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Hydroxypropyl methylcellulose phthalate beads containing a model non-steroid anti-inflammatory drug

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Abstract

When given orally to patients, non-steroid anti-inflammatory drugs (NSAIDs) can provoke mild to severe gastric irritation side effects. Reduction of gastrointestinal irritation caused by NSAIDs can be achieved using enteric beads which are preferable to coated tablets or capsules. The present work reports the studies of formulation of a model NSAID using a recently described method. Drug-loaded hydroxypropyl methylcellulose phthalate (HP_{50}) beads were prepared using a technique which is based on the variation of HP_{50} solubility with pH. Studies carried out to characterise the formulations, such as density, crushing force and encapsulation efficiency, show that the beads are suitable for further pharmaceutical manipulation (e.g. capsule filling). The in vitro release studies confirmed the gastroresistance, and mathematical studies showed that the drug released followed a first order kinetic.

Keywords: Non-steroid anti-inflammatory drugs; Etodolac; Hydroxypropyl methylcellulose phthalate; Enteric beads; Gastroresistance

1. Introduction

Most rheumatic diseases require symptomatic treatment to relieve pain and stiffness. This applies to inflammatory processes both in the adult and juvenile age groups. Non-steroid anti-inflammatory drugs (NSAIDs) have been used as analgesic agents in the treatment of acute and chronic rheumatoid arthritis and osteoarthosis (Brody, 1991). However, the most frequent problem with NSAIDs is their propensity to cause gastrointestinal distress. Gastroresistant beads in which the encapsulated drug is dispersed throughout a polymeric matrix have been developed to afford some protection to the gastrointestinal mucosa. These beads, also called mini-granules (size ranging

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Table 1
Contents of drug/polymer suspensions and final formulations

Formulation	Suspension (w/v)		Beads (w/w)	
	Etodolac (%)	HP_{50} (%)	Etodolac (%)	HP_{50} (%)
A	0.0	14.0	0.0	100.0
B	2.0	14.0	12.5	87.5
C	7.5	10.5	41.7	58.3
D	10.0	14.0	41.7	58.3

from 1 to 3 mm), will be able to pass easily through the pylorus minimising high concentrations of drug build-up in isolated areas of the intestinal mucosa, as observed with enteric-coated tablets or capsules (Follonier and Doelker, 1992).

Hydroxypropyl methylcellulose phthalate (HP_{50}), often used as an enteric coat or matrix material, acts as a physical barrier, protecting the stomach mucosa against irritating drugs.

In the present work, NSAID-loaded HP_{50} beads were prepared using a recently described technique, which is based on the variation of polymer solubility with pH (Zaniboni et al., 1995). Beads were formed by dropping polymer/drug aqueous dispersions in a citric acid solution. The drug's in vitro release mechanism was characterised, and particle size and image analysis were carried out to observe the morphology of polymeric beads after preparation and throughout the dissolution studies.

2. Materials and methods

2.1. Materials

Etodolac, used as a model NSAID, was a gift from Tecnimede (Sacavém, Portugal) and HP_{50} was obtained from Seppic (France). All chemicals and reagents non-specified in the text were of reagent grade or equivalent (Merck, Darmstadt, Germany).

2.2. Preparation of beads

Both empty and drug-containing beads were produced using a modification of a previously described method (Zaniboni et al., 1995). Briefly, an appropriate amount of drug was dispersed in an alkaline solution (2% w/v of $NaHCO_3$) containing HP_{50}. The suspension was then added through one or more needles of known diameters (0.5–0.9 mm), to a citric acid solution (10% w/v), at 2°C, under constant mechanical stirring (Framo-Gerätetechnik, LR20 digitronic, Germany). The pH difference between the drug/polymer suspension and the citric acid solution causes precipitation of HP_{50}, leading to the formation of spherical particles that include the drug. After a stirring period to allow the hardening of the beads, these were collected and washed with distilled water. Finally, the preparations were dried using a fluid bed drier for 2 h at 40°C (Glatt, Germany). The composition of the formulations studied is illustrated in Table 1.

