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Research Article

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Development and Evaluation of a Floating Multiparticulate Gastroretentive System for Modified Release of AZT

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Abstract. The aim of this study was to develop and evaluate a floating multiparticulate gastroretentive system for the modified release of zidovudine (AZT). AZT was used as a model drug water-soluble at therapeutic doses. The floating gastroretentive system was obtained by co-precipitation, after solvent diffusion and evaporation. The proposed system was evaluated *in vitro* for particle morphology, lag time and floating time, loading rate, release profile, and the release kinetic of AZT release. AZT's physico-chemical characteristics were evaluated by differential scanning calorimetry (DSC), X-ray diffraction (XDR) and infrared spectroscopy (IR). The particles obtained were sphere-shaped, hollow, and had porous walls. The floating was immediate, and floating time was higher than 12 h. The loading rate was 34.0±9.0%. The system obtained had an extended release. DSC and XDR results showed a modification in AZT's solid state. IR spectroscopy revealed that the chemical structure of the AZT was unchanged. The hollow microballoons presented gastroretentive, floating, and extended-release properties.

KEY WORDS: AZT; extended release; gastroretentive floating system; microballoons; modified release; zidovudine.

INTRODUCTION

The gastrointestinal tract has physiological and anatomical barriers that make it difficult for absorption of drugs by oral administration. However, this remains the most common means of drug administration. Drugs with a narrow absorption window are not completely absorbed in the higher gastrointestinal tract, stomach, and proximal duodenum. One of the reasons for the poor absorption of drugs in these anatomical segments is transit time, which is relatively short due to the gastric emptying rate (1,2). In such cases, controlling or increasing retention of the drug in the stomach is a valuable resource if bioavailability is improved (2,3). In a bid to minimize the bioavailability problems of drug delivery by the oral route, several modified release systems have been proposed. The purpose of these different systems is to control the site and release speed of the drugs and to provide reproducible, effective, and safe plasmatic concentrations (2,4,5).

Among the target-directed release systems that increase drug retention time, the gastroretentive systems for modified release have been particularly important (3,6,7). Using these systems, drugs may remain in the gastric region for several hours. Besides improving the bioavailability, prolonged gastric retention reduces drug loss, improves control of plasmatic concentrations, and allows introduction of new therapeutic regimens for known drugs with poor bioavailability, yielding substantial benefits to patients (7). The floating gastroretentive systems (FGS) are used to achieve gastric retention of orally administered solid dosage forms (7). The effectiveness and application of these systems have been evaluated *in vitro* and *in vivo*, and widely discussed (1,8–18). Kawashima *et al.* (9) have proposed a system of hollow microspheres (microballoons) to increase the containment time of tranilast and ibuprofen in the stomach. Many studies have been published on the usage of microballoons to achieve FGS for modified release of drugs with different properties (16–18). Although orally administered water-soluble drugs may also present bioavailability problems, the systems of modified release have been proposed mostly for drugs of poor solubility in water (9,10,19).

AZT was the first anti-HIV drug approved for clinical use and is widely used to treat the acquired immune deficiency syndrome (20,21). As a nucleosidic inhibitor of the viral reverse transcriptase, AZT interferes at the end of the HIV-1, HIV-2 replication cycle, in human T cell/lymphoma virus type 1, other mammal retroviruses, and in viral hepatitis B, preventing changes in host DNA (22,23). In the biopharmaceutics classification system (24), AZT (cLogP 0.043999 and

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solubility of 10 mg/mL, pKa 9.8) is classified in the low permeability and high solubility drugs group (class III). AZT half-life reaches approximately 60 min, and bioavailability of the oral form does not exceed 60%. Although clinically effective, the AZT presents dose-dependent toxicity. However, high daily doses (400 to 1,200 mg) are needed due to extensive first-passage metabolism (25,26). The severe toxicity caused by AZT can be minimized if oscillations in its plasma level are avoided and if the total administered dose is reduced (27,28). Given its greater solubility in acid pH, AZT is primarily absorbed in the upper gastrointestinal tract. Confining AZT to the stomach through the use of gastroretentive delivery systems is highly likely to increase the bioavailability of the drug used as a model drug water-soluble at therapeutic doses. The aim of this study was to prepare floating multiparticulate gastroretentive systems for extended release, using the AZT as the model drug.

