Research Article

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Waterborne poly(urethane-urea)s films as a sustained release system for ketoconazole

Abstract: Ketoconazole (KTZ) was incorporated in waterborne poly(urethane-urea)s dispersions (WPUU), aiming at the production of films for drug sustained release. Dispersions based on poly(ethylene glycol-*block*-propylene glycol) (PEG-*b*-PPG) (four monomers with different contents of PEG hydrophilic segments), poly(propylene glycol), isophorone diisocyanate, dimethylolpropionic acid and hydrazine were produced and characterized by apparent viscosity and average particle size (APS). Cast films-drug interaction was investigated by Fourier-Transform infrared spectrometry (FTIR). *In vitro* dissolution assays were performed in simulated gastrointestinal juices, followed by application of kinetic models. Stable pseudoplastic dispersions, with APS between 27 to 320 nm were obtained. FTIR from KTZ-loaded films indicated interactions between polymer and drug. *In vitro* release of KTZ was achieved above 80%, notably influenced by PEG-based segments content up to 2 h, followed by sustained release for 8 h. Higuchi's and first-order equations described the drug kinetic profile, as diffusion of the drug and erosion of the swollen polymer, respectively.

1 Introduction

Polyurethanes (PU) compose a very versatile class of materials, possibly being tailor-made with biocompatible characteristics to biological systems, such as blood, organs and organic tissues and biodegradability (1-3). The properties of those systems differ greatly depending on the composition and stoichiometry of monomers (4,5). The basic morphology of PU chains consists of soft and hard segments, arranged alternately. The domains of the latter, which impart stiffness and reinforcement, are composed mainly of diisocyanate and chain extender, whereas the elastomeric domains of soft segments consist of polyols (4,6), as the polyethers poly(ethylene oxide) (PEO) and poly(propylene oxide) (PPO), or, respectively, poly(ethylene glycol) (PEG) and poly(propylene glycol) (PPG) (different nomenclatures for similar structures) (7).

Studies reported the solubilization and release of drugs using some amphiphilic di- and triblock copolymers of PEO-PPO (8) and PEO-PPO-PEO (9,10), respectively. Lately, matrices of PU based on PEO, produced in organic solvent media, have been applied for the manufacture of oral dosage tablets containing high drug loads (2,11,12). PEO segments improved biocompatibility and increased drug release *in vitro* (12). The main release mechanisms of the tablets involved the swelling of the polymer, when in contact with aqueous medium, due to the high hydrophilicity of PEO segments, followed by partial diffusion of the drug through the swollen matrix, and finally, polymer erosion and drug release (2).

Aiming an improvement in biocompatibility and a reduction in toxicity, the development of waterborne polyurethane dispersions (WPU) and poly(urethane-urea)s (WPUU) systems completely free of organic

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solvents has been arousing great interest for biomedical applications, besides reasonable production cost (13-15). Recent advancements in polymer science have provided great opportunities to manufacture new WPU, developed for the controlled release of drugs, especially in the form of polyurethane nanoparticles (16,17), hydrogels (18), films (13) and biodegradable implants (19,20).

Nevertheless, incorporation of lipophilic drugs in dispersions of WPU or WPUU becomes a challenge because of their low aqueous solubility (21). Currently, a series of PU containing amphiphilic chains have been investigated because of their ability to self-assemble in aqueous solution, forming micelles composed of hydrophobic segments as inner core and hydrophilic segments as outer layer (22-24). In this case, the hydrophobic core may increase the ability to encapsulate the lipophilic drug due to physical-chemical interactions between them (23,24). Thus, the use of the amphiphilic block polyols aforementioned, PEO-PPO or PEG-PPG, consisting of a hydrophilic and a hydrophobic block, respectively, could be extremely relevant for promoting interactions between the lipophilic drug and the hydrophobic segments of the polymer, facilitating the miscibility of the former in the polymer matrix.

In the present investigation, ketoconazole (KTZ) was selected as a model drug to study the performance of WPUU films, as systems for oral release. KTZ is a lipophilic drug, synthetic derivative of phenylpiperazine, with antifungal properties and potential antineoplastic activity (25). Its antifungal action allows to inhibit the growth of dermatophytes, such as *Trichophyton*, *Microsporum* and *Epidermophyton*, as well as more common yeasts, such as *Candida albicans* (26). In this way, KTZ is widely used for the treatment of fungal infections, especially against thrush, gastrointestinal infections, and infections of the skin, nails, and scalp (25,27). In the market there are immediate release tablets of ketoconazole 200 mg administered once daily, with a short half-life time of only 2 h (28,29). Thus, the production of a sustained release system of ketoconazole would be interesting and convenient in order to increase the drug time of pharmacological action. In the scientific literature, some prolonged release systems for oral administration of ketoconazole have been reported (30-32), but none of them employed WPUU films for sustained release. Furthermore, as far as we are concerned, no study has addressed the use of WPU or WPUU cast films for application in oral drug delivery systems (DDS).

Thus, the objective of this study was to evaluate the performance of WPUU films, prepared with PEG-*b*-PPG

block copolymers, contained different contents of PEG hydrophilic segments, for sustained release of KTZ as a model drug. In addition, the application of some kinetic models was used to study the possible mechanisms of release of ketoconazole.

2 Experimental

2.1 Materials

All chemicals employed in the synthesis and experiments were used as received. The monomers are described as follows. Polyols: (1) four types of block copolymers based on poly(ethylene glycol-*block*-propylene glycol) (PEG-*b*-PPG), with different PEG-segments ratio: 7%, 17%, 25% and 38%, in terms of copolymer molar mass ($\overline{M}_n$ = 1850, 2250, 2350 and 2900 g·mol^{-1}, respectively) and number of hydroxyls (n° OH) = 60.6, 54.2, 47.7 and 38.7 mg KOH·g^{-1}, respectively), specifications supplied by the manufacturer, Dow Química S.A.; and (2) poly(propylene glycol) (homoPPG) ($\overline{M}_n$ = 1000 g·mol^{-1}), number of hydroxyls (n° OH) = 108 mg KOH·g^{-1}, specifications supplied by the manufacturer, Dow Química S.A.. Diol containing anionic sites: dimethylolpropionic acid (DMPA), Aldrich Chemical Company, Inc.. Neutralizing agent: triethylamine (TEA), Vetec Química Fina Ltda. Isophorone diisocyanate (IPDI), donated by brasilian Aerospace Technical Center (CTA). Chain extender: hydrazine hydrate, 64% solution (HYD), Vetec Química Fina Ltda.

