EC microparticles was assayed and compared to bulk PIP. The test was performed for 24 hours in a dissolution tester with 0.1 M hydrochloric acid containing 2% SDS as a release medium, keeping sink conditions.

According to the release graphic representation, PIP-MP displayed two release phases: a burst phase within the first hour, which may be because of the PIP present in the surface of the microparticles, and a controlled phase, from 2 hours on. Considering the correlation coefficients obtained for the data adjustment to zero ($r = 0.9655$) and first order ($r = 0.9438$), the best fit was zero order, which characterizes a controlled release.

In the first 10 minutes, pure PIP release was 27.4 ± 0.6% (Figure 2). On the other hand, PIP release from microparticles, in the same time, was 12.2 ± 0.9%. These results and the release profile demonstrated that the microparticles were able to control the PIP release until the end of the experiment where approximately 81% of PIP and 35% of PIP were released from the microparticles.

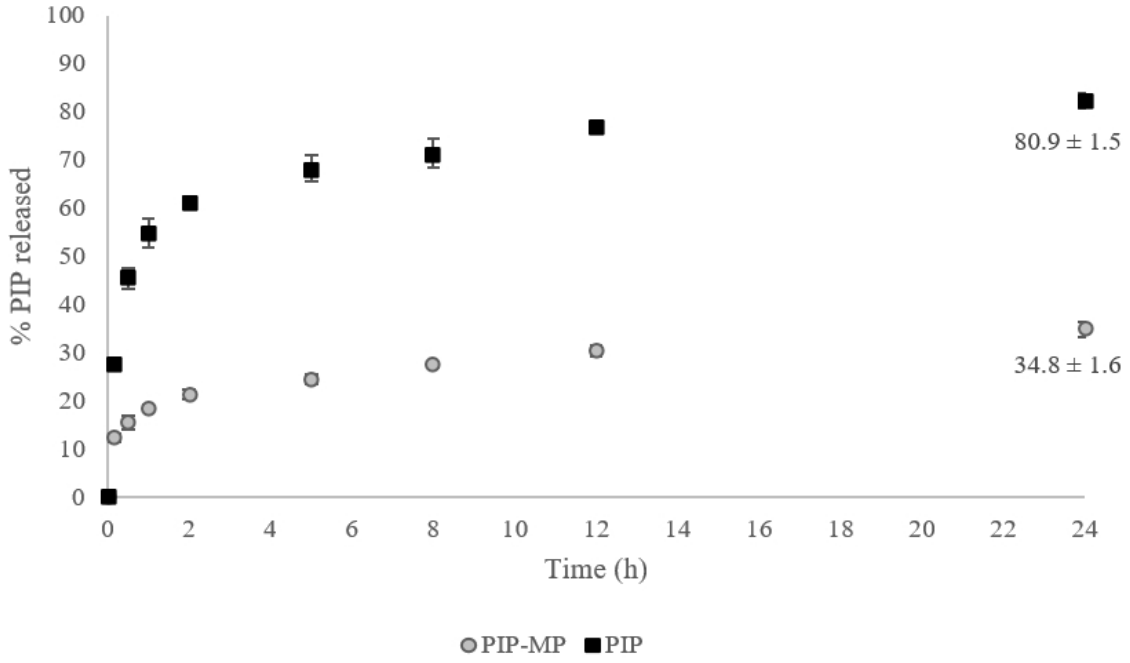

FIGURE 2 – PIP *in vitro* release from microparticles (PIP-MP) and pure PIP.

Babay *et al.,* in 1988, developed indomethacin microparticles also using EC as polymer. The *in vitro* release was performed in a phosphate buffer solution containing 0.02% polysorbate 20. In 24 h, 21% of the drug was released and the maximum released in 4 weeks was 53%, also demonstrating the EC ability to modify drug release (Babay, Hoffman, Benita, 1988).

Bonepally *et al*., in 2008, also developed PIP microparticles, however using poly-ε-caprolactone (PCL) as polymer. The *in vitro* release was performed in distilled water. In 24 h, approximately 50% of the drug was released and 100% of PIP was released in 16 days (Bonepally *et al*., 2008).

Pi *et al*., in 2018, evaluated the release of curcumin from EC microparticles using as dissolution medium simulate gastric fluid containing 0.1 mol/L HCl and 0.25% SDS. 96% of curcumin was released in 24 h (Pi *et al*., 2018).