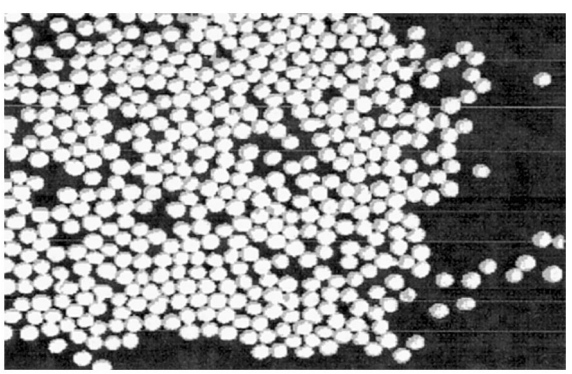

Fig. 1. Macroscopic aspect of etodolac-containing HP_{50} beads (41.7% w/w).

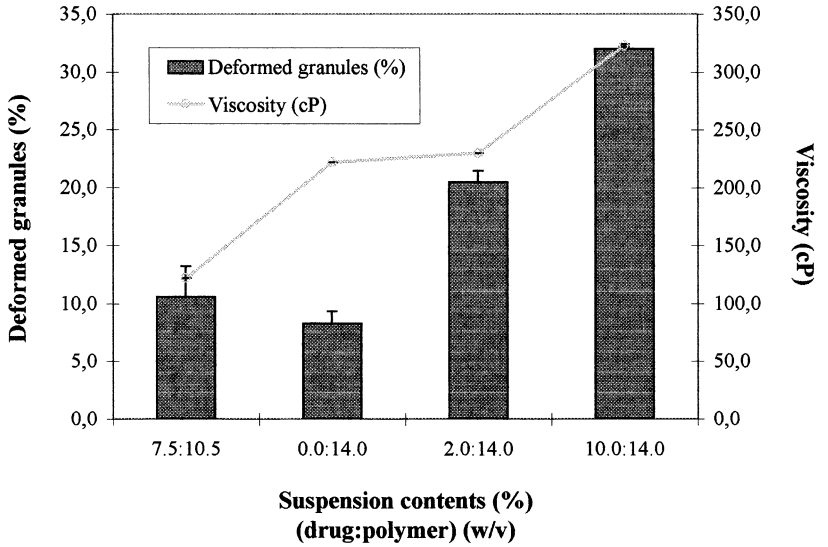

Fig. 2. Influence of suspension viscosity and drug/polymer contents on beads' macroscopic aspect.

2.3. Morphology

The formation of good quality beads with a spherical shape depends mainly on the viscosity of drug/polymer suspensions. When viscous liquids are 'dropped' they tend to cause spherulation, i.e. to produce beads with an attached satellite sphere (Shi et al., 1994). To evaluate the incidence of bead spherulation, samples equivalent to 100 beads were weighed and studied with a magnifying glass. Three measurements were made per sample and results were expressed as mean ± S.D. To further characterise the morphology, photographs were also taken and scanning electron microscopy (SEM) was used to assess the surface topography and inner matrix texture (Jeol/JSM 35 CR Scanning Microscope provided with a Jeol Coat Sputter JFC-1100, Japan).

Table 2
Influence of needle diameter on particle size and macroscopic aspect of beads (study carried out with formulation A)

Needle diameter (mm)	Particle size (± IQR) (mm)	Deformed beads (± S.D., $n = 3$) (%)
0.50	0.92 ± 0.08	10.96 ± 1.50
0.60	0.92 ± 0.10	2.26 ± 0.58
0.80	1.08 ± 0.10	11.90 ± 2.11
0.90	1.08 ± 0.09	8.28 ± 1.06

2.4. Particle size analysis

Samples of 5 g of beads were sieved during 10 min using a vibrating sieve shaker (Retsch, Germany). Results were expressed as the median of a weight distribution ± inter-quartile range (IQR).

2.5. Density

The bulk density of the produced beads was determined using a pycnometer (Micromeritics Accupyc 1330, EUA). Three determinations were automatically made and the results presented by the mean ± S.D.

2.6. Crushing force

The crushing force was evaluated using a strength tester (Engineering Systems-Nottm 1/2 CT5, England), with a load cell of 50 kg. For each sample, six determinations were made and the results presented by the mean ± S.D.