The chemicals employed in the release studies were: ketoconazole (KTZ), Pharma Nostra (lot KET/11407233 and concentration 100.91%); hydrochloric acid 38% P.A., Vetec Química Fina Ltda.; potassium phosphate monobasic 99%, Spectrum Chemical MFG Corp.; sodium hydroxide P.A., Vetec Química Fina Ltda.

2.2 Preparation of aqueous dispersions of poly(urethane-urea)s

WPUU were prepared in the absence of organic solvent and catalysts, as well as in methods previously described by our research group (4,5,33,34). The formulations were named according to the different percentages of PEG segment, in terms of molar mass, in the copolymer: 7%, 17%, 25% and 38% PEG, respectively, as WPUU-7, WPUU-17, WPUU-25 and WPUU-38.

The reaction was conducted in four stages: (1) synthesis of a bulk prepolymer containing pendant

groups capable of neutralization; (2) neutralization of the carboxylic groups forming ionomers; (3) dispersion in water of the ionomer chains and (4) chain extension reaction, between the reactive terminal groups and a difunctional molecule of low molar mass, to increase the molar mass of the polymer. The steps of the synthesis were described in Figure 1.

WPUU systems were prepared in a kettle-type reactor placed on a heating mantle (Fisatom, Mod. 202E) and equipped with a mechanical stirrer (IKA Labortechnik, Mod. RW-20M). The polyols (PEG-*b*-PPG and homoPPG), DMPA and IPDI were added and the synthesis of the prepolymer was conducted at 90-100°C, for 45 min. Then the neutralization of the carboxyl

groups with TEA was carried out at 40°C, for 30 min. Next step consisted of dispersing the bulk in water under vigorous stirring. An extra volume of water was need in WPUU-25 and WPUU-38 in order to reduce the viscosity of prepolymer. The subsequent chain extension reaction was carried out for 30 min, at 15-20°C, by adding HYD drop-by-drop (4,5,33,34). The dispersions were stored at room temperature for further characterization and application. All syntheses were performed in duplicate.

The theoretical solids content was 35% and the ratio between the number of gram-equivalents of isocyanate and hydroxyl groups (NCO/OH) were fixed in 2.3 for all systems. Hydroxyl groups were derived from [Diol (DMPA) + Polyols (homoPPG + PEG-*b*-PPG)]. In this
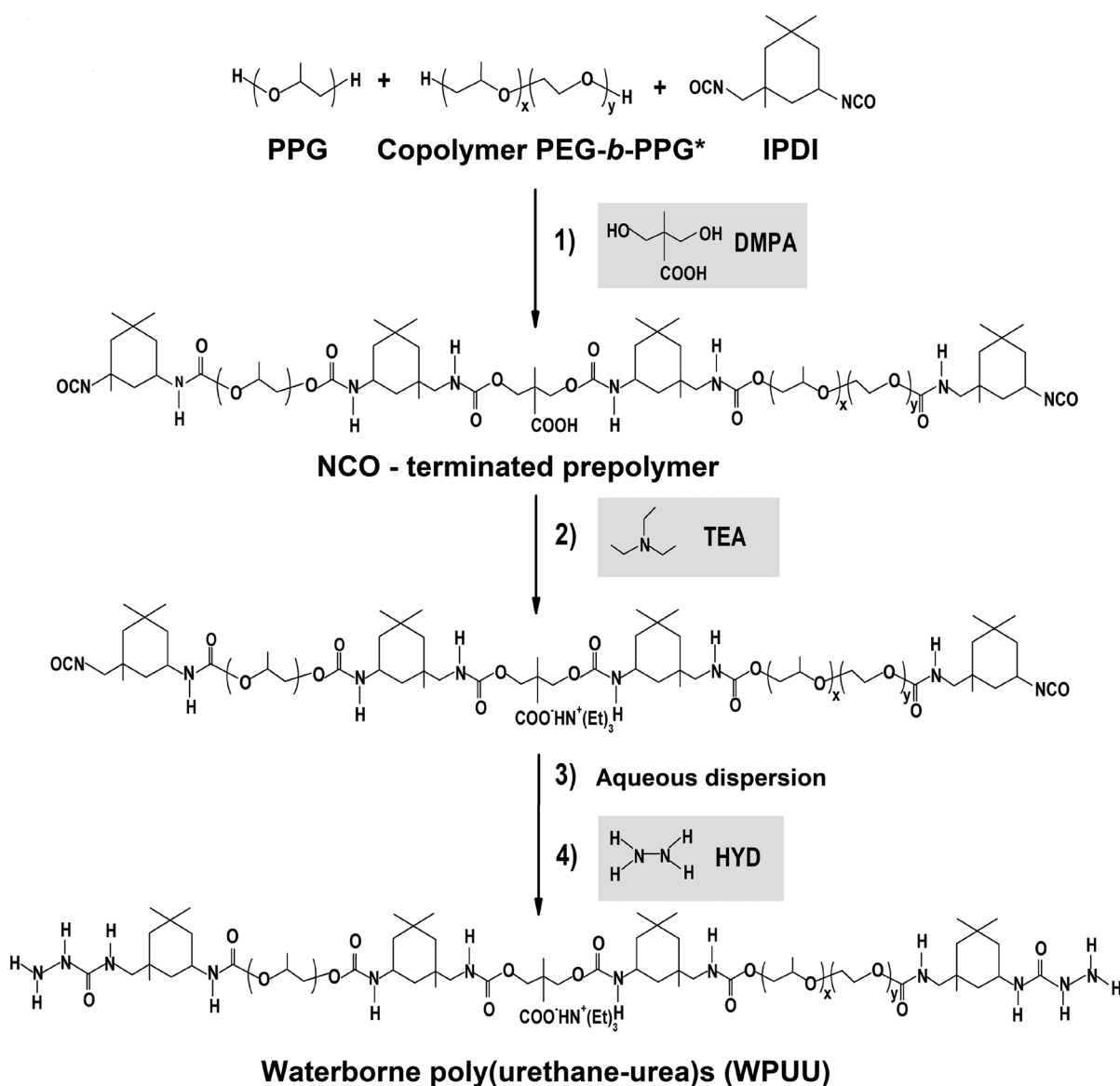

Figure 1: Schematic representation of the chemical reactions involved in the preparation of the waterborne poly(urethane-urea)s (WPUU). The percentages of PEG segment (y) in the copolymer samples (*) were 7%, 17%, 25% and 38%.

relation, Diol content was fixed in 50% and Polyols in 50% terms of gram-equivalent. Considering the amount of copolymer in Polyols, all the synthesis were carried out with the fixed value of (25% homoPPG and 75% PEG-*b*-PPG), also in terms of gram-equivalent. Table 1 presents the composition (wt%) of monomers and reagents in the formulations.

