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Gastro-Resistant Controlled Release of OTC Encapsulated in Alginate/Chitosan Matrix Coated with Acryl-EZE® MP in Fluidized Bed

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ABSTRACT: A gastro-resistant system of acryl-EZE® MP coated alginate/chitosan microparticles was developed to improve the controlled release of oxytetracycline (OTC). Microparticles were obtained by complex coacervation and, thereafter, were coated using fluidized polymer dispersion with acryl-EZE® MP solution. OTC distribution inside the microparticles was determined by multiphoton confocal microscopy, demonstrating the efficiency of encapsulation process. *In vitro* OTC release kinetic was performed in order to obtain the release profile in gastric and intestinal simulated fluids. A fast initial release, or burst effect, was observed with uncoated microparticles loaded with OTC in gastric conditions. When a 50% mass increase in acryl-EZE® MP coating was achieved, OTC release in acidic medium was greatly reduced, resulting in the expected gastro-resistant effect. Different mathematical models were applied to describe the drug diffusion across the polymer matrix. The Logistic model was the best tool to interpret the experimental data in most of the systems studied. © 2014 Wiley Periodicals, Inc. J. Appl. Polym. Sci. **2014**, *131*, 40444.

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INTRODUCTION

When selective delivery of a drug to a specific gastrointestinal region is pursued, protective coating is required to ensure that the formulation delivers and releases its drug content to the target site.[1] Processes for coating and/or surface modification have been investigated[2–6] with the aim of obtaining materials with specific characteristics in order to obtain formulations with specific characteristics. Some gastro-resistant pharmaceutical formulations slowly release the active ingredient rather than promptly after administration, allowing for a controlled released profiles.[7] These formulations allow gastric disorder reduction, protect active principle ingredients from instability at acidic pH, and facilitate gastrointestinal tract's distal regions absorption.[8] Polymers for enteric coating, such as cellulose acetate phthalate or Eudragit® L, are chosen due to their ability to dissolve at different pH values.[9] The most effective enteric coatings are the long-chain ionizable carboxylic groups, which remain insoluble at acidic pH and disintegrate at intestinal pH allowing drug release.[10] Among some alternatives for microparticles coatings, Eudragit® polymers, have the property to dissolve in the enteric environment[11] and accordingly are widely used in gastro-resistant pharmaceutical formulations.

OTC is a member of the tetracycline antibiotic family and causes gastrointestinal disturbances when orally administrated to the patient, irritating the gastric mucosa, and causing nausea and dyspepsia. These collateral effects limit the use of this antibiotic in conventional oral administration and have encouraged many researchers to find alternatives to minimize these effects. Studies using biopolymers and a microencapsulation process were conducted aiming to develop a modified OTC release system that would overcome this issue.[12,13] Both studies, showed a burst effect of the microparticles in acidic medium resulting in an undesirable high drug release. This can be attributed, in part, to the uneven surface of polymeric

microparticles, since cracks and micropores can be present on it.[13–16] Furthermore, the high solubility of OTC in an acidic medium accelerates drug release even after encapsulation.

Huang and Brazel discussed the importance of preventing the burst phenomena during drug release, aiming to avoid or reduce such an effect.[17] Surface modification of the drug carrier, by depositing an outer coating layer using polymers, is one of the strategies used to reach this objective.[18] This alternative has been used in tablet coating in order to obtain regular and uniform surface without the presence of cracks and pores, ensuring drugs controlled release.

The utilization of fluidized beds for particles coating has been extensively studied due to its high efficiency of high heat and mass transport, besides short particle circulation time.[19] In this process, the particles are fluidized by air, while a coating material in the form of a solution or a suspension is atomized and sprayed onto the surface of solid particles.

This article proposes the use of a fluidized bed to coat OTC loaded alginate/chitosan microparticles with acrylic-EZE® MP to ensure the release of the intact drug in the enteric tract. Encapsulation technique efficiency was assessed by *in vitro* liberation tests in both gastric and intestinal simulated medium. The use of multiphoton confocal microscopy and Fluorescence Lifetime Imaging (FLIM) made it possible to observe OTC distribution in alginate/chitosan polymeric matrix.

MATERIALS AND METHODS

Reagents

Oxytetracycline (OTC) hydrochloride crystalline (≥ 95% HPLC) and the encapsulating agent Chitosan (≥ 75% deacetylated) were purchased from Sigma-Aldrich. Another encapsulating agent, sodium alginate with low molecular weight and its calcium chloride gelling were purchased from Fluka Chemika, Switzerland, and Synth, PA, Brazil, respectively. The gastroresistant coating solution, acryl-EZE® MP based on Eudragit® L100-55, was supplied by Colorcon, Brazil.

Methods

Preparation of Alginate/Chitosan Microparticles. Microparticles were prepared by complex coacervation, dripping an alginate/OTC solution into a chitosan and calcium chloride mixture, under constant stirring. The OTC/alginate solution was obtained dissolving 4 g of OTC in 400 mL of 1.75% sodium alginate and 0.9% NaCl solution. A 1% acetic acid aqueous solution was the solvent used to prepare a 0.3% chitosan solution under a magnetic stirrer (PC model - 420 Stirrer Corning) for 24 h. After this period, 2.0% $CaCl_2$ was added to this solution and its pH adjusted to 5.7 with 1*M* NaOH. Then, it was under vacuum using 14 μm filter paper.