Characterization of tablets containing PIP-loaded microparticles

Considering the good flow properties exhibited by PIP-MP, it was not necessary to use excipients to improve this characteristic. First, 100 mg of PIP-MP were tableted, with no diluent (PIP-MP-Tnd). The tablets produced presented adequate macroscopical characteristics and the microparticles were intact after the compression (Figure 3), demonstrating the importance of the flow properties presented by microparticles. However, the tablet's hardness was not adequate and Pullulan was chosen to be the diluent, since it has cohesive properties that provide suitable hardness to tablets and it was proven to protect microparticles from rupture due to the compression force, even more than usual diluents such as microcrystalline cellulose and lactose (Ferreira *et al*., 2015). Furthermore, EC is reported to produce tablets with poor dissolution (Rowe, Sheskey, Quinn, 2009) and the first *in vitro* release tests indicated the need for a dissolution improvement. Due to this, polacrilin potassium (6.0%, w/w) was used in the formulation. This polymer is obtained by the crosslinking of polycarboxylic acids and is used as a disintegrating agent from 0.5% to 4.0% and as a dissolution improver from 2.0% to 6.0%, due to its ability to break the tablets in smaller particles, which increases the surface area and increases the active ingredient dissolution (Corel Pharma Chem, 2010).

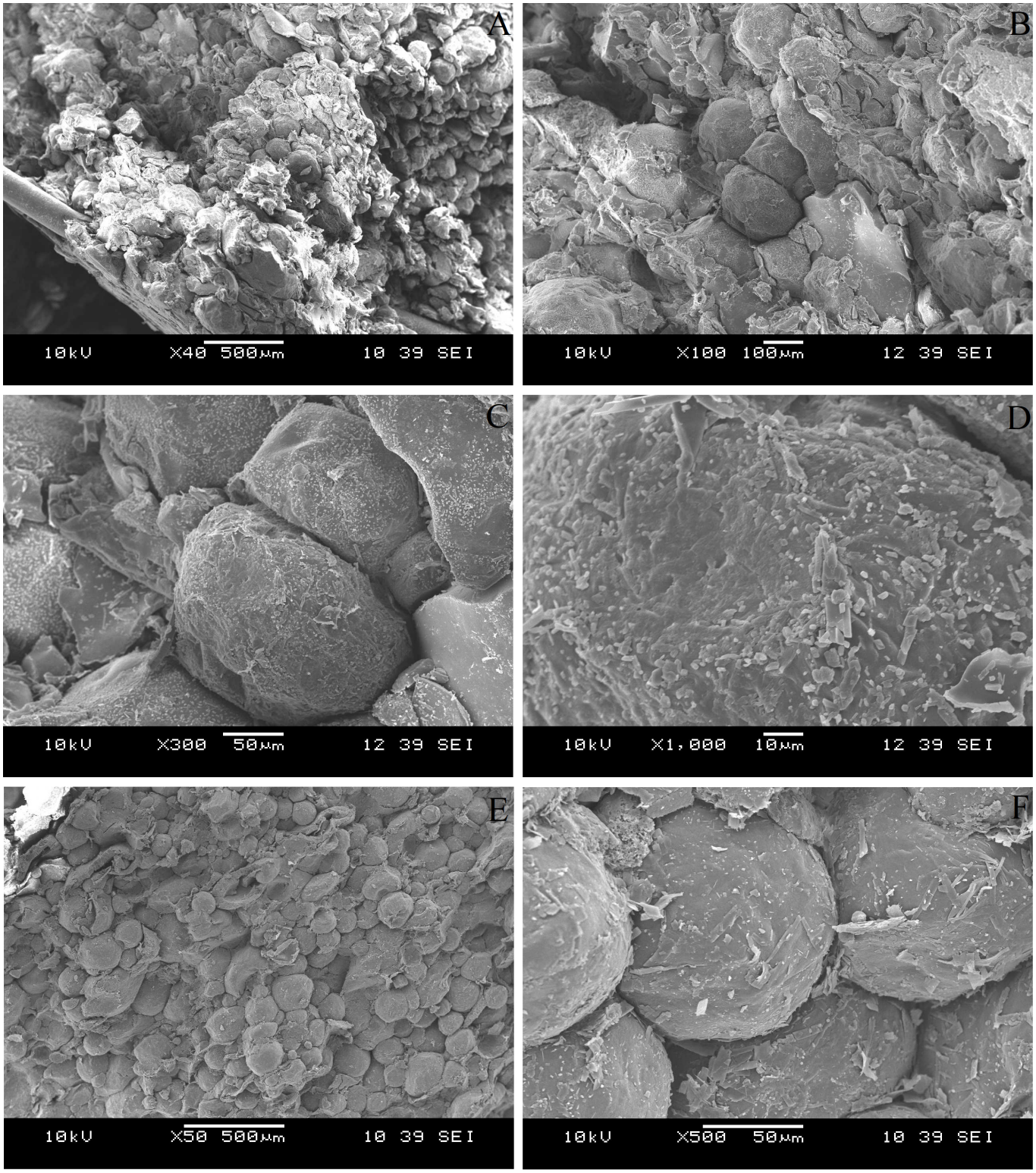

FIGURE 3 – Scanning electron micrographs of tablets made with PIP-MP and adjuvants (PIP-MP-T) with magnification of 40x (A), 100x (B), 300x (C) and 1000x (D) and only with PIP-MP (PIP-MP-Tnd) with magnification of 50x (E) and 500x (F).