2.3 Incorporation of ketoconazole and preparation WPUU films

The dispersion-drug systems were prepared by dispersing 5 wt% of ketoconazole (KTZ) in WPUU formulations, with homogenization of the mixture for 24 h, with magnetic stirring (IKA, Mod. HS 7), at 25°C.

Pristine WPUU and KTZ-loaded WPUU films were obtained by pouring the dispersions on polyethylene non-stick molds leveled on a flat surface. Films were obtained after evaporation of water for seven days, at 25°C, and for 24 h in a stove (Icamo, Mod. 3), at 60°C (33-35).

The dried KTZ-loaded WPUU films were cut into squares (3.5 cm^2 size) having approximately 100 mg each one. At the end of the process, thin films with a mean thickness of 0.32 ± 0.03 mm and 8.8 cm in diameter were attained.

2.4 Characterization

Stability of the aqueous poly(urethane-urea)s dispersions (WPUU) was evaluated macroscopically, at room temperature, by observing the formation of sediment in the

Table 1: Composition of WPUU formulations.

Monomers and reagents	Formulations (wt%)[a]			
	WPUU-7	WPUU-17	WPUU-25	WPUU-38
homoPPG	15.00	15.00	15.00	15.00
PEG-*b*-PPG (7% PEG)[b]	45.00	–	–	–
PEG-*b*-PPG (17% PEG)[b]	–	45.00	–	–
PEG-*b*-PPG (25% PEG)[b]	–	–	45.00	–
PEG-*b*-PPG (38% PEG)[b]	–	–	–	45.00
DMPA	05.19	04.84	04.50	04.01
IPDI	39.57	36.98	34.31	30.58
TEA	03.91	03.65	03.39	03.02
HYD	05.04	04.70	04.37	03.89
Deionized water	211.17	204.60	197.92	188.50

[a]Solids content = 24-31%; NCO/OH = 2.3; 100% hydroxyl compounds: 50% polyols (25% homoPPG/ 75% PEG-b-PPG) and 50% DMPA, in terms of grams-equivalent. bPEG-b-PPG with different PEG-segments ratio: 7%, 17%, 25% and 38%, in terms of copolymer molar mass (= 1850, 2250, 2350 and 2900 g·mol^{-1}, respectively).

bottom over time (4). Dispersions were characterized in terms of solids content, pH, apparent viscosity and average particle size. These determinations were carried out in triplicate (*n*=3) for each formulation and respective duplicates.

Solids content was determined 24 h after the synthesis by adding 1.0 g of the dispersion in an aluminum capsules. The capsules were then placed in an oven at 60°C, for 4 h. After drying, the residual masses were correlated to the masses of the initial dispersions, the values being expressed as a percentage (4,33,34,36).

pH values were determined at 25°C in a digital pHmeter (Bante Instruments, Mod. 922), calibrated with standard solutions 4.0 and 10.0 (Hanna Instruments).

Apparent viscosity was measured in a Brookfield LVT viscometer using two spindles, which depended on the viscosity of the formulation: SCA-31 (for WPUU-7 and WPUU-17) and SCA-18 (for WPUU-25 and WPUU-38). A universal UL adapter for reduced sample volumes coupled to a thermostated bath with temperature set at 25 ± 0.1°C was used.

Average particle size (APS) and the polydispersity index (PDI) were determined by the dynamic light scattering (DLS) in Zetasizer Nano ZS at 25 ± 0.1°C, at a laser radiation wavelength of 633 nm and 90° detection angle. The samples were diluted (1:100) and placed in polystyrene cuvettes.

Cast films (pristine and containing the drugs) were characterized in a Fourier-transform infrared spectrometer (FTIR) absorption (Perkin Elmer, Spectrun One – Frontier), using an attenuated total reflectance (ATR) accessory with a diamond crystal/ZnSe. The FTIR device operated with 4 cm^{-1} resolution, with accumulation of 4 sweeps in the infrared radiation range between 4000 and 650 cm^{-1} and velocity of 0.2 cm·s^{-1}.

2.5 Drug content uniformity in the WPUU films

Ketoconazole content uniformity in the WPUU films was evaluated by cutting the films in four samples of uniform size (3.5 cm^2), each being weighed individually. The KTZ-loaded WPUU films samples were dissolved in 25 mL of methanol by magnetic stirring, for 6 h, at room temperature. The final solution was filtered on poly(tetrafluoroethylene) (PTFE) filters (0.45 μm porosity) and the absorbance was measured using a ultraviolet-visible (UV-Vis) spectrophotometer (Jasco, Mod. V-630; software Spectra Manager) in the wavelength of 270 nm. Also, the pristine WPUU films without drug were analyzed using the same conditions, to ensure the selectivity of the method. Figure 2 shows the standard curves obtained

(linearity $R^2 = 0.9998$) and a detail of the UV spectrum of the KTZ, indicating a typical absorption at 270 nm (37). The parameter was determined using Eq. 1 (38).

Drug content uniformity

$$= \frac{\text{actual weight of KTZ in film}}{\text{theoretical weight of KTZ in film}} \times 100\% \quad (1)$$

2.6 Dissolution tests - *in vitro* release

A Dissolutor (Nova Ética, Mod. 299) with apparatus II was used in the dissolution tests, according to the United States Pharmacopeia (USP, 2008) (39). In a previous step, tests of solubility of the drug were carried out to determine sink conditions. Two receptor media were chosen to simulate the physiological conditions of the gastrointestinal tract: simulated gastric juice (HCl solution 0.1 N) in pH 1.2 and simulated intestinal fluids (phosphate buffered saline solution – PBS) in pH 7.4. The KTZ-loaded WPUU films (3.5 cm^2 size) were immersed in the different receptor media: simulated gastric juice, for 2 h, and simulated intestinal fluids, for 8 h. A temperature of $37 \pm 0.5°C$ and a speed gradient of 50 rpm in 900 mL of test medium (*n*=3) were employed in the assay.