The OTC/alginate solution was then dropped into $CaCl_2$/chitosan solution at a flow rate of 2.9 mL/min, using a peristaltic pump (77800-60 model, Brand Masterflex) placed at a height of 30 cm from the level of that $CaCl_2$ chitosan solution. Microparticles were formed and left for 24 h to ensure complete gelling. After, the microspheres were washed and dried at room temperature.

Profile of OTC Distribution in Alginate/Chitosan Microparticles. Distribution of OTC within the microparticles was detected using multiphoton confocal microscopy and FLIM. OTC fluorescence was obtained after irradiation of the alginate/chitosan microparticle at 780 nm using a femtosecond Ti : sapphire laser (Mai Tai HP Spectra-Physics, Mount View). A Zeiss confocal microscope (Model LSM780-NLO, Carl Zeiss AG, Jena, Germany) and a time correlated single photon counting (TCSPC) Becker & Hickl FLIM system (SPC-830, from Becker & Hickl, Berlin, Germany) were used.

Characterization of Fluidized Alginate/Chitosan Microparticles. Particle size analysis was performed by optical microscopy (DMLM Leica model, Germany). To obtain an average value, the diameter of 50 microparticles was measured. Absolute density of OTC loaded alginate/chitosan microparticles was determined by helium pycnometry (Accupyc 1330 V2.02, Micromeritcs), while the density of acryl-EZE® MP polymer solution was determined by liquid pycnometry.

Alginate/Chitosan Microparticles Circularity. Shape Factor (SF) circularity is defined by $SF = \frac{4\pi \times \text{Area}}{\text{Perimeter}^2}$, (one for a perfect circle and smaller than one for any other geometric shape). Such parameter was obtained with the aid of Sigma Scan Pro software and optical microscopy images of over 50 microparticles.

Coating Polymer Solution Preparation. As mentioned before, acryl-EZE® MP was the polymer used to coat microparticles. This polymer is based on Eudragit® L100-55 (methacrylic acid copolymer type C), a nontoxic substance well known in pharmaceutical industry. A 20% acryl-EZE® MP aqueous solution was prepared and submitted to mechanical stirring for one hour. After, the solution was filtered using a 170 μm mesh sieve.

Characterization of Acryl-EZE® MP Coating Solution. The evaluation of surface tension, contact angle and work of adhesion of the Acryl-EZE® MP polymeric solution were carried out to investigate the wettability and the adhesion strength between this solution and the solid surface of the microparticles.

Contact angle analysis, using a manual goniometer (Tantec of CAM-MICRO, Germany), was performed according to the sessile drop method. This method requires a flat surface of the sample. Thus, in the present work, flat surface was obtained by pressing the microparticles in a stainless steel mold, with the aid of a hydraulic pressloaded with 6 tons. To facilitate the angle measurement, the droplet was projected on a graduated screen using a beam of light. Surface tension determination was performed by the Du Nouy ring method, using KSV Sigma 701 equipment. The ring lifting and lowering speeds were 5 and 10 mm/min, respectively. The mathematical correction proposed by Huh and Mason was also applied in this determination.

Lastly, the work of adhesion (W_{ad}) was determined by the equation of Neumann and Good,[20] using the measured values for surface tension and contact angle and the equation,

Table I. Mathematical Models used to Describe the Dissolution Profile of OTC Microencapsulated in Alginate/Chitosan Matrix Coated with Acryl EZE® MP in Gastrointestinal Conditions

Mathematical modeling	Equation
Korsmeyer et al. Model	$\frac{M_t}{M_\infty} = a \cdot t^n$. Here, k is a constant and n is the diffusional exponent
Quadratic Model	$\frac{M_t}{M_\infty} = a_0\left(1 - \frac{1}{1-k \cdot t}\right)$. The parameters a_0 and k were the parameters of the Quadratic model
Logistic Model	$\frac{M_t}{M_\infty} = \frac{a_0}{1+e^{-k\cdot(t-ym)}} - \frac{a_0}{1+e^{k\cdot(ym)}}$. The parameters a_0, k e ym were the parameters of the logistic model
Gompertz Model	$\frac{M_t}{M_\infty} = \frac{a_0}{e^{c_0 - k\cdot ym}} - \frac{a_0}{e^{c_0 + k\cdot(t-ym)}}$. The parameters a_0, c_0, k, and y_m were the parameters of the Gompertz model

$$W_{ad} = \gamma_{lv}(1 + \cos\theta)$$

Here, γ_{lv} = liquid-vapor surface tension and θ = contact angle.

Alginate/Chitosan Microparticles Coating in Fluidized Bed. With an aim to evaluating ideal coating thickness to obtain gastro-resistant particles with good drug release performance in pH 6.8, that is, the expected profile to avoid the burst effect it was performed a mass gain study for each coating layer carried out in a bench fluidized bed (VFC-LAB Micro, from Freud-Vector Corporation). The operating parameters were an inlet air temperature of 50°C, an air flow fluidization rate of 100 L/min, an atomizing air pressure of 12 psi, and suspension flow injection coating done with a 7 rpm pump. The microparticle's load in the fluidized bed was 10 g and a continuous suspension spray system was used during coating.

Characterization of Acryl-EZE® MP Coated Alginate/Chitosan Microparticles. Mass gain of alginate/chitosan microparticles coating with the base Acril-EZE® MP during the process was realized by bead growth (δ) determined by the equation, $\delta = \left(\frac{M_{film}}{M_{initial\ granules}}\right) * 100$, where: M_{film} and $M_{initial\ granules}$ are, respectively, the film mass formed on the granules entire surface and its initial mass.