Table 3
Density, crushing force, drug loading and drug encapsulation efficiency of beads prepared using a 0.9 mm needle diameter

Formulation	Particle size ($\pm$ IQR) (mm)	Encapsulation efficiency ($\pm$ S.D., $n=3$) (%)	Drug loading ($\pm$ S.D., $n=3$) (%)	Density ($\pm$ S.D., $n=3$) (g/cm^3)	Crushing force ($\pm$ S.D., $n=3$) (N)
A	1.08 ± 0.10	—	—	1.26 ± 0.01	20.78 ± 0.58
B	1.40 ± 0.10	94.09 ± 1.53	11.76 ± 0.19	1.29 ± 0.01	24.50 ± 0.94
C	1.40 ± 0.10	100.80 ± 1.09	42.03 ± 0.45	1.29 ± 0.01	42.34 ± 0.78
D	1.40 ± 0.10	99.16 ± 0.68	41.35 ± 2.80	1.29 ± 0.01	52.14 ± 0.61

2.7. Encapsulation efficiency

The amount of drug encapsulated was determined by dissolving an amount of beads equivalent to 200 mg of drug in dichloromethane/methanol (50:50). After an appropriate dilution with the same solvent, samples were analysed by high-performance liquid chromatography (HPLC) using a modification of a previously described method (Ficarra et al., 1991), with a Spectra-Physics apparatus (Isochrom LC pump, Spectra 100 detector, EUA). The HPLC procedure employed a 5 μm column (Lichrospher 100 RP-18, Merck, Darmstadt, Germany) and a mobile phase of phosphate buffer:acetonitrile (70:30), pH 6, with UV detection at 289 nm.

2.8. In vitro release studies

Release studies were carried out using the USP XXIII paddle apparatus (Sotax AT 7, Switzerland), following the procedure for enteric formulations. Briefly, amounts of beads equivalent to 200 mg of drug were used in this study and samples of the dissolution medium (5.0 ml) were withdrawn at various time intervals. The collected samples were filtered through 0.22 μm membranes (Millex-GS, Millipore, USA) and analysed by the HPLC method previously described. Each experiment was carried out in triplicate. At various time intervals (2-h incubation in HCl 0.1 N, and after 30 min in phosphate buffer, pH 6.8), beads were collected for image analysis by both macroscopic and microscopic methods described in Section 2.3.

3. Results and discussion

3.1. Morphology

The beads were prepared using a method based on the precipitation of HP_{50} when the droplets of an alkaline suspension come in contact with an acidic medium (Fig. 1). To assess the influence of the production variables on the number of beads presenting small spheres, beads containing different percentages (w/w) of drug were prepared (Table 1). The results obtained are in accordance with the study carried out by Shi et al. (1994), who demonstrated that as the viscosity of the liquids to be dropped is increased, the shape of the drop undergoes great changes (Fig. 2). Viscous drops develop long necks and form structures not observable in dripping water. The breaking-up of drop necks originates spheres with a smaller sphere attached. As shown in Fig. 2, an increase in viscosity causes, in general, a higher number of beads presenting spherulation. In suspensions presenting the same drug/polymer ratio (C and D), i.e. those containing 7.5:10.5 (w/v) and 10.0:14.0 (w/v), the increase of viscosity, resulting from the increasing solids concentration, originates preparations with higher percentages of spherulation.

No direct correlation could be established between the needle diameter and the percentage of deformed particles (Table 2). Nevertheless, the final macroscopic aspect of the preparations also depends on the drying conditions to which beads were submitted. It was observed that drying in

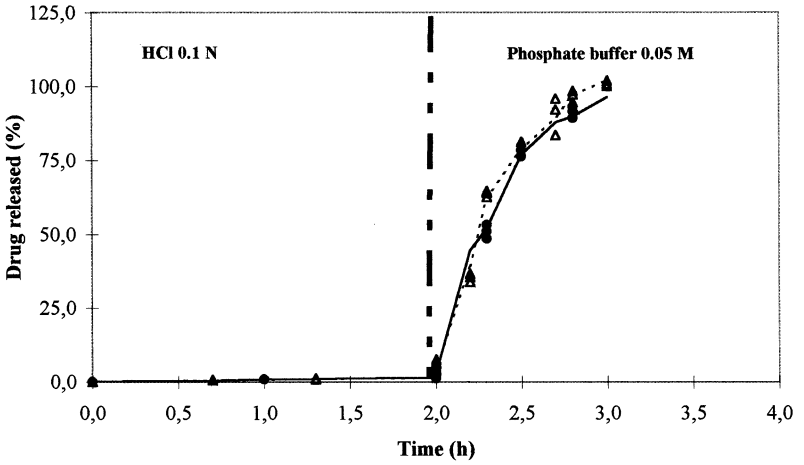

Fig. 3. In vitro release studies of two formulations containing 41.7% (w/w) etodolac, at two pH values: △, experimental data for formulation C; ●, experimental data for formulation D; ----, exponential fitting for formulation C; —, exponential fitting for formulation D.

desiccators or air ovens (40°C) produced particle aggregates and distorted beads. Fluid-bed drying was found to be the most adequate method due to the fact that the movement of particles during the drying period (2 h/40°C) prevents agglomerate formation, thus preserving their original shape.