The quantification of KTZ was determined by UV-Vis spectroscopy at the wavelength of 270 nm, according to standard methodology (40). Aliquots of 3.0 mL were extracted from the receptor media and filtered on PTFE filters (0.45 μm porosity), being that the same volume was completed with the standard solution. The samples were withdrawn from the dissolution medium at pre-established times of 30, 45, 60, 120 min, from the simulated gastric medium (pH 1.2), and 180, 240, 300,

360, 420, 480 min, from the simulated enteric medium (pH 7.4). The drug concentrations (μg/mL) in the release medium were determined based on linear equations, obtained from calibration curves of the KTZ. The cumulative amount of KTZ released from the samples was calculated using Eq. 2, where M_t is the amount of KTZ released from the WPUU films at time *t* and M_{total} was the total amount of KTZ loaded in the WPUU films.

$$\text{Cumulative amount released} = \frac{M_t}{M_{total}} \times 100\% \quad (2)$$

2.7 Kinetic drug release models

Kinetic models were applied to investigate the possible release mechanisms of KTZ. The release data were analyzed mathematically according to Eq. 3-5, where Q is the amount of drug released at time (*t*) and *k* is the kinetic constant.

$$\text{Zero – order kinetics: } Q = (kt) \quad (3)$$

$$\text{First – order kinetics: } Q = (kt)/2.303 \quad (4)$$

$$\text{Higuchi's equation: } Q = (kt)^{1/2} \quad (5)$$

The choice of the model that best fit the release kinetics was based on the linear correlation coefficient (R^2) obtained in each linear regression analysis ($R^2 > 0.999$) (38,41,42).

2.8 Statistical analysis

The experimental data were presented as mean ± SD (standard deviation) using the Origin Pro 8 software (OriginLab, USA) and *p*-value or probability value (*p*) < 0.05 was considered statistically significant.

3 Results and discussion

3.1 Characterization of the aqueous dispersions

3.1.1 Total solids and pH determination

Stable aqueous dispersions in terms of sedimentation were obtained, on a period of more than twelve months. All formulations presented a milky appearance with slight differences in terms of opacity. According to Table 2, the
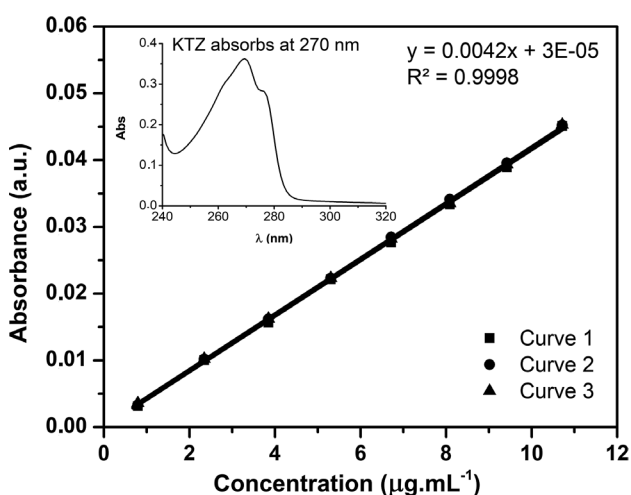

Figure 2: Standard curves of ketoconazole (KTZ) by linear regression and a detail of UV-spectrum of the drug.

values of total solids ranged from 24 ± 1% to 31 ± 4%, deviating more from the theoretical value of 35%, as PEG segments content increased in formulation. An increment in molar mass of the copolymer provoked an increase in the viscosity of the prepolymer and the need of extra water addition in dispersion stage, causing a decrease in total solids values (7,35). pH values remained in the range of 7.5 ± 1.0 for all systems, being within the ideal range for stable dispersions, specified between 7 and 9 (43).

3.1.2 Apparent viscosity

Viscosimetric analysis provides important information regarding the properties of flow and deformation of the materials. The viscosity of polymer dispersions may be influenced by many factors, among them: temperature, solids content, volume fraction of the dispersed particles, particle size distribution and respective morphology, and finally pH and ionic strength of the aqueous phase (4,44).

At the first stage of the synthesis, differences in viscosity of prepolymer were observed, increasing with higher amounts of PEG-based segments, leading to more viscous dispersions, in accordance with previous works (5,33,34). This tendency can be explained because PEG block of the copolymer is highly hydrophilic, presenting capacity to interact with water as opposed to hydrophobic PPG segments (33).

WPUU-25 and WPUU-38 showed higher viscosity values than WPUU-7 and WPUU-17 because the first two formulations contained higher amounts of PEG-based segments, which improved the interactions with the aqueous phase. In addition, PEG-*b*-PPG may form hydrogels and micelles in water, increasing the surface of the polymer due to the swelling of the particles (45,46). Figure 3 shows viscosity values plotted against shear force for the aqueous systems, at 25°C. WPUU formulations presented characteristics of non-Newtonian pseudoplastic fluids, defined by the decrease of viscosity as shear rate increases (34).

3.1.3 Average particle size (APS)

The average particle size (APS) values of the dispersions and polydispersity index (PDI), obtained by dynamic light scattering (DLS), are shown in Table 3. All formulations presented APS values within the range in which the dispersions are considered stable (generally below 1000 nm) (7,33).

Considering WPUU-7, WPUU-17 and WPUU-25, APS values show a slight tendency to decrease as copolymer content increases, notwithstanding an abrupt increase occurs in WPUU-38. Depending on the formulation, high levels of PEG segments may impart more hydrophilicity and, instead of the production of dispersed particles, the dispersion of the prepolymer in water produces a gel (5,33).

The results therefore suggest that higher amounts of hydrophilic segments may have facilitated the dispersion, leading to a reduction in particle size to a limit (WPUU-25), from which greater hydrophilicity caused a swelling in the
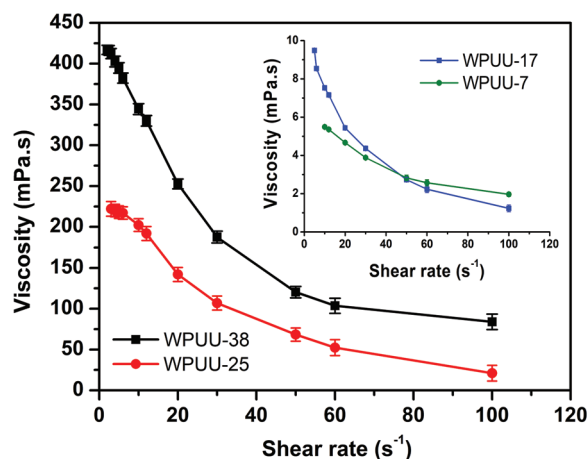

Figure 3: Viscosity curves of the pristine WPUU systems containing different PEG-based segments in the copolymer, varying from 7% to 38% PEG. Data are expressed as mean number (*n*=3). The error bars indicate standard deviations.

