A novel gastroretentive floating system for zidovudine, based on calcium-silicate beads

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The aim of the research effort entertained herein was to develop, evaluate and fully characterize a multiparticulate floating gastroretentive system for the modified release of zidovudine (AZT), an antiretroviral drug. AZT was used as a water-soluble model drug at therapeutic doses. The floating gastroretentive system was obtained via polymer coating of calcium silicate-adsorbed AZT. The proposed system was evaluated in vitro for particle micromorphology, lag time for floating and duration of floating, drug loading capacity, drug release profile, and drug release kinetics. The physicochemical properties of AZT were evaluated by scanning electron microscopy (SEM) analyses, differential scanning calorimetry (DSC) analyses, X-ray diffraction (XRD) analyses, and infrared spectroscopy (FTIR) analyses. Results from SEM analysis of the AZT-containing floating gastroretentive granules allowed observation of an irregular surface and the apparent absence of pores. Floating of the AZT-containing gastroretentive granules was immediately achieved, that is lag time for floating was virtually zero and duration of floating was higher than 12 h. The drug loading capacity of the floating gastroretentive granules was ca. 81.09 ± 14.66%, and the release system thus obtained exhibited an extended drug release profile. Results from DSC and XRD analyses showed a modification in the AZT solid state, while the FTIR spectroscopy analyses revealed that the chemical structure of AZT remained unchanged upon adsorption to calcium silicate followed by polymeric coating. Hence, the coated granules produced presented gastroretentive, floating, and extended drug release properties.

Key words: 3-azidothymidine (AZT), cal-sil floating granules, gastroretentive floating system, extended drug release, zidovudine (AZT), polymer coating.

INTRODUCTION

The gastrointestinal tract (GIT) has a natural physiological and anatomical barrier that makes difficult the absorption of drugs after their oral administration. Drugs with a narrow absorption window are not completely absorbed in the upper GIT, namely in the stomach and proximal duodenum (Narendra et al., 2006). One possible
reason for the poor drug absorption in these anatomical segments lies in the relatively short transit time, which is mainly due to the gastric emptying rate (Narendra et al., 2006; Shah et al., 2009). In such cases, the control of drug residence time, particularly aiming at increasing drug retention time in the stomach, is a valuable resource to improve bioavailability (Shah et al., 2009; Arora et al., 2005). In an effort to minimize bioavailability problems following drug delivery by the oral route, several modified release systems have been proposed, the aim of which was to control the site of, and/or the release rate of drugs, while providing reproducible, effective, and safe plasmatic concentrations (Shah et al., 2009; Talukder and Fasshi, 2004; Lopes et al., 2005; Yoshida et al., 2011).

Among the target-directed drug release systems that increase the drug retention time, gastroretentive modified drug release systems are of particular significance (Arora et al., 2005; Soppimath et al., 2001; Garg and Sharma, 2003). By using such systems, drugs may remain in the gastric region for longer periods of time, typically several hours. Besides improving the drug bioavailability, prolonged gastric retention times reduces drug loss and improves the control over plasmatic drug concentration, allowing introduction of new therapeutic regimens for known drugs with poor bioavailability with concomitant substantial benefits to the patients (Garg and Sharma, 2003). The floating gastroretentive systems (FGS) are used to achieve prolonged gastric retention of orally administered solid dosage forms (Garg and Sharma, 2003; Pandya et al., 2011). The use and effectiveness of these FGS systems have been evaluated both in vitro and in vivo, and also widely discussed in the specialty literature (Kawashima et al., 1992; Benita et al., 1990; Cui et al., 2003; Sato et al., 2004a, b; Gupta and Pathak, 2008; Ramachandran et al., 2010; Pandya et al., 2011).