MATERIALS AND METHODS

Materials

Polyvinyl alcohol (PVA) was purchased from Vetec Química Fina, Ltda. (Brazil). Dichloromethane was supplied by Synth (Brazil). Ethanol was purchased from Merck (Brazil). Isopropyl alcohol P.A. was purchased from Ecibra (Brazil). Eudragit S100® was supplied by Almapal (Brazil). AZT was supplied by Nortec Química (Brazil). All other chemicals and reagents used were of pharmaceutical grade.

Floating Gastroretentive System Preparation

The FGS was prepared using the diffusion and evaporation of the solvent (9,10,19). AZT and Eudragit S100 (1:5) were dissolved separately in an adequate amount of ethanol and mixed to obtain an isopropanol/dichloromethane (2:5) solution. This solution, containing AZT/Eudragit S100, was transferred at a constant flow of 2.0 mL.min^{-1} to an aqueous dispersion of 0.4% (*w*/*v*) PVA and kept at a temperature of 26±2.0°C, under constant agitation of 250 rpm. The co-precipitate of AZT/Eudragit S100/PVA was separated from the aqueous medium by filtration, oven-dried (50°C) and kept in a dessicator until a constant weight was obtained.

Assessment of AZT Loading

The assessment of AZT's incorporation was performed using approximately 100 mg of particles. These were dispersed in ethanol, and AZT was extracted during 24 h, under stirring. The solution was filtered, and the amount of AZT was determined spectrophotometrically at λ_{max} 266 nm (Spectrophotometer UV-Vis. Shimadzu-MultiSpec-1501). Measurements were carried out for each series of particles (n=3).

Floating Properties *In Vitro*

The floating properties were determined according to lag time (time particles took to reach water surface) and total floating time (time particles constantly floated on water surface) and were evaluated in a dissolution vessel (American Lab®-AL 1000) containing 900 mL of simulated gastric fluid without pepsin (pH 1.2) at 37°C stirred at 50 rpm, using dissolution apparatus II (29). The amount of time needed for the particles to float on the fluid (lag time) was recorded. The floating time was monitored during 24 h and registered as the total floating time of the particles. At the end of this period, the particles still floating were collected, placed on filter paper, and dried in an oven (50°C) until a constant weight was obtained. Measurements were carried out for each series of particles (n=6). The percentage of floating particles after 24 h was determined by Eq. 1, where P_i is the initial mass of the dry particles, P_f is the final mass of the particles after being dried in the oven, and m_f is the mass of the released drug. The m_f was determined in the dissolution medium by UV spectroscopy.

$$\text{floating}\ (\%) = \left(\frac{P_f + m_f}{P_i}\right)100 \quad (1)$$

Microballoon Morphology

The particles' gold powder-coated external and internal topographic structure was analyzed using a Spatter Coater plating machine (model SC7620) and high-resolution scanning electron microscope (Leica, model Leo 440i). The samples were randomly scanned, microphotographed at 5 kV, and magnified at ×500 to ×5,000. The hollow cavity and wall structure were visible in the fragmented particles.

Analysis by Infrared Spectroscopy, Differential Scanning Calorimetry, and X-ray Diffraction

The infrared spectra of AZT and microballoons (with and without AZT) were obtained by the KBr technique and recorded on a Fourier transform infrared (FTIR) spectrophotometer (Perkin Elmer, Spectrum One). The FTIR spectra were obtained by scanning at between 400 and 4,000 cm^{-1}. The samples were subjected to differential scanning calorimetry analysis (DSC) on a DSC-Q100 calorimeter (Shimadzu DTA 50), at heating cycles from 30°C to 350°C. The samples, weighing approximately 3 mg, were heated continuously at a rate of 10°C min^{-1} under constant nitrogen flow. The X-ray diffractograms were obtained on a Siemens D5000 X-ray diffractometer (filtered Ni and CuKa radiation). Analyses were done at a diffraction angle of 2 Φ (4° and 40°). The voltage and currents used were 30 kV and 30 mA, respectively.