Table 2: Total solids (ST) and pH values of pristine WPUU.

Sample	ST (%) ± SD[a]	pH ± SD[a]
WPUU-7	31 ± 4	7.517 ± 0.008
WPUU-17	28 ± 2	7.570 ± 0.006
WPUU-25	25 ± 3	7.466 ± 0.005
WPUU-38	24 ± 1	7.391 ± 0.003

[a]Average values (n=3) ± standard deviation (SD).

Table 3: Average particle size (APS) and polydispersity index (PDI) obtained for the dispersions pristine WPUU and KTZ-loaded WPUU.

Sample	pristine WPUU		KTZ-loaded WPUU	
	APS (nm) ± SD[a]	PDI	APS (nm) ± SD[a]	PDI
WPUU-7	208 ± 1.0	0.1	228 ± 1.4	0.2
WPUU-17	47 ± 0.3	0.2	310 ± 9.6	0.1
WPUU-25	27 ± 0.1	0.2	293 ± 23.8	0.1
WPUU-38	223 ± 2.0	0.2	272 ± 8.7	0.2

[a]Average values (n=3) ± standard deviation (SD).

particles, consequently increasing the particle diameter (WPUU-38). The higher viscosity of prepolymer respective to WPUU-38 formulation, caused by the presence of larger amounts of copolymer, led to greater difficulty in being dispersed, which caused an increase in particle size and a resulting loss in solids occurs (33).

According to Figures 4a and 4b, the distribution of the particle diameter of pristine WPUU systems and drug-loaded WPUU presented a monomodal profile, with only one peak. The polydispersity index (PDI), which evaluates the distribution width of the particles, ranged from 0.1 to 0.2. Some dispersions presented lower values of PDI (0.1), being considered monodisperse fluids (47). However, some other systems presented a wide distribution of size (PDI>0.2), mainly drug-loaded ones.

After the incorporation of 5 wt% KTZ in WPUU aqueous dispersions, a small increase was observed in APS values in relation to the pristine dispersions, varying in a narrow range from 228 ± 1.4 nm to 310 ± 9.6 nm (Table 3), within the range of stability against sedimentation (7,33). Except for WPUU-7/KTZ dispersion, statistical differences were not observed ($p<0.05$) in average particle size of the other dispersions, which varied in a very close range.

Figure 4c also shows a representation of the possible interactions between lipophilic drug and WPUU micelles. According to the literature, WPU colloidal particles are usually formed by an internal layer constituted of hydrophobic segments and an external layer composed of hydrophilic segments and/or ionic groups, and urethane and ureic bonds (33). The lipophilic nature of KTZ enables the interaction with the hydrophobic segments present in the micelle nucleus, constituted mainly by PPG segments, resulting in a narrow particle diameter increase, as reported in previous studies using similar systems based on amphiphilic copolymers (23,24). In this case, hydrophobic compatibility was more determinant than the presence of PEG-based segments. In addition, several factors may be involved in the formation of dispersed particles in the presence of drugs, such as temperature, pH, quantities, ionic nature, presence of additives and methods of incorporation (48).

3.2 Characterization of cast films

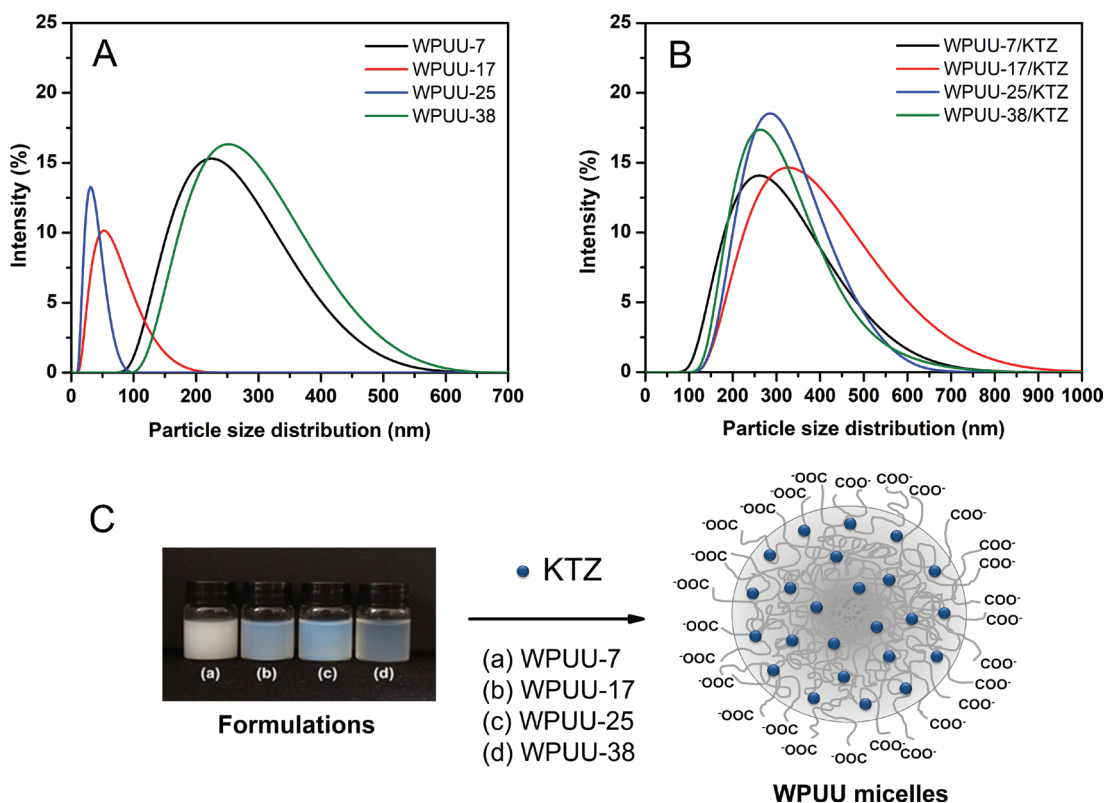Whole and homogeneous films were demolded, with flexible characteristics, absence of visible bubbles

Figure 4: Particle size distribution curves of (a) pristine WPUU and (b) KTZ-loaded WPUU. (c) Formulations and representation of the possible interactions between drug and WPUU micelles.

and presenting non tacky surfaces. Little variation in thickness was observed after drying. The pristine films were transparent, whereas KTZ-loaded films were in opaque white color.