Jain et al. (2008) investigated the use of ranitidine hydrochloride as a model drug adsorbed onto calcium silicate doubly coated with hydroxypropylmethylcellulose and ethylcellulose dispersions, obtaining a system consisting of polymeric-coated granules that exhibited a gastroretentive release profile with a flotation duration timeframe of 8 h. Both in vitro and in vivo assays demonstrated the potential of that system for attaining the sustained release of the drug when compared with their non-floating counterparts. The nucleoside analog 3'-azidothymidine (AZT), or zidovudine, has been shown to efficiently block the replication of HIV virus in (in vitro) cell culture (Mitsuwa et al., 1985; Rachlis, 1990). Subsequent studies demonstrated that the AZT action mechanism occurs via the selective inhibition of HIV virus reverse transcriptase by its triphosphate metabolite. These discoveries have established the appearance of the first generation of antiretroviral agents: nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs) (Cihlar et al., 2010). As a viral reverse transcriptase nucleoside inhibitor, AZT interferes with the ending of the replicative cycle of HIV-1 virus, HIV-2 virus-1 in T cells/lymphoma in hu-mans, in other mammalian retroviruses and in hepatitis B antiviruses, thus preventing changes in the host DNA (Dienstag et al., 1995). The AZT half-life in the human body reaches approximately 60 min, with the bioavailability of the oral dosage form not exceeding 60%. However, high daily administration doses (from 400 mg up to 1200 mg) are usually required due to extensive hepatic first-passage metabolism (Klecker et al., 1987; Sharma et al., 2008).

The severe toxicity caused by AZT can be minimized if oscillations in its blood plasma level are avoided and if the total daily administered dose is reduced (Carvalho et al., 2009). The confinement of AZT to the stomach through the use of floating gastroretentive delivery systems is highly reliable in increasing the bioavailability of this drug. Hence, the major goal of the research effort entertained herein was to optimize, prepare, and fully characterize physicochemically, a floating multiparticulate gastroretentive system for the extended release of AZT, consisting of calcium silicate, ethylcellulose, hydroxypropylmethylcellulose and Eudragit® L100.

**MATERIALS AND METHODS**

**Reagents**

AZT was supplied by Nortec Química S.A. (Duque de Caxias RJ, Brazil). Ethylcellulose (Ethocel® 100 cp) and hydroxypropylmethylcellulose (HPMC) (Methocel K4M®) was supplied by Colorcon do Brasil Ltda. (Cotia SP, Brazil). Anionic copolymers based on methacrylic acid and methyl (Eudragit® L100) was supplied by Almapal (São Paulo SP, Brazil). Low density calcium silicate (Ca₂SiO₄ or Cal-Sil) was purchased from Vetec Química Fina Ltda. (Duque de Caxias RJ, Brazil). Sodium bicarbonate (NaHCO₃) was purchased from Dubon Ltda. (São Paulo SP, Brazil). All other reagents were of pharmaceutical grade, PA grade or better, and the water used was purified in a Milli-Q Plus 185 system (Molsheim, France) to a final conductivity of ca. 18.2 MΩ cm⁻¹.

**Experimental**

**Preparation of calcium silicate (Cal-Sil) particles with adsorbed AZT**

Low density Cal-Sil was dispersed into ethanol (1:3 w/v) containing 0.2 g AZT and 0.25 g sodium bicarbonate, so as to produce a slurry. The resulting slurry was ultrasonicated for 10 min at 40°C (in a ultrasonicator from UNIQUE®, model UC, Indiaituba, Brazil), so as to enhance penetration of the dissolved drug into the core of Cal-Sil via particle pores. The excess ethanolic solution was then removed by vacuum filtration, followed by drying of the resulting particles with adsorbed AZT under vacuum at room temperature.

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Polymer coating the produced granules of calcium silicate with adsorbed AZT

Preparation of polymer-coated granules of calcium silicate with adsorbed AZT was carried out in two steps: (i) 5 g of Cal-Sil AZT-sodium bicarbonate-adsorbed particles were dispersed in 10 ml of Ethylocellulose:Eudragit® L100:HPMC (70:10:20) in ethanolic dispersion at 5% (w/v), until production of a cohesive wet mass with moldable consistency for further granulation; (ii) 5 g of the primary coated granules (PCG) were dispersed in 10 ml of an ethanolic dispersion at 5% (w/v) of Ethylocellulose:HPMC (80:20), until production of a cohesive wet mass with moldable consistency for further regranulation. The granules obtained after the second coating process were labeled as SCG.