Dissolution Test

The AZT release rate from the microparticles was examined *in vitro* for a 24-h period, using the dissolution method described in USP 31(Dissolutor American Lab, AL 1000, Brazil). The dissolution medium contained 900 mL of simulated gastric fluid (pH 1.2), without pepsin, at pH 1.2. The medium temperature was kept at 37°C (±0.5), and the stirring speed of the blades remained at 50 rpm. At

predetermined intervals, 5-mL samples were withdrawn from the dissolution medium and centrifuged at 3,500 rpm for 5 min. The supernatant was collected, with a micropipette, and the AZT concentration dissolved in the medium was determined by spectrophotometry (266 nm). The dissolution medium volume was kept constant by means of immediate reposition.

Model of Drug Release Kinetic

The quantitative analysis of the AZT release values obtained in dissolution tests is easier when mathematical formulas that express the dissolution results as a function of some of the dosage forms characteristics are used. Three mathematical models (summarized in Table I) were applied in this interpretation (30), where the scale parameter (a) defines the time scale of the process, the shape parameter (b) is obtained from the slope of the line, Q_t is the amount of drug dissolved in time, t, Q_0 is the initial amount of the drug in the solution, K_1 is the proportionality constant of first order, and K_H is the Higuchi dissolution constant.

RESULTS AND DISCUSSION

Eudragit S100 is a polymer derived from methacrylic acid that is easily soluble in an isopropanol/dichloromethane solution but practically insoluble in water. PVA K30 is a vinyl polymer with emulsifying properties. The mixing of AZT/Eudragit S100 and PVA K30 solutions led to the formation of microcoacervates of AZT/Eudragit S100/PVA K30/water. Evaporation of water produced a solid, multiparticulate, coated, hollow system with rigid walls (Fig. 1). Similar structures to this have been denominated microballoons (9,12–14,19,31). To attain this structure, the flow rate of the AZT/Eudragit S100 solution was adjusted to 2 mL.min^{-1}, the stirring speed of the PVA K30 solution set to 250 rpm, and the temperature of the system kept between 24°C and 28°C. Kawashima *et al.* (8) called this as quasi-emulsion system. In parallel with the coacervation process, diffusion of the isopropanol/dichloromethane alcohol mixture took place, with the consequent entry of water into the particle. Water evaporation from within the coacervates formed solid and multiparticulate structures with porous walls (Fig. 1). Similar structures were called microballoons (9,12–14,31). The microballoon formation mechanism proposed in this study is similar to the method proposed by Benita *et al.* (19). Prior to obtaining this system, several pre-formulation studies (data not presented) were carried out, under different conditions and using different kinds of polymers. The AZT/Eudragit S100 solution flow rate of 2 mL.min^{-1} was adjusted to the stirring speed of the PVA K30 solution to allow the formation of a strongly hydrated film on the surface of the dispersed drop and formation of the coacervate. The adjustment between the flow rate and the stirring speed influences microballoon rigidity and format. At higher stirring speed, the coacervate takes on a more longilinear shape as a result of mechanical stress. The interface created by the PVA K30 adsorbed on the coacervate surface prevented the coalescence of the dispersed drops and intercoacervate aggregation (9).

Table I. Representation of the Mathematical Models Used to Describe the Release Profiles

Model	Equation
Weibull	$\log [-\ln(1-(Q_t/Q_\infty))] = b \times \log\ t - \log\ a$
First order	$\ln Q_t = \ln Q_0 + K_1 t$
Higuchi	$Q_t = Q_0 + K_H t^{\frac{1}{2}}$