Morphological Analysis. Scanning Electron Microscopy (SEM; model 440i, Leo Electron Microscopy, Cambridge, UK) was used to observe the morphology of the microparticles, both the surface characteristics before and after coating and as well as the thickness obtained after the coating of acryl-EZE® MP.

OTC Release from the Alginate/Chitosan Microparticles Before and After Coating in Fluidized Bed. An OTC release profile was determined in solutions simulating the gastrointestinal environment. Concentrations of OTC released from the alginate/chitosan microparticles, before and after coating, were measured in both 0.1M hydrochloric acid (pH 1.2) and 0.2*M* Tris/HCl (pH 6.8) solutions by direct absorbance measurement at 268 nm, using a Cary 1G spectrophotometer Varian, Mulgrave, Australia. Approximately 0.05 mg of the microparticles were placed into the dissolution medium and left in an orbital shaking water bath (Marconi Laboratory Equipment, type Dubnoff), and with a rotational speed of 100 rpm, at 37 ± 0.5°C for 24 h. Aliquots were taken at 30 min intervals during the first 2 h, then at 1 h intervals over the next 3 h. After each measure, the sample returned to the dissolution medium.

Mathematical Modeling. The transport and release of drugs in pharmaceutical systems involve several steps that can lead to different physical and chemical phenomena. This hinders researchers' ability to the use of rigorous models to describe all the mechanisms involved in the process.[21] In the literature, there are several mathematical models, and as well as empirical phenomenology, which have been used to describe the release of drugs in different matrices. In order to determine the model that best describes the drug release in gastrointestinal conditions, different models were applied to represent the release of the following the four OTC systems profiles below:

- System 1: OTC released in an acidic medium from alginate/chitosan microparticles coated with acryl-EZE® MP 50%.
- System 2: OTC released in acidic medium from alginate/chitosan microparticles uncoated.
- System 3: OTC released in a buffered medium (pH 6.8) from alginate/chitosan microparticles coated with acryl-EZE® MP 50%.
- System 4: OTC released in buffered medium (pH 6.8) from uncoated alginate/chitosan microparticles.

The studied mathematical modeling is presented in Table I. To adjust the parameters of the mathematical models, the Downhill Simplex[22] method of mathematical optimization was employed, using the following equation as the objective function:

$$F_{OBJ} = \sum_{i=1}^{n} (Y_i^{MOD} - Y_i^{EXP})^2$$

Y^{MOD} and Y^{EXP} refer to mass of drug released ratio values experimentally determined and calculated using the mathematical model. F_{OBJ} is the objective function and n is the number of experimental analysis. To assess which of the models is more effective in describe in the experimental data, R^2 (Correlation coefficient) and AIC (Akaike Information Criterion) were chosen as criterion. R^2 was obtained using the following mathematical equation:

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (Y_i^{MOD} - Y_i^{EXP})^2}{\sum_{i=1}^{n} (Y_i^{MOD} - \overline{Y})^2}$$

AIC, a measure of the quality of the adjustments based on the best fit probability, was calculated according to the following mathematical equation:

$$AIC = n \cdot \ln\left(\sum_{i=1}^{n} (Y_i^{MOD} - Y_i^{EXP})^2\right) + 2 \cdot p$$

Here, n is the number of experimental data and p is the number of the parameters adjustable to the model in question. When comparing a set of different models for a given data set, the model with a lower AIC value is the model that best describes the experimental data.

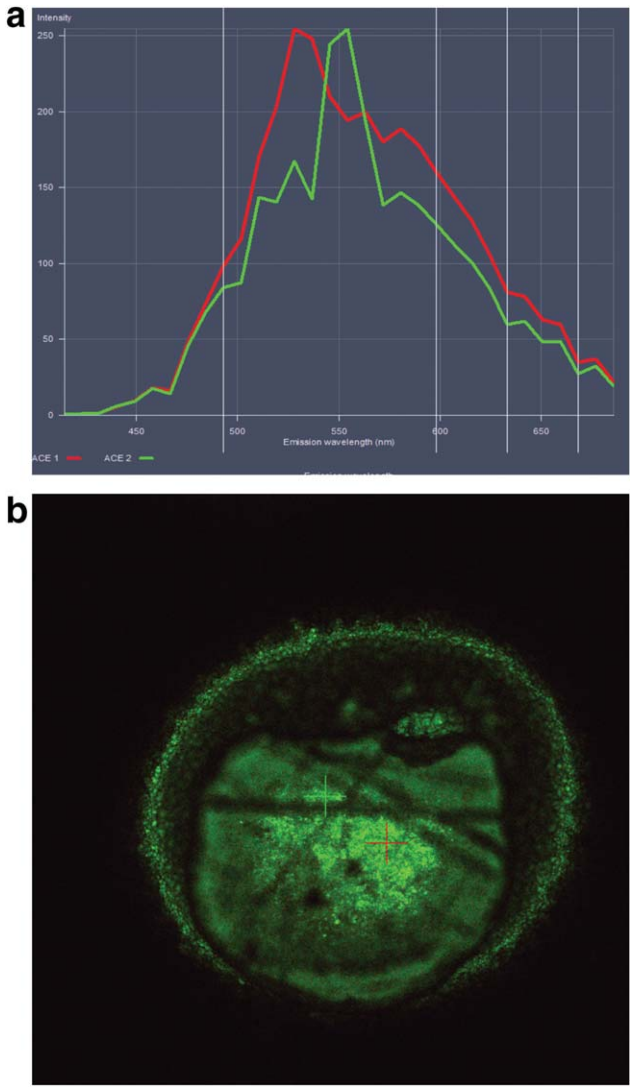

Figure 1. (a) OTC fluorescence emission spectrum; (b) image of alginate/chitosan microparticle with encapsulated OTC.