3.2.1 Fourier-transform infrared spectrometry (FTIR)

The spectra of the pristine WPUU films are shown in Figure 5, while the ketoconazole spectra is presented in Figure 6. The KTZ-loaded WPUU films spectra are depicted shown in Figure 7 in comparison to the pristine WPUU systems.

Figure 5a shows that all pristine WPUU spectra indicated bands related to methyl (CH_3) (1374-1373 cm^{-1}) groups present in homoPPG, IPDI and PEG-b-PPG (4). No significant variations were observed for the

A

B

Figure 5: (a) ATR-FTIR absorption spectra of pristine WPUU films, and (b) detailing of bands: −NH stretching vibrations (3331-3317 cm^{-1}) and carbonyl vibration C=O amide I (1705-1700 cm^{-1}, for urethane carbonyl, and 1657-1649 cm^{-1}, for urea carbonyl).

vibrations relative to the bands of the axial deformation of the ether group (C−O−C) (1243-1242 cm^{-1}) and the angular deformations of the methylene CH group (1461-1459 cm^{-1}). Nonappearance of absorption around 2270-2265 cm^{-1} suggested the absence of unreacted NCO groups (33,49-51).

The vibration of N−H stretching (3500 and 3150 cm^{-1}) and carbonyl vibration, C=O (amide I) (1800 and 1600 cm^{-1}), are usually the two regions of greatest interest for the analysis of polyurethanes and poly(urethane-urea)s (7,33,51,52). Hydrogen bonds may occur between hard/hard segments or phases and/or between hard/soft segments or phases. In general, the hydrogen bonds formed between hard/hard segments are stronger when compared to hydrogen bonds formed between hard/soft segments (33,49,50). This premise is related to the degree of miscibility between the hard and soft phases of polyurethane chains (4,49).

Therefore, amide I vibration consists of several components that reflect in carbonyl groups, suggesting the presence of weak and strong hydrogen bonds attached to C=O (8,42). Frequently, the respective band is divided in two regions: absorptions between 1750 and 1696 cm^{-1}, corresponding to urethane carbonyl; and absorptions ranging from 1684 to 1636 cm^{-1}, corresponds to urea carbonyl (4,33). These groups may also be associated to hydrogen bonds with ether groups of the soft segments, since the lower the degree of association, the higher the absorption values for the urethane and urea carbonyl (4,49).

Figure 5b shows the detailing of the vibration regions of bands N−H and C=O. In WPUU samples, hydrogen bonds can be formed among the groups N−H, from urethane and urea linkages, and urethane C=O, within the hard phase, and also with the oxygen atoms of the ether groups of the polyethers (homoPPG and PEG-b-PPG), which constitute the soft phase.

According to Figure 5b, the bands of N−H linkages showed a slight tendency to displacement to higher wavenumbers, as the content of PEG segments increases in PEG-b-PPG. The displacement was more evident when WPUU-7 and WPUU-38 were compared, the latter being the sample containing the highest content of PEG-based segments. Absorption values increased from 3317 to 3331 cm^{-1}, for WPUU-7 and WPUU-38 films, respectively, being an indication of a reduction in the intensity of hydrogen bonds caused by the presence of higher levels of PEG-based segments, suggesting some interaction between hard and soft (49).

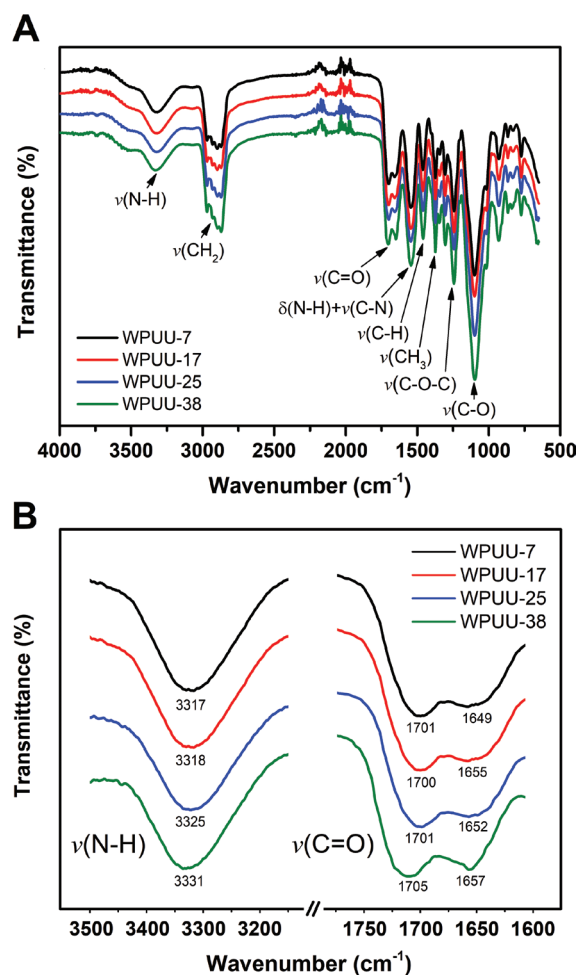The same tendency was observed for the carbonyl bands (Figure 5b). The absorption values for the urethane

carbonyl ranged between 1700 cm⁻¹(WPUU-7) and 1705 cm⁻¹ (WPUU-38), as PEG-based segments content increased. This may have occurred due to a rearrangement of the urethane hydrogen bonds in the WPUU samples, since hydrogen bonds between ether and urethane groups were favored at the expense of those between the carbonyls of urethane groups (7). In addition, these values may indicate that the hydrogen bonding in the WPUU-38 sample is weaker, suggesting that the hard domains were more associated with soft segments, indicating higher miscibility between phases (4). Urea-carbonyl band displacement showed the same profile, from 1649 cm⁻¹ (WPUU-7) to 1657 cm⁻¹ (WPUU-38). The absorptions obtained for urea carbonyls, at lower frequencies, probably correspond to groups bound by stronger hydrogen bonds (predominantly between hard segments), while the absorptions related to urethane carbonyls, at higher frequencies, may be due to weaker hydrogen bonds (4,7,49).

Figure 6 shows the major bands of the ketoconazole absorption. The typical bands of the drug were observed at 2966 cm⁻¹, corresponding to the axial deformation of the C−H bond present in aromatic systems, and at 2884-2833 cm⁻¹, due to the methyl C−H group. The carbonyl (C=O) of the amide absorbed at 1645 cm⁻¹, while the axial stretching of the C-N and C−O−C bonds appeared around 1244 and 1201 cm⁻¹, respectively. An intense band at 814 cm⁻¹ was due to the axial deformation of the C−Cl bond (25,27).