Determination of drug loading efficiency

The drug content of the granules was determined by dispersing ca. 100 mg of formulation (accurately weighed) into 100 ml ethanol under magnetic stirring (set at 200 rpm) for 24 h, to extract AZT. Following filtration through a membrane with 0.25 µm pore size, the drug concentration was determined spectrophotometrically at a wavelength of 266 nm, in a UV-Vis spectrophotometer from Shimadzu (model MultiSpec 1501, Tokyo, Japan). All spectrophotometric determinations were performed in triplicate. Drug loading efficiency (particle percent drug loading) was calculated as the ratio between the drug determined via interpolation of the absorbance readings in an analytical curve (Abs (266 nm) = f([AZT] mg/L)) and the drug offered in the preparation of the particles (that is, the theoretical drug loading) (Equation 1).

\[
\text{Drug loading (\%) = } \frac{\text{Calculated drug loading}}{\text{Theoretical drug loading}} \times 100
\]  

Determination of buoyancy

Cal-Sil AZT granules (100 mg) were poured in a simulated gastric fluid without pepsin (pH 1.2; 37°C; 900 ml) kept in a dissolution device equipped with a type-II apparatus (shaft) from American Lab (model AL1000, São Paulo, Brazil). Following a 24 h timeframe under stirring at 50 rpm, the layer of floating granules was separated by filtration and dried in an oven (50°C) until constant weight was attained. The resulting dry residue (consisting of floating granules) was weighed, and the buoyancy ability was determined in sextuplicate by using Equation 2, where \(P_i\) is the initial mass of the dry coated particles before introduction in the dissolution device, \(P_f\) is the final mass of the particles gathered (floating layer) after being dried in the oven, and \(m_r\) is the mass of drug released in the dissolution medium as measured by UV spectrophotometry (Yoshida et al., 2011).

\[
\text{Buoyancy (\%) = } \frac{P_i + m_r}{P_f} \times 100
\]  

Structural microanalysis of the double-coated calcium silicate particles with adsorbed AZT, via scanning electron microscopy

The external morphology of the Cal-Sil granules with adsorbed AZT was evaluated via scanning electron microscopy (SEM) analyses using a Stereoscan scanning electron microscope from Leica (model Leo 440i, Leica-Weiss, Cambridge, UK), using a Sputter coater from Leica (model SC7620, Cambridge, UK). The samples for SEM analysis were prepared by lightly sprinkling the powdered particles on an adhesive double face tape kept adhered on an aluminium stub. The samples were then sputter-coated with gold to a thickness of about 300 Å, under inert (argon) atmosphere with high-vacuum evaporator. The samples were randomly scanned, photomicrographed at 5 kV, and magnified at ×500 up to ×5000.

Infrared spectroscopy, differential scanning calorimetry, and X-ray diffraction analyses

The infrared spectra of free AZT and of both coated Cal-Sil granules with and without AZT were gathered via use of a KBr technique, and recorded on a Fourier transform infrared (FTIR) spectrophotometer (from Perkin Elmer, model Spectrum One, Shelton CT, USA). The FTIR spectra were obtained by scanning at a wavelength ranging from 400 to 4000 cm\(^{-1}\). The samples of free AZT and of both coated Cal-Sil granules with and without AZT were also analyzed by differential scanning calorimetry (DSC) on a differential scanning calorimeter from Shimadzu (model DSC-Q100, Tokyo, Japan) coupled with a thermal analyzer also from Shimadzu (model DTA 50, Tokyo, Japan). Samples weighing ca. 3 mg were placed inside aluminum pans, duly sealed, and subject to a heating cycle from 30 to 350°C at a constant heating rate of 10°C min\(^{-1}\) under inert (nitrogen) atmosphere. The X-ray diffractograms of samples of free AZT and of both coated Cal-Sil granules with and without AZT were obtained on an X-ray diffractometer from Siemens (model D5000, Munich, Germany) using filtered Ni and CuKα radiation. Analyses were performed at a diffraction angle of 2θ (from 4 to 40°), with voltage and current set at 30 kV and 30 mA, respectively.

In vitro AZT release assays from the double-coated Cal-Sil granules

The release rate of AZT from the double coated Cal-Sil granules was followed during a 24 h timeframe using the afore mentioned dissolution apparatus (Dissolutor from American Lab, model AL 1000, Charqueada, São Paulo, Brazil) and the dissolution method described in US Pharmacopeia 31 (2008), with 900 ml of simulated gastric fluid (pH 1.2) without pepsin as dissolution medium, at a constant temperature of 37 ± 0.5°C and under magnetic stirring set at 50 rpm. At predetermined time intervals, 5 ml-samples of dissolution medium were withdrawn and centrifuged at 3500 rpm for 5 min. The supernatant was then collected carefully and filtered through a 0.25 µm pore size membrane filter and the concentration of dissolved AZT determined via spectrophotometry at a wavelength of 266 nm. The total volume of dissolution medium in the dissolutor was kept constant at all times via addition of 5 ml of fresh dissolution fluid with the same temperature, immediately after every sample withdrawal. All assays were performed in sextuplicate.