RESULTS AND DISCUSSION

OTC Distribution in Alginate/Chitosan Microparticles

Multiphoton confocal microscopy allows visualization and characterization not only the surface but also the sample interior. OTC already by itself is a fluorochrome, with emission band between 500 to 600 nm, excited by two photons at 780 nm, as shown in Figure 1(a). Figure 1(b) shows the exact points where spectra were recorded, visualizing OTC distribution within alginate/chitosan microparticles.

Figure 2 shows 3D multiphoton confocal microscopy images, displaying the area where encapsulated fluorescent OTC is located within the alginate/chitosan microparticles. According to the fluorescence exhibited, the orthogonal cutting on Figure 2(a) shows that OTC is predominantly distributed in the microparticle core area. The xy plane image is shown in the central image. The green line defines the xz plane fluorescence profile in the left image, and the red line defines the yz plane of upper images. Quantitative mapping of the OTC fluorescence intensity, inside alginate/chitosan microparticles, is shown in Figure 2(b). Note that the drug is mainly localized in the central area, confirming the efficiency of the employed encapsulation system. Not surprisingly, there is also another fluorescent layer in the particle's interface, probably due to adsorbed OTC molecules from the initial solution.

FLIM is a technique, which is very sensitive to the chemical environment around fluorophores. It can sense pH, oxygen, and ionic concentrations. Briefly stimulated electrons can sense electric fields around them, all generated by ions and dipoles that change their fluorescence lifetimes. Other mechanism that can modify the decay time making it faster, is the Förster Resonant Energy Transfer (FRET)[23] between two molecules that can belong to the same species (homo-FRET), depending on their separation distance.

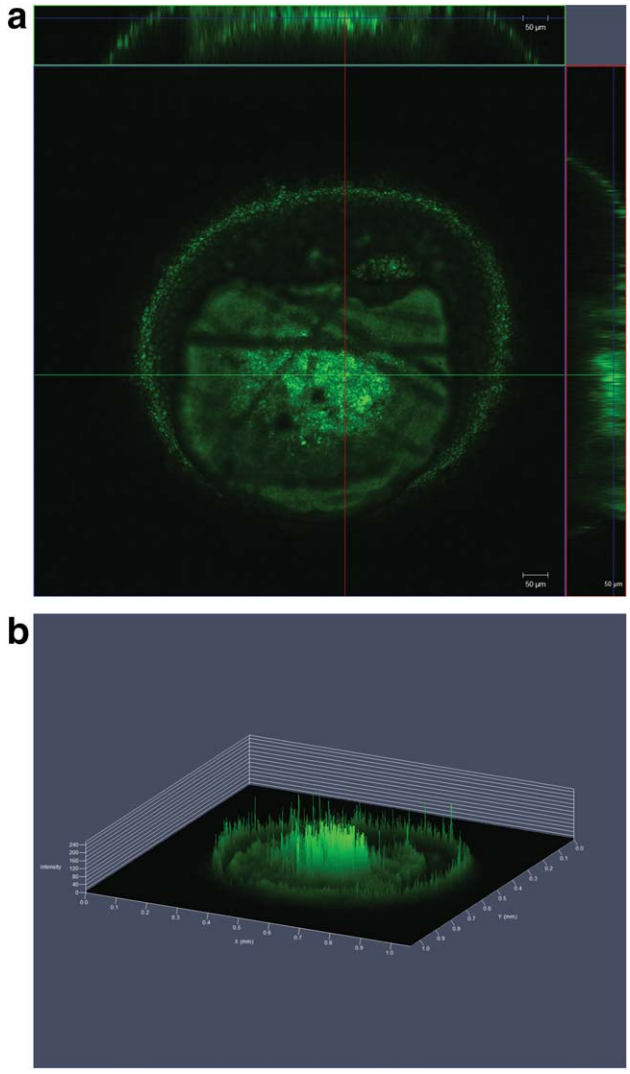

Figure 2. (a) The orthogonal cutting, from 3D images, indicates OTC encapsulation in alginate/chitosan microparticles; (b) fluorescence intensity distribution, within the microparticles.