Floating and Loading

After a lag time of a few seconds, all microballoons (378.0 mg) remained afloat for 12 h. After 24 h, around 80% (222.0 mg) of them remained on the dissolution medium surface. Giving that AZT is highly hydrophilic (10 mg/mL), its 34.0±9.0% loading into the interior of the microballoons was considered satisfactory. Floating microparticulate gastroretentive systems similar to that obtained in this study have shown higher loading rate for poorly water-soluble drugs (9,10,12–14,19). The low yield here was probably related to the drug's diffusion into the aqueous medium during microballoon formation. Assuming that, when the drug's distribution coefficient is high, the efficiency of loading the drug into the microballoon walls increases (12); the loading rate achieved can be attributed to the drug's distribution coefficient in the solvent mixture. Using oil as a potentially less favorable diffusion medium for AZT, Rao *et al.* (32) obtained an encapsulation efficiency of between 41% and 54%. Mandal *et al.* (33,34) reported loading rates of between 5% and 17% for PGLA/AZT microcapsules, well below the levels obtained in the present study.

We believe the encapsulation efficiency can be optimized if the microballoons are formed more quickly. However, more studies will be needed to clarify the exact reasons underlying the encapsulation rates obtained in this and in similar studies.

Scanning Electron Microscopy

Figure 1a–d shows microballoon micrographs showing some morphological characteristics such as diameter, shape, and surface characteristics. Figure 1a, b shows the particles were sphere-shaped, with no surface pores, and with varying diameters. The microballoons' internal structure is characterized as a closed spherical cavity with a rigid wall made up of AZT, Eudragit S100, and PVA. The microballoons obtained in this study are very similar to those described by Kawashima *et al.* (9) but differ in the porous microspheres described by Benita *et al.* (19). Mateovic-Rojnik *et al.* (35) reported that 10°C and 40°C temperatures generated slow and quick solvent diffusion, respectively, and thus the granulometric distribution could reflect the distribution in the emulsion drop size which occurs immediately after combination of the two phases. This speculation may be justified by considering the microballoons' formation mechanism and the role of temperature in solvent diffusion and quasi-emulsion formation. However, we understand that adjustments to the flow rate of AZT/Eudragit S100, the stirring speed, and the hotness of the PVA K30 solution could produce considerable changes in the granulometric distri-