Mathematical description of AZT release pattern from the double-coated Cal-Sil granules

The quantitative analysis of the AZT release values produced in the dissolution tests becomes easier when mathematical models that express the dissolution results as a function of some characteristics of the dosage forms are utilized. Three mathematical models (Table 1) were applied to describe AZT release pattern from the double-
coated Cal-Sil granules, according to the work by Costa and Lobo (2001), where $Q_t$ is the amount of drug dissolved in time $t$, $Q_0$ is the initial amount of the drug in solution, $K_0$ is a zero-order constant, $K_1$ is a first-order proportionality constant, and $K_H$ is the Higuchi dissolution constant. $R^2$ values were calculated via linear regression fittings of the dissolution models (Table 1) to the transformed experimental data.

**RESULTS AND DISCUSSION**

**Structural morphology of the double-coated Cal-Sil granules with adsorbed AZT**

Double-coated, low density Cal-Sil-based floating granules with adsorbed AZT were prepared by wet granulation. The Cal-Sil granules with adsorbed AZT were coated with ethylcellulose, Eudragit® L100 and HPMC, which can produce porous structures within the granules. The undissolved polymer particles produced irregular rough surfaces on the granules (Figure 1).

**Structural microanalysis of the Cal-Sil particles with adsorbed AZT, via scanning electron microscopy**

Figure 2a showed a SEM image of a low density Cal-Sil particle at ×5000 magnification, allowing observation of a porous and rough surface. The presence of pores suggested that Cal-Sil has a good capacity for drug loading. Figure 2b shows a SEM microphotograph of primarily coated Cal-Sil granule with adsorbed AZT (PCG), at ×1000 magnification, clearly showing some pores on the surface of the coated particle, thus demonstrating that the polymer blend was not able to thoroughly coat the Cal-Sil particles. Hence, this PCG structure would not be able to increase sufficiently the diffusion layer of the granules so as to allow attainment of the desired AZT release rate. Figure 2c shows a SEM microphotograph of a secondarily coated Cal-Sil granule with adsorbed AZT (SCG), also at ×1000 magnification, now showing less pores on the particle surface. Therefore, increasing the diffusion layer can provide a modified and more controlled release of AZT from the Cal-Sil granules.

**Buoyancy and drug content**

Immediately after being sprinkled on the surface of the simulated liquid gastric fluid, the granules sunk to the bottom of the container. Despite the relatively high surface tension of simulated gastric fluid, the time taken for the double-coated Cal-Sil granules with adsorbed AZT to float (that is, the lag time) was only a few seconds. After this short lag time, all granules floated and remained afloat for more than 12 h. After a 24 h timeframe, ca. 40 ± 3% of the granules still remained floating in the simulated gastric fluid. The short time needed for the granules to float can be attributed to the release of carbon dioxide produced in the reaction of (simulated) gastric HCl with the sodium bicarbonate present in the granules. On the other hand, the permanence of the granules on the surface of the simulated gastric fluid can be attributed to the high swelling capability of HPMC, which promoted swelling of the granules with concomitant decrease in density. Buoyancy of 100% of the granules for ca. 12 h was considered to be very good. The percentage of adsorbed AZT was 81.00 ± 14.66%, which may be considered a satisfactory drug loading efficiency despite the standard deviation of ±14.66%.

**Thermal analyses by Differential Scanning Calorimetry**

The thermograms of pure AZT and of both double-coated Cal-Sil granules with and without adsorbed AZT are displayed in Figure 3. The thermogram of pure AZT (Figure 3a) showed an endothermic peak at 125°C that corresponds to the AZT melting point. After the endothermic fusion event, one can observe two consecutive exothermic events (between 225 and 250°C) probably implicated in AZT degradation, and another endothermic event (at 310°C). The results obtained are similar to those reported by Rodrigues et al. (2005) in a study about application of thermal analytical techniques for the characterization, purity determination, and degradation kinetics of AZT. The results obtained from the DSC analysis of the double-coated Cal-Sil granules without AZT (Figure 3b) and of the double-coated Cal-Sil granules with adsorbed AZT (Figure 3c) clearly suggest that AZT is in an amorphous form in the double-coated Cal-Sil granules (Figure 3c). The differences in peak size may be interpreted either as being related to the amount of AZT adsorbed in the Cal-Sil granules or as a decrease in the degree of crystallinity upon adsorption onto the Cal-Sil granules.