Spectra of WPUU-7/KTZ and WPUU-38/KTZ films and respective pristine samples are shown in Figure 7. The major changes in the N−H and C=O bands related to hydrogen bonds formation were highlighted in the spectra. By comparing WPUU-7 film spectrum with the respective drug-loaded one, urethane and urea-carbonyl bands were displaced from 1700 and 1649 cm⁻¹, in the former, to 1701 and 1659 cm⁻¹, in the latter. Considering now WPUU-38 and the corresponding drug-loaded spectra results, the shifts moved, respectively, from 1705 and 1652 cm⁻¹ to 1705 and 1657 cm⁻¹. Urethane carbonyl absorption were not affected whereas urea carbonyl hydrogen bonding was weakened by the presence of KTZ, for both systems. An interaction of the lipophilic drug with the soft segments, which have hydrophobic portions of PPG (in homoPPG and in the copolymer PEG-*b*-PPG) is suggested. Therefore, the higher displacement of the urea carbonyl observed in WPUU-7/KTZ sample may be associated with the lower content of PEG in the copolymer. No appreciable displacement was observed for N−H absorption. In addition, KTZ-loaded WPUU spectra showed a displacement of the C−Cl band (characteristic of the drug), previously in 814 cm⁻¹, for 774-772 cm⁻¹, also suggesting that the presence of the lipophilic drug may have caused changes in the structure of the polymer (20,53).

3.2.2 Drug content uniformity in the WPUU Films

Drug content uniformity is related to the accuracy and homogeneity of the drug in different regions of each film (38). The results of KTZ content uniformity are shown in Table 4. The concentrations were calculated from the equation obtained through linear regression analysis (Figure 2). KTZ content ranged from $89.3 \pm 1.2\%$ to $92.2 \pm 1.3\%$, with no significant differences between films ($p > 0.05$). These close results reveal that KTZ-loaded WPUU films were uniform and homogeneous. In this
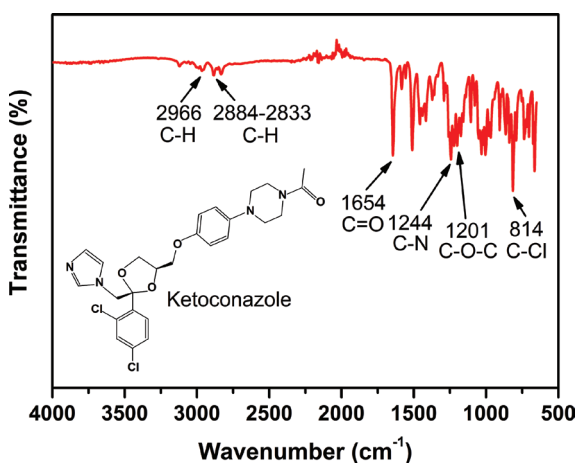

Figure 6: ATR-FTIR absorption spectra of ketoconazole.
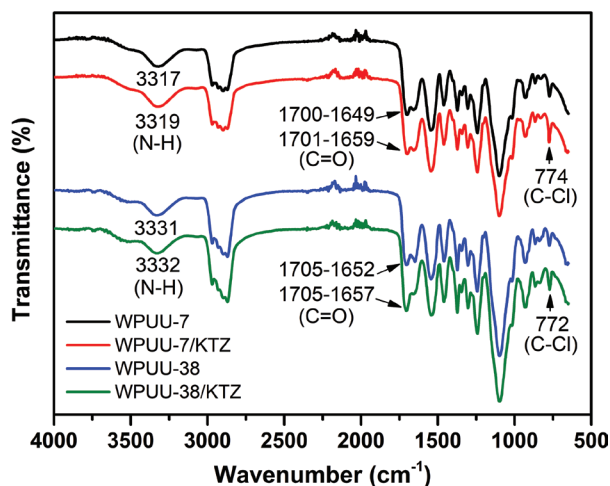

Figure 7: ATR-FTIR absorption spectra of pristine and KTZ-loaded WPUU-7 and WPUU-38 films.

way, our method of drug incorporation is simple and efficient to prepare films with high drug content.

3.2.3 Dissolution profile – in vitro release studies

In vitro dissolution studies of KTZ-loaded WPUU samples, in simulated gastric juice (pH 1.2) and simulated intestinal fluids (pH 7.4) were used to mimic the physiological conditions (45). In Figure 8, the release profiles of KTZ are shown.

According to the cumulative percentages of drug release under sink conditions, in the first 120 min in the simulated gastric juice (pH 1.2), WPUU-7/KTZ, WPUU-17/KTZ, WPUU-25/KTZ and WPUU-38/KTZ films had a progressive increase in release rate, with percentages of $25.1 \pm 2.42\%$, $30.9 \pm 1.32\%$, $36.8 \pm 1.52\%$ and $43.3 \pm 1.50\%$, respectively. After 480 min (8 h) of release study in the simulated intestinal fluids (pH 7.4), the same films presented a slower and prolonged release, with percentages of $82.8 \pm 5.26\%$, $83.4 \pm 6.83\%$, $87.4 \pm 2.29\%$ and $90.8 \pm 4.21\%$, respectively.

By statistical analysis with ANOVA, significant differences were observed in the mean amount of the drug released at 120 min, for the different KTZ-loaded

Table 4: Medium values of KTZ content in WPUU samples.

Sample	KTZ content uniformity (%) ± SD[a]
WPUU-7/KTZ	90.1 ± 1.4
WPUU-17/KTZ	89.3 ± 1.2
WPUU-25/KTZ	91.5 ± 1.2
WPUU-38/KTZ	92.2 ± 1.3

[a]Average values (n=4) ± standard deviation (SD).

Figure 8: Release profiles from KTZ-loaded WPUU films in different dissolution media.

WPUU films ($p > 0.05$), suggesting that the different percentages of PEG-based segments have influenced the release of KTZ in simulated gastric juice. Therefore, the increase of KTZ release rate suggests an association with the progressive increment of the hydrophilicity of the systems. Thus, the greater the amount of PEG, the higher the hydrophilicity, which enhance the permeation of solvent into the delivery system, promoting the dissolution of the KTZ and its subsequent release from the polymer matrix. Studies relate that an increase in the amount of PEG or PEO segments on polymeric matrix is capable of enhancing the hydration of the chains of the delivery system and consequently raises the rate of drug release (12,54-56).