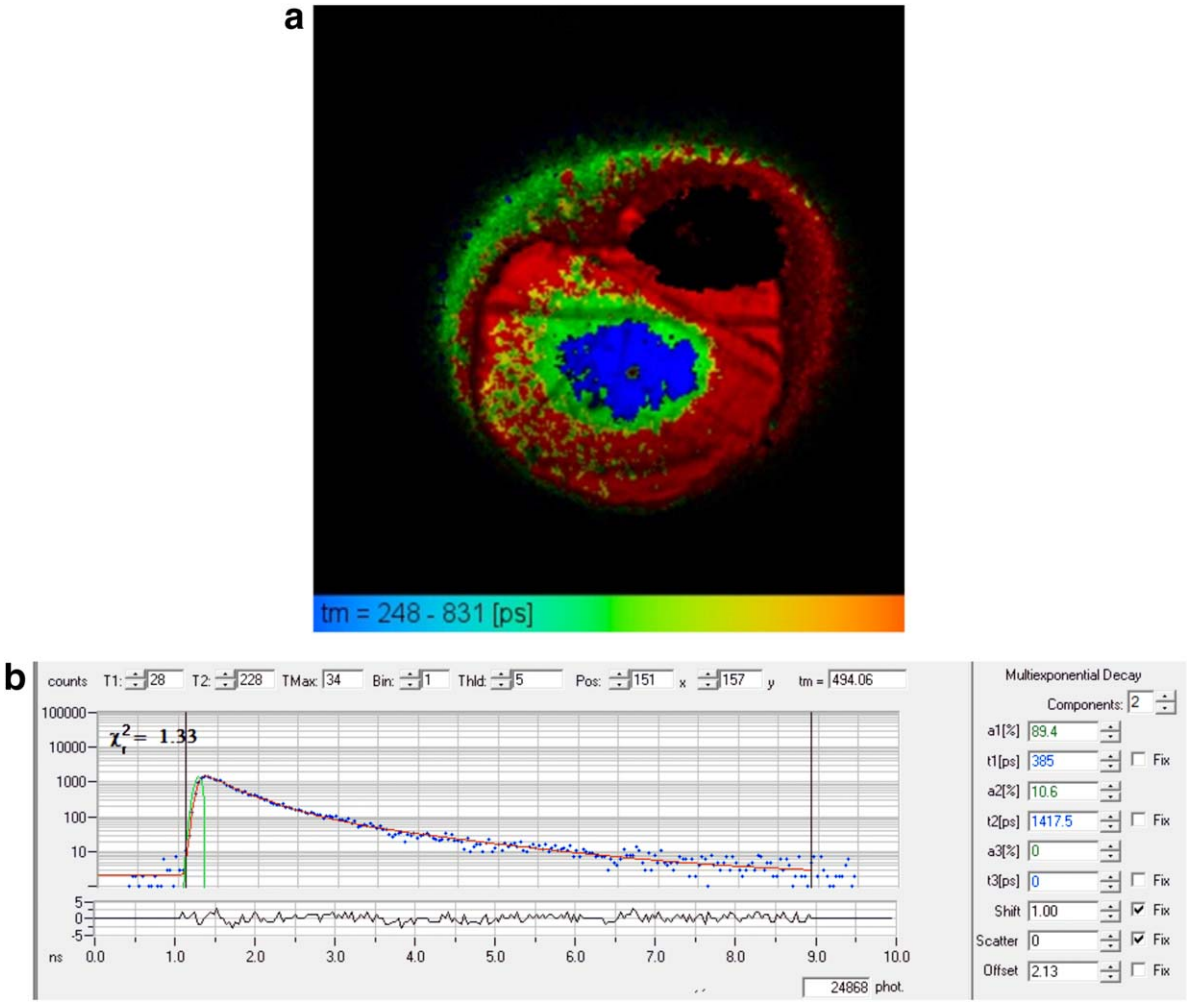

Figure 3. (a) FLIM image showing fluorescence decay time for microparticle components; (b) OTC fluorescence decay curve. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

FLIM arrival time of each emitted photon in the detector is recorded on a TCSPC card along with pixel coordinates the image laser scan. Final processing consists of fitting the decay curve from each pixel, as shown in Figure 3(b), and then assigning a false color to each pixel, which corresponds to different fluorescence lifetimes. Brightness is provided by the total number of photon in each pixel. FLIM, therefore, provides contrast based on fluorescence lifetime, which is depends on the particular fluorophore and its surrounding chemical environment. A color code associating lifetime values and colors shall be provided by the software Figure 3(a) shows a FLIM image of an OTC loaded microparticle, differing in color from blue to red in relation to the fluorescence decay time in picoseconds. Figure 5(b) shows the time decay curve at the two blue lines crossing in Figure 3(a) pixel, showing an average lifetime, $\tau_m = a_1\tau_1 + a_2\tau_2$, of 385 picoseconds.

Microparticle central area shows a short lifetime represented by the blue color, extending to longer lifetimes towards particle surface, represented by green and red areas. It can be explained by homo-FRET between OTC molecules, which is stronger, corresponding to shorter lifetimes, at most concentrated areas. Therefore, FLIM image is consistent with fluorescence intensity distribution in Figure 3(b).

Characterization of Alginate/Chitosan Microparticles for Fluidization

Alginate/chitosan microparticles presented an average diameter of 1051.3 ± 49.6 μm and a true density of 1.47 ± 0.02 g/cm^3. Compared to polymer solution density, 1.13 ± 0.01 g/cm^3 it has a 0.36 g/cm^3 difference. According to Geldart,[24] the particles were classified under Category B, or the "bubbling fluidization type." Although the material presented good fluidization conditions, not forming agglomerates, it was not possible to observe a defined fluidization regime during the coating process due to the small amount of microparticles used. Such process regards itself a diluted system.