**X-ray Diffraction analyses (XRD)**

X-ray diffraction analytical techniques are especially significant for the analysis of solid materials. The decisive
advantage of X-ray diffraction methods over other analytical techniques is based on the unique character of the diffraction patterns of crystalline substances, the ability to distinguish between elements and their oxides, and the possibility to identify chemical compounds, polymorphic forms, and mixed crystals by a non-destructive examination. The results obtained in the X-ray diffraction analysis performed to pure AZT, and to both double-coated Cal-Sil granules with and without adsorbed AZT, are displayed in Figure 4. Since the intensity of the peaks in the diffraction patterns also depends on the drug concentration, a decrease in the size of peaks was expected for the systems encompassing double-coated granules. Figure 4a showed the diffractogram of pure AZT, Figure 4b shows the diffractogram of double-coated Cal-Sil granules without AZT, and Figure 4c shows the diffractogram of double-coated Cal-Sil granules with adsorbed AZT. The diffractogram of pure AZT (Figure 4a) indicated the crystalline structure of the drug while the diffractograms of both double-coated Cal-Sil granules with and without adsorbed AZT presented the same pattern, thus suggesting that AZT adsorbed to Cal-Sil and further double-coated with polymer may in fact be in an amorphous or crystalline state, hence confirming the results obtained in the thermal analyses via differential scanning calorimetry. Similar results have been reported by other research groups (Cui et al., 2003; Gupta and Pathak, 2008; El-Kamel et al., 2001; Mateovic-Rojnik et al., 2005).

Analysis by Fourier transform infrared (FTIR) spectroscopy

The results obtained in the FTIR analyses performed are displayed in Figure 5. The FTIR spectra of pure AZT is displayed as Figure 5a while that of double-coated Cal-Sil granules with adsorbed AZT is displayed as Figure 5b. Both spectra of pure AZT and of double-coated Cal-Sil granules with adsorbed AZT exhibit characteristic peaks between 3,200 and 3,500 cm\(^{-1}\), which represented the wavelength range assigned to the O-H stretching band, a carbonyl group at 1,683 cm\(^{-1}\), and an azide group at 2,083 cm\(^{-1}\). One peak at 1,380 cm\(^{-1}\) was assigned to methylene (CH\(_2\)) and the one at 1281 cm\(^{-1}\) is assigned to C–O–C and C–OH groups. The intervals of the stretching peaks in the research effort entertained herein were similar to those reported by Araújo et al. (2003), and indicated the stable nature of AZT during the production process of the double-coated Cal-Sil granules. All the chemical functional groups of AZT were present in the FTIR spectra. The lower intensity of some peaks displayed in Figure 5b was due to the dilution effect upon
Figure 2. Scanning electron microphotographs of (a) Cal-Sil particles (magnification: x5000), (b) Primary coated Cal-Sil granules (PCG) (magnification: ×1000), and (c) double-coated Cal-Sil granules (SCG) (magnification: ×1000).
AZT adsorption onto the Cal-Sil granules prior to double-coating with the polymer. Comparison between Figures 5a and 5b shows no peak displacement at all, denoting a full conservation of the spectrum profile, which can most likely mean that AZT virtually does not undergo chemical interaction with the polymer upon double-coating after its adsorption onto the Cal-Sil particles, just being carried by the gastroretentive system, which is in close agreement
with the release profile observed for AZT (Figure 6).