On the other hand, the maximum amount of KTZ released after 8 h did not indicate statistical difference ($p < 0.05$) with PEG-content segments variation. This effect may be related to degradation of the polymer matrix, since, for 300 min of KTZ release, the polymer began to offer no resistance to the drug, which was released to the dissolution medium with a total percentage close to 90%, regardless of the amount of PEG (57,58).

In order to better evaluate the mechanisms involved in the release of KTZ from WPUU films, a linear regression analysis was applied to the release curves in two stages of the dissolution assay (pH 1.2 and 7.4). KTZ release curves were adjusted to distinct models, zero-order, first-order and Higuchi release model, to investigate the possible mechanisms of drug release. The linear regression coefficients (R^2) are given in Table 5 and the best-fit model was selected on the basis of R^2. The different mechanisms involved in drug release are suggested in Figure 9.

According to Table 5, in simulated gastric juice (pH 1.2), all KTZ-loaded WPUU samples followed the Higuchi's kinetic model, because they presented better linearization of the curves, consequently, higher values of R^2. Higuchi

Table 5: The different kinetic models and regression coefficient (R^2) from KTZ-loaded WPUU films.

Sample	R^2 (pH 1.2)			R^2 (pH 7.4)		
	Zero-order	First-order	Higuchi	Zero-order	First-order	Higuchi
WPUU-7/KTZ	0.9593	0.7491	**0.9868**	0.9878	**0.9965**	0.9579
WPUU-17/KTZ	0.9341	0.7967	**0.9670**	0.9903	**0.9927**	0.9661
WPUU-25/KTZ	0.9072	0.7596	**0.9530**	0.9921	**0.9928**	0.9707
WPUU-38/KTZ	0.8712	0.7355	**0.9242**	0.9879	**0.9990**	0.9580

Polymer swelling and diffusion drug release

Polymer erosion and drug release
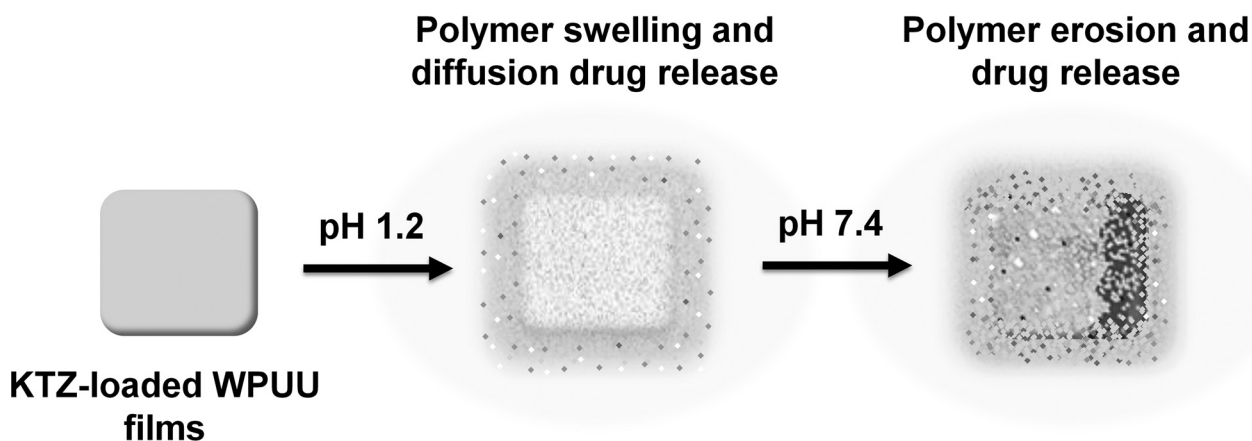
pH 1.2

pH 7.4

KTZ-loaded WPUU films

Figure 9: Schematic representation of the release mechanisms of KTZ-loaded WPUU films.

describes drug release as a diffusion process based in the Fick's law, square root time dependent. This means that the amount of drug released decreases with time of exposure to the dissolution medium (38,41,42). Therefore, it is suggested that the first stage of drug release may have occurred through the mechanism of drug diffusion from the polymer matrix, shown in the scheme of Figure 9. In addition, due to the hydrophilicity promoted by the PEG-based segments, a hydration (swelling) of the material and progressive gelation of the polymer chains occurred (33,55). The relaxation of the polyurethane chains, with volume expansion, enhanced drug dissolution and subsequent diffusion through the polymer matrix (54). This effect can be observed when films containing larger amounts of PEG-based segments have an increase in the release rate.

Considering the medium composed of simulated intestinal fluids (pH 7.4), again all KTZ-loaded WPUU films followed the same kinetic profile, but, in this case, the curves were more linear following the first-order model. The release occurred in a more sustained process, due to slow erosion of the polymer matrix (with gradual mass loss of polymer), wherein the amount of drug released per unit time decreased (Figure 9) (40). Release systems controlled by this mechanism have many advantages and can be applied as oral delivery systems (57). Therefore, the results of this study suggest that KTZ release has been determined, mainly, by the kinetic mechanisms of swelling of the polymer (with the formation of a gel layer), diffusion of the drug and, finally, erosion of the swollen polymer. Thus, KTZ-loaded WPUU systems based on amphiphilic copolymers of PEG-*b*-PPG, showed potential for application as controlled oral drug delivery systems (DDS).

4 Conclusions

In this work, pseudoplastic aqueous poly(urethane-urea)s dispersions (WPUU) were obtained with high contents of hydrophilic segments based on poly(ethylene glycol) (PEG). The incorporation of 5 wt% of ketoconazole (KTZ) in the dispersions produced stable systems against sedimentation and whole and homogeneous cast films with high drug content uniformity (more than 90%). Results of average particle size and FTIR suggested that KTZ, of lipophilic nature, may remained physically trapped within the micelle of the dispersions, by interaction with the PPG-based hydrophobic segments. Films containing different amounts of PEG-based segments provided controlled and sustained release of KTZ for a total period of 8 h, releasing more than 80% of the drug. WPUU systems containing higher percentages of PEG-based segments (25 and 38%) demonstrated higher capacity of releasing within the first 2 h, due to higher hydrophilicity, promoting greater release of the active in the gastrointestinal simulated juices. A combination of kinetic mechanisms of swelling of the polymer, diffusion of the drug and erosion of the swollen polymer commanded KTZ release kinetics. Thus, a novel drug delivery system (DDS) was produced from waterborne poly(urethane-urea)s showing to be promising for prolonged release of ketoconazole.

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