It is important to highlight that, there are no papers focusing on the production of microparticulated PIP-based tablets. Therefore, the tablets were produced with PIP-MP in amount equivalent to 20 mg PIP, 6% polacrilin potassium and Pullulan q.s 100 mg (PIP-MP-T). SEM images of tablets cross-section show many spherical particles, similar to those shown by SEM of PIP microparticles, suggesting the microstructures withstood the compression. This may be attributed to the diluent employed, as reported by Ferreira (2015), as well as EC, the polymer used in microparticles preparation since similar SEM images were obtained for the compression of the microparticles alone (PIP-MP-Tnd - Figure 3).

The tablets containing PIP-loaded microparticles showed low variations regarding mean weight, thickness and hardness, demonstrating the consistency of the compression process employed. The tablets presented a mean weight of 99.1 ± 0.9 mg, thickness 3.38 ± 0.03 mm, hardness of 3.0 ± 0.2 kgf, and friability was 0.4%, being below 1.5%, demonstrating the abrasion resistance.

Content uniformity was performed as described in the Brazilian Pharmacopoeia, with 97.0 ± 2.0 %, RSD 2.11, resulting in an acceptance value of 6.4, below 15, that is the limit value, and the batch was considered uniform in terms of PIP content. The drug loading of a batch was 19.7 ± 0.4 mg of PIP, close to the theoretical 20 mg.

PIP *in vitro* release from tablets

Polacrilin potassium was used as a dissolution improver at a dose of 6% in the preparation of PIP-MP tablets (PIP-MP-T) and PIP tablets (PIP-T). The *in vitro* release was performed in the same conditions as PIP-MP and pure PIP, for 24 hours.

In 10 minutes, 11.9 ± 0.6% of PIP was released from the tablets, while 7.6 ± 0.2% of PIP associated with microparticles was released (Figure 4). Comparing PIP-MP and PIP release at the same time, it represents a slower release from the tablets, which is expected, once the compact has to disintegrate first to favor drug dissolution.

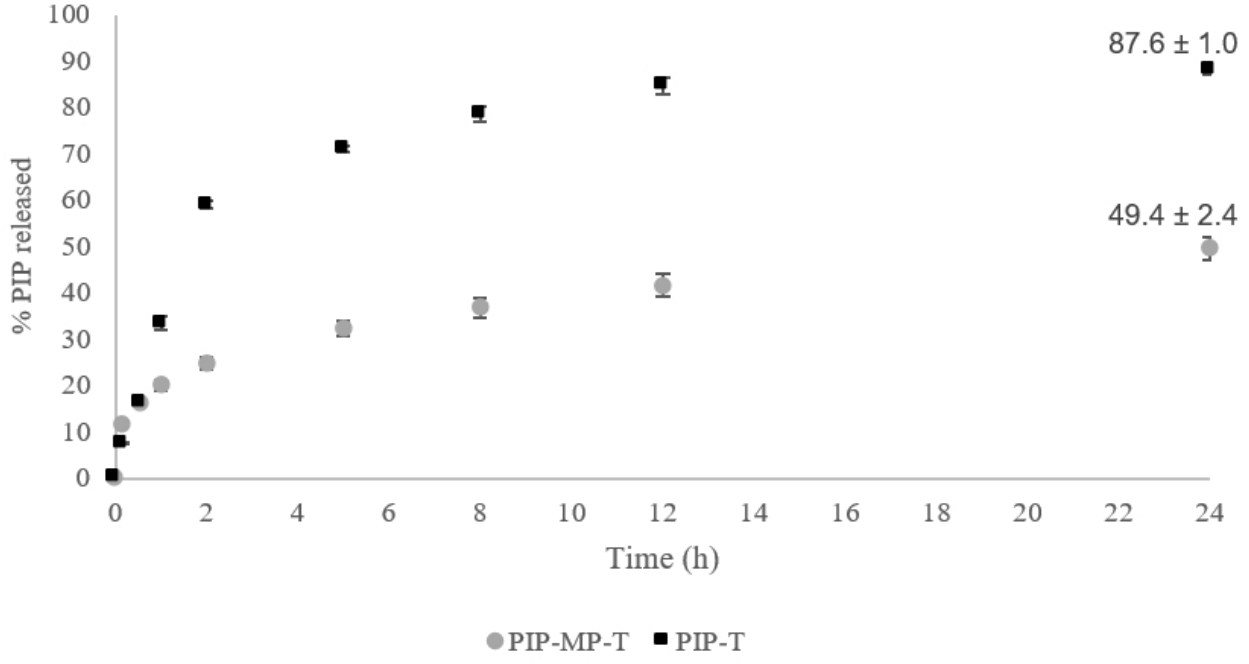

FIGURE 4 – PIP *in vitro* release from tableted microparticles (PIP-MP-T) and from tablets (PIP-T).