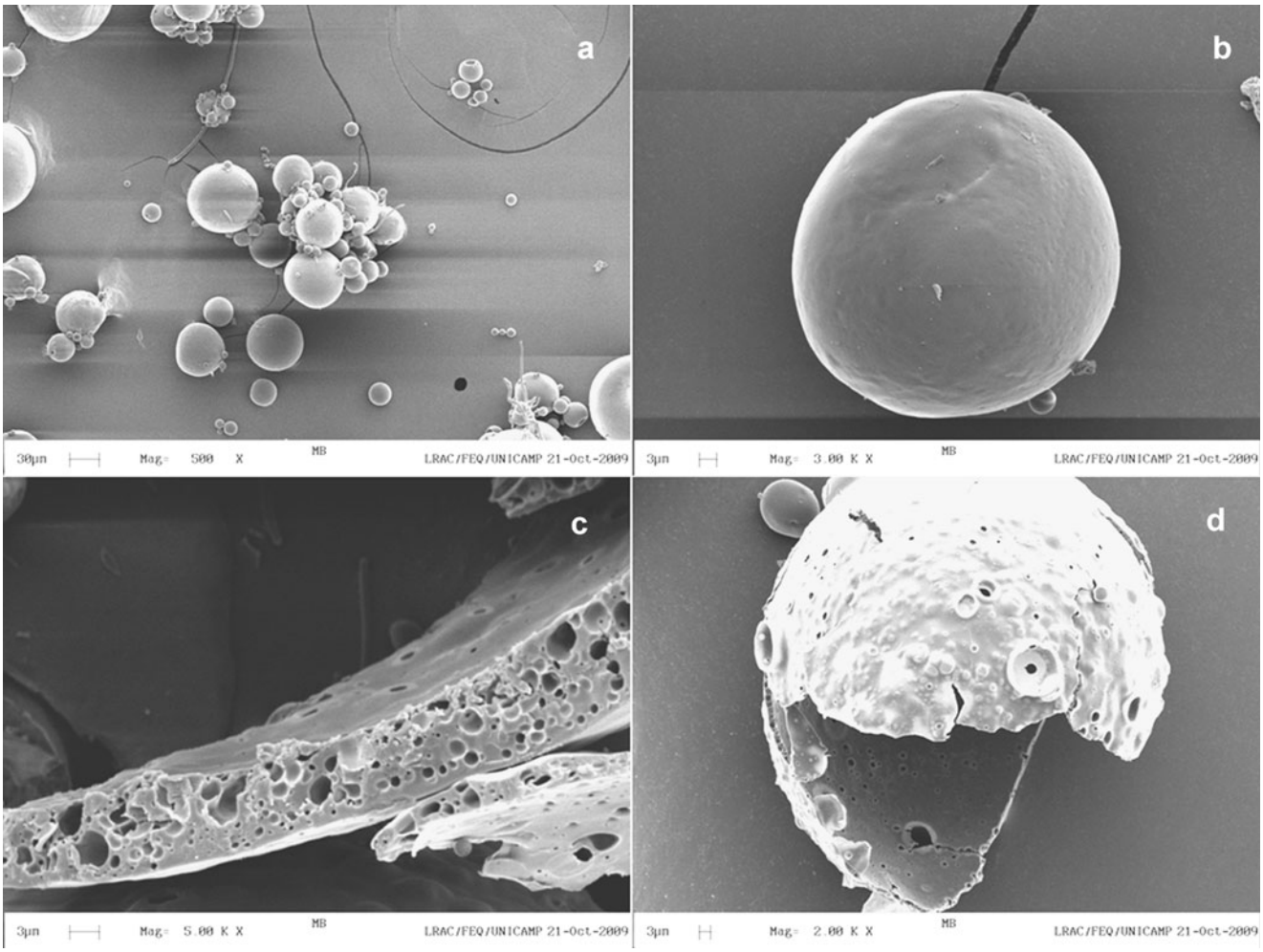

Fig. 1. SEM photographs: **a**, **b** External morphology of the microspheres, **c** fragment of the microsphere's wall, and **d** internal hollow cavity of a microsphere not completely formed

bution of the microballoons. Figure 1c shows a fragment of the microballoon wall revealing the presence of cavities that contribute to the floating process. It was assumed that these cavities were created initially by the diffusion of the solvent mixture and subsequently by water evaporation, forming cavities in the interior and in the wall of the microballoons (9). Figure 1 shows a microballoon with a partially formed internal structure.

Analysis by Differential Scanning Calorimetry

Thermograms of pure AZT and microballoons with and without AZT are shown in Fig. 2. The DSC curve of AZT (Fig. 2a) showed an endothermic peak at 125°C that corresponds to the AZT fusion point (32.36). After the endothermic fusion event, two consecutive exothermic events (between 225°C and 250°C) and one endothermic event, (at 310°C) are evident. This result is similar to that obtained by Rodrigues *et al.* (36) in study about application of thermal analytical techniques on characterization, purity determination, and degradation kinetic of AZT. The DSC results for the microballoons, with and without AZT (Fig. 2b, c, respectively), does not show the fusion endothermic peak of the crystalline form of AZT. This suggests that AZT is not in this form in the microballoons. El-Kamel *et al.* (37) and Mateovic-Rojnik *et al.* (35), respectively, encountered similar results for Eudragit S100