Alginate/Chitosan Microparticles Circularity

The circularity of the alginate/chitosan microparticles is an important parameter with respect to coating efficiency. The more spherical the particle is, the more regular and uniform the coating layer will be. The mean circularity obtained from 50 microparticles was $SF = 0.82 \pm 0.05$, lower than the ideal

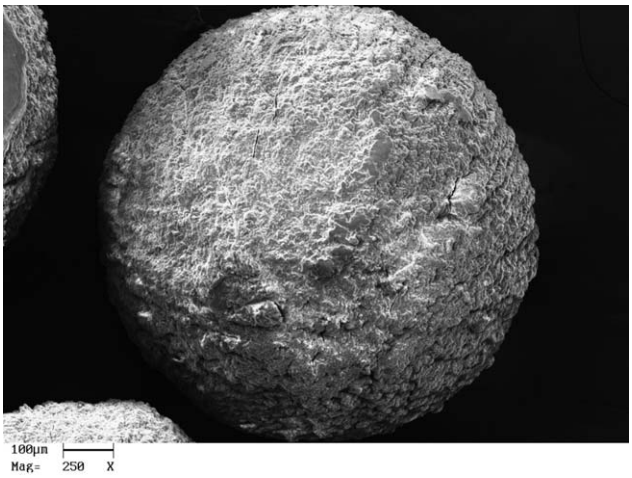

Figure 4. SEM Image of alginate/chitosan microparticles with OTC before coating.

spherical case which is SF = 1. However, compared with particles produced using the industry's most common grinding processes, which generally present a circularity range of 0.5–0.7,[25] the SF result found in this study can be considered quite good.

Characterization of Acryl-EZE® MP Solution for Microparticles Coating

An average contact angle of $56 \pm 3°$ was obtained from ten measurements. A result smaller than 90° indicates that there was a good wettability between the acryl-EZE® MP polymer solution and the microparticulate surface, which is a prerequisite for ensuring good adhesion bonding. Calculated values for surface tension and work of adhesion were 37.1 ± 0.1 and 57.84 mN/m, respectively, indicating good interaction between liquid and solid.

Morphological Analysis of Alginate/Chitosan Microparticles Before and After Coating

Figure 4 shows SEM images of an OTC containing alginate/chitosan microparticle before coating, where it is noted that the surface of the microparticles is irregular. The initial covering of the microparticles was performed and achieved an increase in mass of ~30%. However, the obtained thickness of 30 μm was not enough to promote the gastro-resistant effect indicated by the United States Pharmacopeia (USP XXXII, 2009), which states a pharmaceutical formulation is only considered gastro-resistant if less than 10% of the drug is released after 2 h of exposure to an acidic medium. This 2 h period is related to a drug's stomach residence time during gastrointestinal transit. Therefore, the acryl-EZE® MP covering was increased to a range, which corresponded to an increase in mass of ~50%, as shown by the SEM images in Figure 5(a,b). Figure 5(a) shows a uniform coating, with a thickness of 50 μm around the microparticle, while Figure 5(b) shows a homogeneous barrier around the entire microparticle.

Study of OTC Release Before and After Coating

The OTC release profiles in acidic and pH 6,8 medium are illustrated in Figures 6 and 7, respectively. Figure 6 shows that

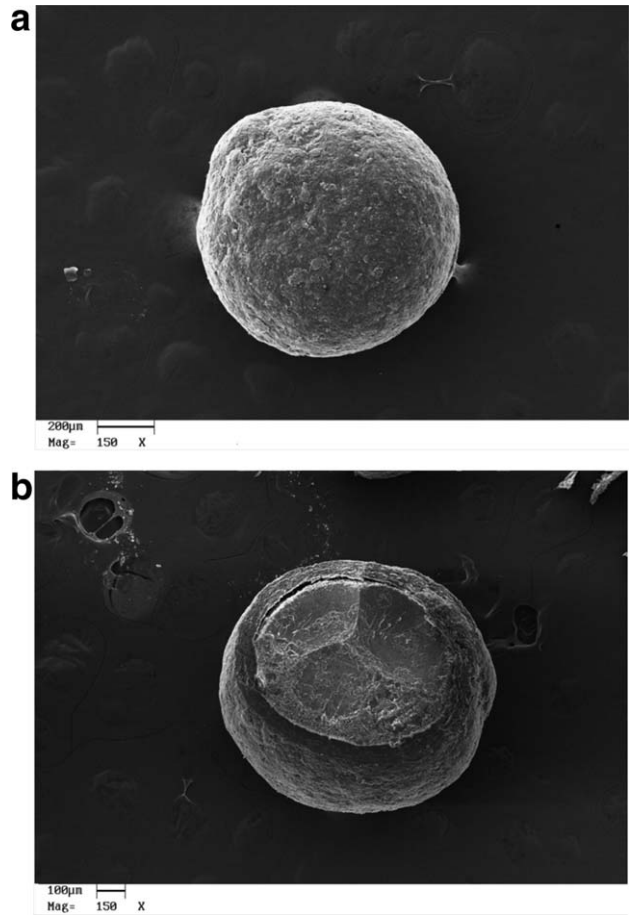

Figure 5. Micrograph of polymer coating based on with acryl-EZE® MP (a) alginate/chitosan microparticle; (b) microparticle cutted.

uncoated microparticles in acidic medium exhibited a quick OTC release within the first 30 minutes, which can be explained by the drug's high solubility in such medium and the presence of cracks in microparticles. The acidic solution is able to penetrate these cracks and make its way into the matrix, rapidly dissolving the drug and causing its fast diffusion out of the