3.2. Particle size

For drug-free batches, the increase in the mean particle size was not significant when the production was carried out using needles of larger diameters. However, the range of needle diameters used may be too narrow to allow the establishment of a clear relationship between needle diameter and particle size. When drug is included, the mean diameter of beads increases and the particle size distribution becomes narrower, which confirms the results obtained by Bodmeier and Paeratakul (1989), using a similar technique (Table 3). The increase in the mean diameter obtained for the preparations containing the drug may be due to a higher viscosity originated by the inclusion of the drug, resulting in a great amount of suspended solids.

3.3. Density and crushing force

Determinations were carried out to assess whether this is a suitable method for the production of beads for subsequent pharmaceutical manipulations, such as capsule filling or tableting. The inclusion of the drug in the formulations causes an increase of the dried beads' density values. Nevertheless, density appears not to change when different amounts of etodolac are added to the formulations (Table 3). On the other hand, the inclusion of the drug seems to have great influence on crushing force values, since an increase on drug loading from 12.5 to 41.7% (w/w) causes an increase on this physical parameter (Table 3). Thus, the dried beads herein described present crushing force and density values that allow capsule filling with an appropriate therapeutic dose of drug.

3.4. Encapsulation efficiency

High encapsulation efficiency levels ($\geq 94\%$) of etodolac were achieved with this method, which may be due to the fact that this drug is insoluble in acidic media and does not partition to the citric acid solution during the preparation (Table 3). The values found are of the same magnitude as those obtained with a similar technique for the preparation of either alginate or chitosan beads (Bodmeier and Paeratakul, 1989), thus suggesting that beads resulting from drop formation methods can efficiently entrap therapeutically beneficial molecules. Moreover, the encapsulation of etodolac in HP_{50}