**In vitro release pattern of AZT**

The release of AZT from the double-coated Cal-Sil granules in simulated gastric fluid (pH 1.2) is influenced more significantly by parameters such as the polydispersity, the mean diameter of particles, the porosity, and the homogeneity of drug distribution pattern inside the particles. Mateovic-Rojnik et al. (2005) studied the correlation of some particle features in the release of ketoprofen, and concluded that the surface characteristics of the particles had a more pronounced effect on the release profile of the drug. Figure 6 displays the results obtained for the release pattern of AZT from the double-coated Cal-Sil granules in simulated gastric fluid. Since the acrylic polymer used for double-coating the Cal-Sil granules with adsorbed AZT is soluble at pH values above 6.0, it can be assumed that the drug release occurred by diffusion. From a close inspection of Figure 6, one can notice that ca. 30% of AZT was released from the granules in the first hour, 70% after 12 h and 100% after 24 h. The initial burst effect may be attributed to the high aqueous solubility of AZT. The release profile obtained and displayed in Figure 6 is very likely related to the thickness of the diffusion layer and its saturation. During the whole dissolution test, the physical structure of the granules remained almost unchanged, except for a light swelling, thus virtually excluding the occurrence of any erosion of the granules.

**In vitro AZT release mechanisms study**

The release behavior of AZT from the floating double-coated Cal-Sil granules was also investigated on the basis of theoretical dissolution models, including a zero-order, a first-order, and Higuchi mathematical models. The regression coefficients ($R^2$) produced via linear regression fittings of the dissolution models (Table 1) to the experimental data from in vitro release trials of AZT in simulated gastric fluid, after data transformation, were 0.9522, 0.9677, and 0.9922, respectively for the zero-order, first-order, and Higuchi mathematical models. As the plain diffusion process based on Fick’s law, the Higuchi matrix model was the one that better described the AZT release from double-coated Cal-Sil granules, which was indicative of a drug release indicating process by diffusion mechanism, excluding from further consideration any erosion of the particles. This was in fact duly confirmed by the fact that all double-coated Cal-Sil granules remaining afloat in the simulated gastric fluid, far beyond the experimental timeframe.
Figure 6. In vitro release profile of AZT from the double-coated Cal-Sil granules with adsorbed drug, and associated standard deviations (n=6).

Conclusions

The present formulation study of AZT was performed in an attempt to prepare a floating drug delivery system consisting of a floating multiparticulate system. The use of low density calcium silicate proved successful, achieving a good loading rate. The double coating proved to be an effective method for producing intra-granular pores and achieving the desired release and buoyancy behavior. Low density Cal-Sil-based floating granules with adsorbed AZT (percentage of adsorbed AZT of 81.00 ± 14.66%), prepared by wet granulation, and further double-coated with ethylcellulose, Eudragit® L100 and HPMC, produced irregular rough surfaces and porous structures within the granules. Immediately after being sprinkled on the surface of the simulated liquid gastric fluid, the granules sunk to the bottom of the container but only for a few seconds, quickly floating towards the surface where they remained afloat. Buoyancy of 100% of the granules for ca. 12 h was considered to be very good. The results obtained from the calorimetric analysis of the double-coated Cal-Sil granules without AZT and of the double-coated Cal-Sil granules with adsorbed AZT clearly suggests that AZT is in an amorphous form upon adsorption onto the Cal-Sil granules prior to double-coating with polymer.

The X-ray diffractogram of the pure (free) drug and the diffractograms of both double-coated Cal-Sil granules with and without adsorbed AZT presented the same pattern, thus suggesting that AZT adsorbed to Cal-Sil and further double-coated with polymer was in fact in an amorphous state, hence confirming the results obtained both in the thermal analyses via differential scanning calorimetry and in the FTIR spectrophotometry. Additionally, the FTIR analyses performed allowed to conclude about the stable nature of AZT during the production process of the double-coated Cal-Sil granules, which can most likely mean that AZT virtually does not undergo chemical interaction with the polymer upon double-coating after its adsorption onto the Cal-Sil particles, just being carried by the gastroretentive system, which is in close agreement with the release profile observed for AZT. Since the acrylic polymer used for double-coating the Cal-Sil granules with adsorbed AZT is soluble at pH values above 6.0, it can be assumed that the drug release occurred by diffusion.

The release profile obtained for AZT is very likely related to the thickness of the diffusion layer and its saturation. The Higuchi matrix model was the one that better described the AZT release from double-coated Cal-Sil granules, which was indicative of a drug release process via a diffusion mechanism, virtually excluding from further consideration of any erosion of the particles, this was in fact duly confirmed by the fact that all double-coated Cal-Sil granules remained afloat in the simulated gastric fluid, far beyond the experimental timeframe.
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