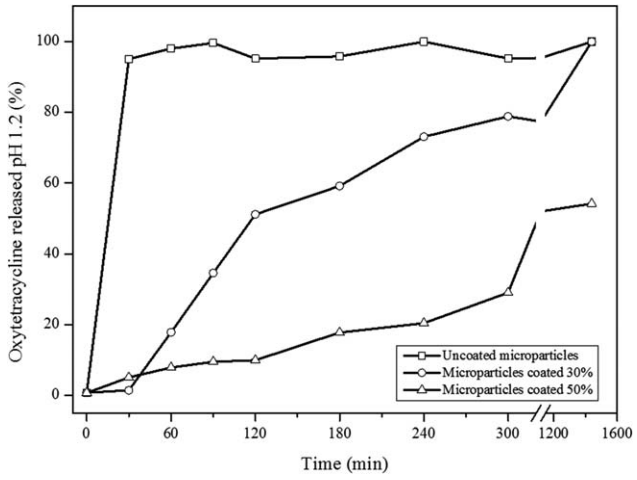

Figure 6. Concentration of OTC released by microparticles in acidic medium versus time.

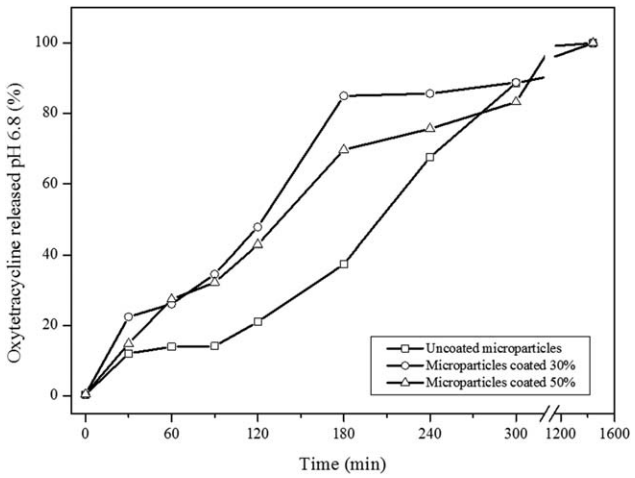

Figure 7. Concentration of OTC released by microparticles in pH 6 and 8 medium versus time.

microparticles. This was also observed by Mi[12] when working with OTC microparticles encapsulated in chitosan. In this study, drug release profile was performed in both a buffered medium (pH 6.8) and an acidic medium. In the acidic medium, a fast initial drug release (burst effect) was observed. The same behavior was also noticed by Cruz[13] who worked with OTC encapsulated in alginate and chitosan microparticles, and again, in accordance with this study and the results of Mi,[12] a fast OTC release was observed in an acidic medium. These results, therefore, show the importance of developing a nontoxic gastro-resistant coating, which is capable of delaying drug release and ensuring the drug's integrity until it reaches the desired target, this is the enteric environment.

Our results show that acryl-EZE® MP coating can perform the expected task. Figure 6 shows that a 30% mass gain acryl-EZE® MP coating can slow down OTC release in acidic medium for 30 min. However, in <2 h, >10% of the drug had been released, indicating the need to further increase coating thickness. Therefore, coating thickness was increased to reach ~50% mass gain relative to particle mass and the drug release curve obtained this time is shown by Figure 6. The expected gastro protection effect was attained, avoiding an initial burst and achieving a drug release profile below 10% 2 h after being exposed in the acidic medium.

Figure 7 shows the results in pH 6.8 buffer, where a gradual OTC release can be observed with both the coated and uncoated microparticles. In such medium, acryl-EZE® MP based coating shows fast dissolution, which is followed by the alginate/chitosan microparticles swelling and disintegration, all processes promoting drug release. According to Hsu and Yao,[26] in a polymer-based drug delivery system, drug release is controlled by polymer degradation and drug loading concentration.

Mathematical Modeling

The values of the adjusted parameters of the models Kormeyer et al.[27] Quadratic, Logistic and Gompertz along with the values

Table II. Parameters Set of Mathematical Models and Statistical Analysis

Gompertz						
	a_0	c_0	k	y_m	R^2	AIC
System 1	0.263735	257.247	0.084092	3074.91	0.99928	−57.489
System 2	0.112444	3.16505	0.002597	587.058	0.9392	−24.447
System 3	0.248501	7.04715	0.003486	1598.81	0.9540	−12.361
System 4	0.247746	16.1812	0.00526	2801.57	0.9902	−29.655
Korsmeyer-Peppas						
	k		N		R^2	AIC
System 1	0.939486		0.0100415		0.999469	−65.351
System 2	0.0146635		0.50932		0.8927	−23.118
System 3	0.0471453		0.440576		0.8696	−7.183
System 4	0.103081		0.334128		0.9052	−11.695
Quadratic						
	a_0		K		R^2	AIC
System 1	1.00349		0.659944		0.999884	−78.966
System 2	0.758839		0.00220658		0.92920	−27.045
System 3	1.35872		0.00321878		0.9340	−13.307
System 4	1.23592		0.00584304		0.97432	−24.127
Logistic						
	a_0	k	y_m		R^2	AIC
System 1	3258.86	0.0673705	119.987		0.996183	−43.723
System 2	0.609224	0.0103901	239.959		0.9714	−32.939
System 3	1.06813	0.0148979	190.359		0.9939	−33.352
System 4	1.75634	0.00912761	34.0593		0.9948	−38.168