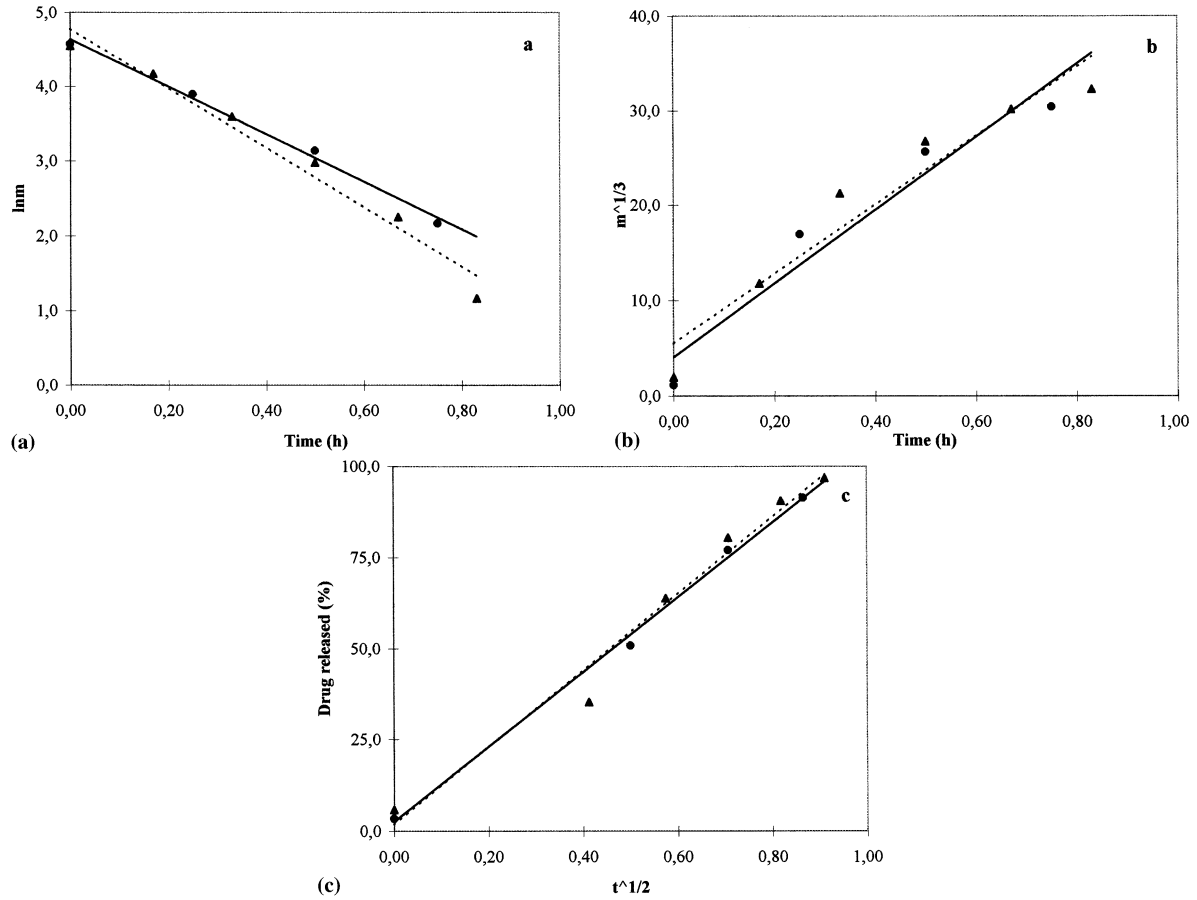

Fig. 4. Application of the mathematical models to the experimental dissolution data: (a) Wagner, (b) Hixson and Crowell, and (c) Higuchi. ▲, Formulation C; ●, formulation D.

beads revealed drug-loading levels higher than those reported for both soluble and insoluble model drug molecules, with the same polymer and preparation technique (Zaniboni et al., 1995). The lower encapsulation efficiencies described by these authors were caused by sedimentation of the insoluble drug prior to drop formation or partition of the soluble drug into the acidic medium during the hardening of the beads. Although etodolac is not soluble in the $HP_{50}/NaHCO_3$ aqueous solution, it could easily be suspended, due to both the viscosity of the latter and the small size of its crystals (6.2 ± 0.4 μm, $n = 4$; determined with a Malvern 2600 C, Malvern Instruments, UK). In fact, droplets collected throughout the droplet formation step showed a constant drug content. Besides, after the hardening period, etodolac content in the citric acid solution was determined and related to the total amount of drug in the formulation. The results show that less than 1% (w/w) of total drug was present in the citric acid solution, thus indicating that no significant losses of etodolac occurred due to partitioning into the acidic medium. This also suggests the suitability of this formulation technique for drugs with similar physicochemical characteristics as etodolac.

3.5. In vitro release studies

Drug release studies were carried out with formulations C and D, which present a theoretical drug loading of 41.7% (w/w). As illustrated in

Fig. 3, the gastroresistance of these formulations was confirmed to fit the USP XXIII specifications. Less than 1.5% of the drug content was released within 2 h in HCl 0.1 N and more than 80% was released after 45 min in phosphate buffer, pH 6.8. To characterise the release mechanism of etodolac from the HP_{50} enteric beads, three different kinetic models were applied, i.e. Wagner, Hixson and Crowell, and Higuchi (Brossard and Wouessidjewe, 1990). Mathematical studies were carried out with the aforementioned kinetic models, so that the experimental data could be explained (Fig. 4). Since the different correlation coefficients (r) are not sufficient on their own to compare the models, the Akaike minimum information theoretical criterion (AIC) was also employed as a measure of fit (Table 4). When there are several competing models, the best fitting model is that which gives the minimum AIC value (Akaike, 1974).

Table 4
Parameters resulting from the application of mathematical models and exponential fitting to the experimental dissolution data (phosphate buffer 0.05 M)

Formulations	C	D
Square-root (Higuchi) $Q=(De/t(2A-eCs)Cs\tau)^{1/2}$		
k_1	105.60	102.45
r	0.978	0.997
AIC	30.14	19.95
First-order (Wagner) $m=m_0e^{-kt}$		
k_2	−3.99	−3.19
r	0.986	0.996
AIC	20.46	11.05
Hixson and Crowell $m_0^{1/3}-m^{1/3}=kt$		
k_3	−36.50	−38.65
r	0.931	0.938
AIC	19.87	13.78
Exponential fitting $y=a+be^{-kt}$		
k_4	2.30	2.67
AIC	15.32	9.21

k_1, (% $h^{-1/2}$); k_2, $=(h^{-1})$; k_3, (%$^{1/3}$ h^{-1}); k_4, (h^{-1});, r, correlation coefficient.
Higachi: Q, cumulative release per unit area; t, time; ε, porosity of the matrix; τ, tortuosity; D and C, diffusion coefficient and solubility in the dissolution medium; A, concentration of drug in the formulation.
Wagner: m, drug remaining to be released at time t; m_0, initial amount of drug; k, first order release rate constant.
Hixson and Crowell: m, drug remaining to be released at time t; m_0, initial amount of drug; k, constant.