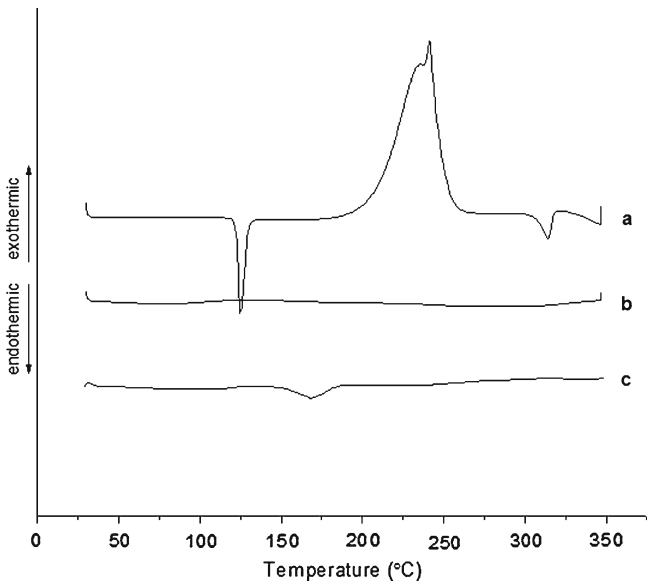

Fig. 2. DSC curves of AZT (**a**) microballoons with AZT (**b**), and microballoons without AZT (**c**)

with Eudragit RL microparticles containing ketoprofen and Eudragit RS 100 microspheres containing ketoprofen and assumed that drug was in amorphous state.

Analysis by X-ray Diffraction

The non-crystalline state of AZT in the microballoons was confirmed by XDR. Figure 3 shows the diffractogram of pure AZT and of the microballoons with and without AZT. The diffractogram of pure AZT indicates the crystalline structure of the drug while diffractograms of the microballoons with and without AZT present the same pattern. This result confirms the change in the solid state of AZT from crystalline to amorphous. Similar results reported for other sustained-release microsphere studies had the same interpretation for nitrendipine, famotidine, and ketoprofen (11,15,35–38). The change from crystalline to amorphous state does not affect the activity of AZT because all of the functional groups were present.

Analysis by Fourier Transform Infrared (FTIR) Spectroscopy

The FTIR spectra are shown in Fig. 4. Both the spectra of pure AZT and microballoons with AZT show the characteristic peaks of the carbonyl group in 1,683 cm^{-1} and of the azide group in 2,083 cm^{-1}. One band in 1,380 cm^{-1} is assigned to CH_2 and one band in 1,281 cm^{-1} is assigned to the C–O–C and the C–OH groupings. The intervals of the stretching bands in this study were similar to those obtained by Araújo *et al.* (38) and indicate the stable nature of AZT during the production process of the microballoons. All of the functional groups were present. The lower intensity of some of the peaks in Fig. 4b was due to the dilution effect.

Release Behavior of AZT *In Vitro*

The AZT release from the microballoons occurred in a four-phase manner, with an initial release burst of 30% (Fig. 5). Mateovic-Rojnik *et al.* (35), studying the existing correlation between polydispersity, average diameter of the particles, porosity and polymer-to-drug ratio in the release characteristics of the drug in multiparticulate systems using a microspheres format, concluded that the factor with the strongest effect on the release profile of the drug was the surface characteristic of the particles. AZT in an amorphous form, in a solid dispersion with the Eudragit S100 present in the most peripheral layer of the microballoon, provides the initial burst. The slower release of AZT, in the time interval between 2 and 10 h, can be attributed to the diffusion speed of AZT, which was controlled by the insolubility of Eudragit S100 at a pH below 6.0. The second burst release occurring between 10 and 12 h can be attributed to the relaxation of the polymeric chains. The initial burst can be considered a positive event as it allows the drug to quickly reach adequate plasma concentrations and to initiate the expected pharmacological effect. The physical structure of the microballoons remained macroscopically unchanged throughout the whole evaluation procedure of the release profile.

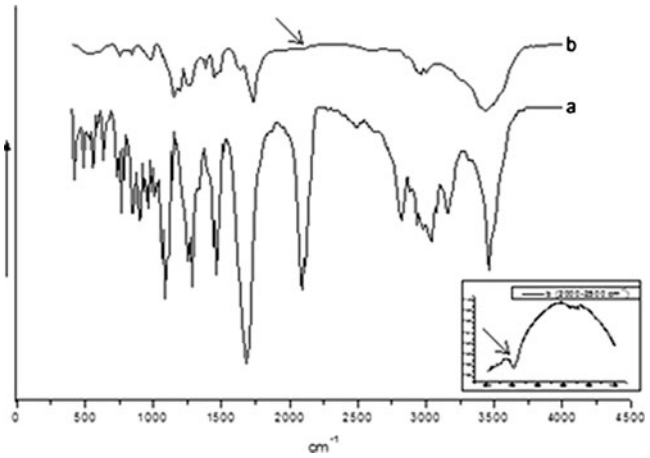

Fig. 4. FTIR spectra of AZT (**a**) and microballoons (**b**)

Release Kinetics

The dissolution profile of AZT was modeled and compared in order to evaluate the release kinetics (30). The models evaluated were Weibull, first order, and the Higuchi.