At the end of 24 hours, 88% of PIP was released from the PIP-T and almost 50% of the PIP-MP-T, more than the concentration of PIP found at the end of MP-PIP and PIP release. This may happen because of the polacrilin potassium influence. The higher drug dissolution is explained by its ability to promote disintegration, which results in the disaggregation and wetting of the drug (Abd-El Bary, Louis, Sayed, 2014).

Besides, the release profile of PIP-MP-T is similar to PIP-MP, as shown in Figure 5. It is possible to see an overlapping of the first data points and after, PIP release from the tablets is higher, possibly because of the dissolution improver influence. These results corroborate with the hypothesis that the microparticles remain intact after the compression, which is very important, once when the tablets disintegrate, they release the microparticles individually and they can provide the benefits associated with the microencapsulation process.

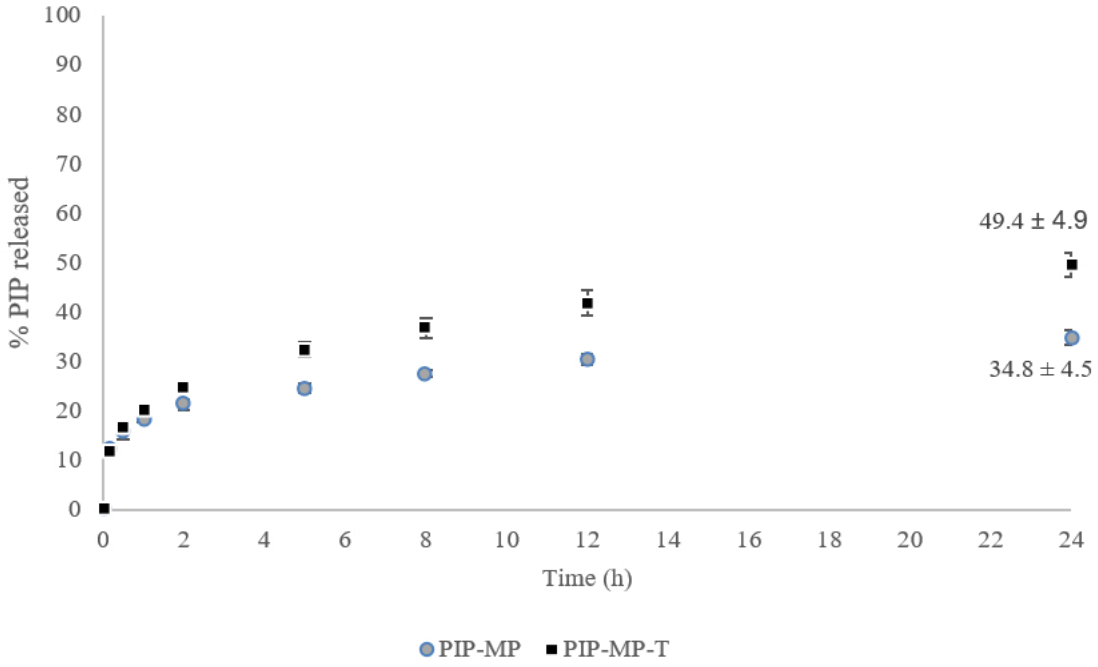

FIGURE 5 – PIP *in vitro* release from tableted microparticles (PIP-MP-T) and from microparticles (PIP-MP).

CONCLUSION

In this study, microparticles containing PIP were successfully developed. The microparticles controlled the PIP release and presented good flow properties, which facilitated the incorporation of the microparticles in tablets. The microparticulated tablets containing PIP were developed for the first time. The SEM images and the release profile of PIP from the microparticles and the tablets containing PIP microparticles suggested that the microparticles were intact after the compression. Therefore, the microparticulated tablet allows the PIP microparticles administration and, more important, when the tablets disintegrate, they individually release the microparticles keeping the benefits related to the microencapsulation. Since many pharmaceutical activities were already attributed to PIP, the microparticulated tablets developed may be a promising dosage form to deliver PIP.

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