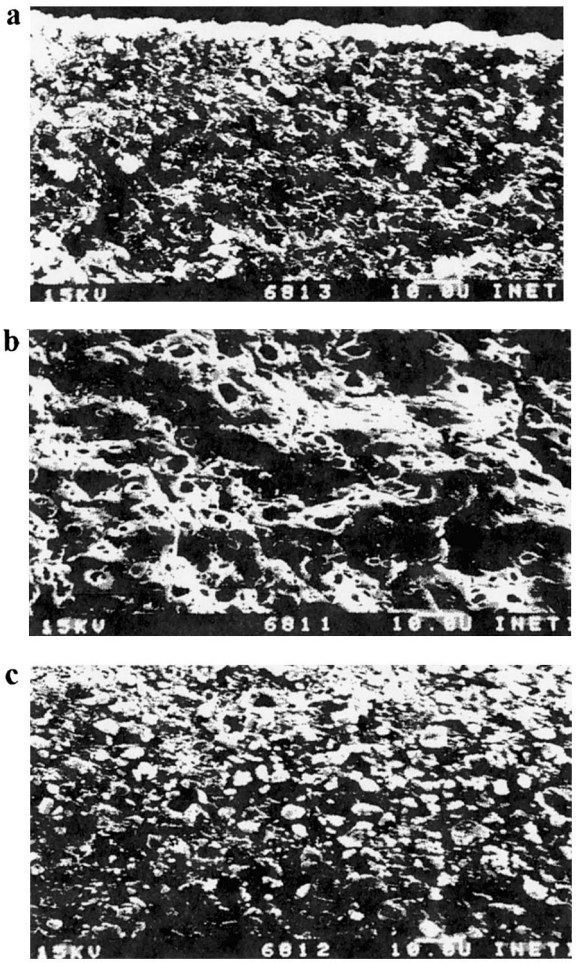

Fig. 5. Scanning electron micrographs of the inner structure of HP_{50} beads containing 41.7% (w/w) etodolac during the dissolution studies. (a) Freshly prepared beads, (b) after 2 h in acidic medium, and (c) after 30 min in phosphate buffer.

According to the data obtained from release in phosphate buffer, the best fit was obtained with the first order kinetic model described by Wagner. However, AIC values presented by formulation C, for the Wagner and the Hixson and Crowell equations, are very close, preventing clear separation between these models. In addition, this model yielded a lower AIC value for formulation D, indicating that this is probably the model that

best describes the in vitro release of etodolac from HP_{50} granular matrices. These results appear to be inconsistent with those of Zaniboni et al. (1995), who reported that the in vitro dissolution of riboflavin from a similar delivery system follows the Hixson and Crowell model. However, this may be due to the different intrinsic physicochemical characteristics of the drugs used in both studies, since the interaction that may occur between drugs and polymers, both during the formulation and release experiments, were not taken into consideration. Furthermore, microscopic analysis of the preparations show a type of polymer erosion which suggests that described by Wagner. In fact, SEM observation showed the erosion of HP_{50} during the dissolution studies. Beads analysed after preparation present a spherical smooth surface (Fig. 5a). An incubation period of 2 h in acidic medium induced the formation of some microscopic pores in the beads' surface (Fig. 5b), due to the insolubility of HP_{50}. However, when the pH of the dissolution medium is raised to 6.8, the polymer starts eroding, exposing the crystals of the drug, and allowing drug release to occur (Fig. 5c).

4. Conclusions

This study indicates that the preparation of beads based on the precipitation of the HP_{50} polymer method can be an effective technique of encapsulating etodolac. Beads with high drug loading and almost monosdisperse particle size distribution could be prepared. The beads obtained were smooth, spherical and suitable to be incorporated into capsules, while the in vitro release profiles confirmed their gastroresistance, thus allowing pH-dependent release of etodolac in the gastrointestinal tract. The application of mathematical models and a fitting curve to the experimental data from the release studies, showed that the dissolution of etodolac contained in HP_{50} matrices follows a first order release mechanism. Finally, the main advantages of this simple and mild technique are the one-step production method, since it does not need a coating process, the absence of organic solvents, and the strict use of non-toxic materials.

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