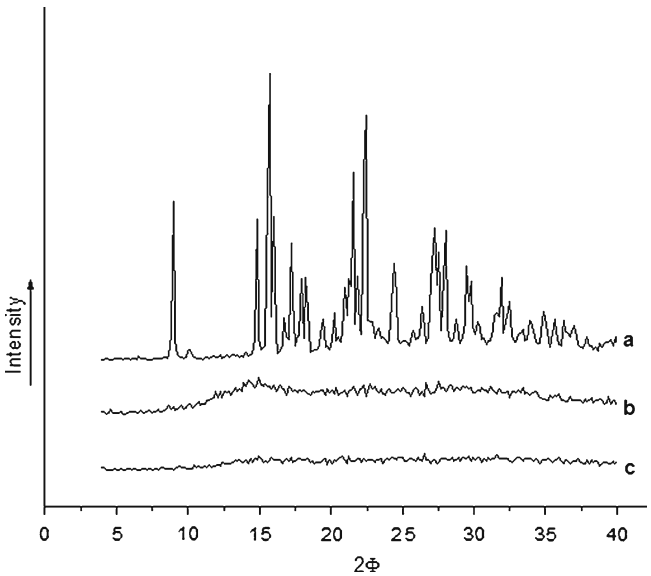

Fig. 3. X-ray diffractograms from AZT (**a**), from the microballoons with AZT (**b**), and without AZT (**c**)

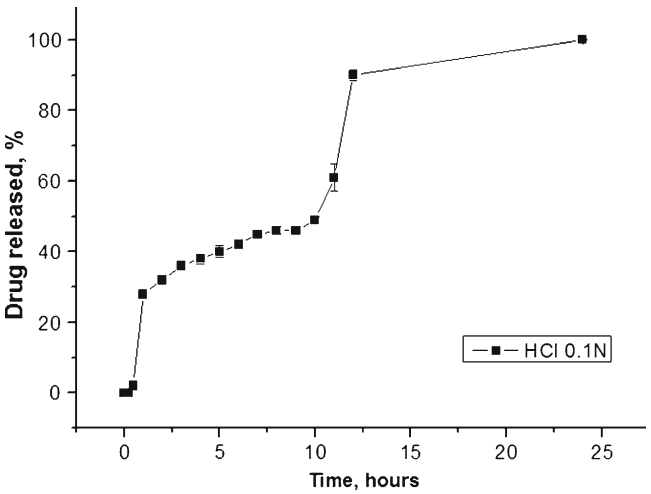

Fig. 5. Release profile of AZT from the microballoons. The *error bars* show the standard deviation for $n=6$

After the linearization of the results obtained in the dissolution test, the determination coefficients (R^2) were 0.889, 0.8062, and 0.8728, respectively. The drug-release profile took the form of a four-phase sigmoid curve. In these cases, the Weibull mathematics model for curve fit yielded R^2=0.889, indicating a minimal initial burst and release system mediated by diffusion. With a diffusion process based on Fick's law, the Weibull model was the one that better described the AZT release. This result is in agreement with the considerations proposed in this study regarding the release profile of AZT from the microballoons.

CONCLUSION

This study has shown that it is possible to achieve floating gastroretentive systems of extended release for AZT and drugs primarily absorbed in the stomach or the proximal duodenum. The results showed that the floating properties were obtained as a result of the cavity and porous walls of the microparticles. AZT in a solid dispersion with Eudragit S100 and PVA permitted the control of AZT release. Further experiments will be carried out to increase the loading rate of water-soluble drugs in floating multiparticulate gastroretentive systems.

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