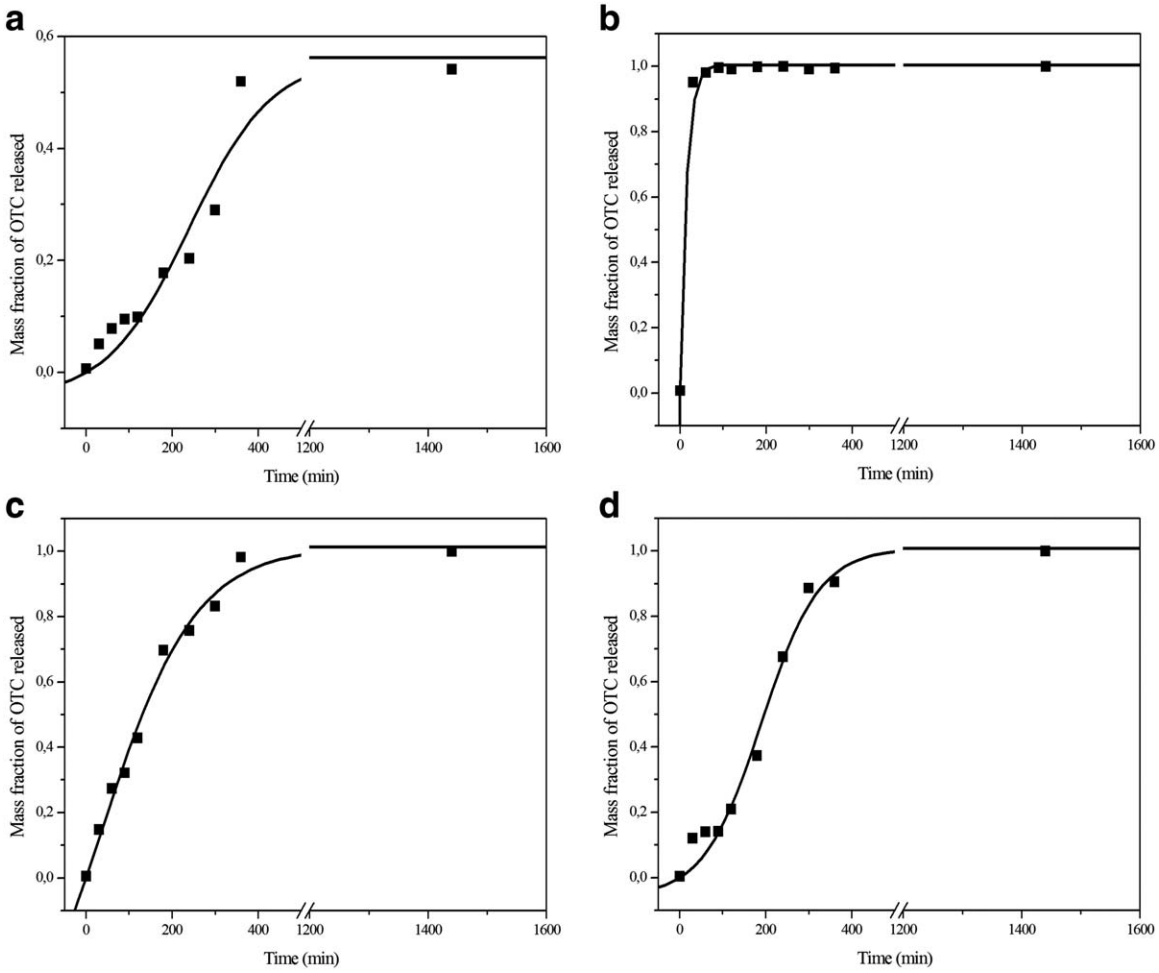

Figure 8. Dissolution profile of OTC according with the experimental data and Logistic model (a) from the system 1; (b) from the system 2; (c) from the system 3; (d) from the system 4.

of R^2 and AIC respective to each mathematical model, from the four systems studied, are presented in Table II.

For system 1, all values of the R^2 presented in Table II for all models tested showed values close to unity. Thus, all models could well represent the dissolution behavior of the drug into the system. For the other systems (2, 3 and 4), Logistic model was best for representing the dissolution behavior of the drug, because it presented the highest correlation coefficient (close to unity) and the lowest AIC parameter values. Figure 8 shows a graphical representation of dissolution profile of OTC from the systems studied, according with the experimental data and Logistic model.

These mathematical models described the experimental data of release of OTC encapsulated in alginate/chitosan matrix before and after coating with Acryl-Eze ® MP to 50% by means, which simulate the gastrointestinal conditions efficiently, requiring the use of AIC to determine the model that best describe the experimental data.

CONCLUSIONS

In this study, a gastroresistant microparticulate system for controlled drug release was developed, which consisted of coating alginate/chitosan microparticles with acryl-EZE® MP in a fluidized bed to improve release kinetics during enteric delivery, avoiding the burst effect before the drug reaches the enteric system. SEM results showed that coating the alginate/chitosan microparticles with an even and uniform layer of about 50 μM acryl-EZE® MP was enough to prevent OTC release in an acidic medium for the critical 2 h period. Confocal microscopy results showed volumetric drug distribution inside the particle, proving that OTC does indeed become internalized within the particle. Under conditions simulating the gastrointestinal environment, the Logistic mathematical model was best for describing the drug release profile of OTC from alginate/chitosan microparticles, before and after being coated with acryl-EZE® MP 50%.

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