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CELLULOSE ACETATE TRIMELLITATE MICROSPHERES CONTAINING NSAIDs

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ABSTRACT

Indomethacin and ketoprofen (non-steroidal anti-inflammatory drugs) were incapsulated with cellulose acetate trimellitate, enteric polymer, using a spray drying technique.

Organic solutions of polymer and drug were prepared in different weight ratios and sprayed, achieving drug loaded microspheres.

The obtained spray dried microparticles were characterized in terms of yield of production, shape, size, morphological characteristics and drug content.

The *in vitro* drug release tests, carried out using a pH change method with a flow-through cell apparatus, show a typical delayed drug release due to the pH-dependent solubility of the polymer.

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INTRODUCTION

Oral dosing with non-steroidal anti-inflammatory drugs (NSAIDs) is a common treatment for different inflammatory conditions, such as rheumatoid arthritis and osteoarthritis (1).

Non-steroidal anti-inflammatory drugs are usually good candidates for the development of controlled release preparations, particularly through the oral route. However, adverse effects on the gastric mucosa have been observed by several authors (2), furthermore short biological half-lives can require different daily administrations (even three times and more) (3).

To reduce or eliminate the irritation of the gastrointestinal mucosa, microencapsulation has been used for the preparation of oral formulations (3,4). In fact multiparticulate delivery systems spread out more uniformally in the gastro-intestinal tract, and reduce the local irritation with respect to single-unit dosage forms, such as tablets (5).

Furthermore, the administration of NSAIDs incorporated into microparticulate delivery systems can avoid undesidered intestinal retention of polymeric materials, which can occur in the case of not disintegrating matrix tablets, particularly in the case of chronic dosing (6).

For all these reasons, NSAIDs loaded in microparticulate delivery systems have already been reported. Bodmaier and Chen (5) describe the preparation of NSAIDs loaded microspheres obtained using ethylcellulose and poly(methyl)methacrylate as polymers, and prepared with a solvent evaporation method; Khodairy et al. (7) report the encapsulation of ketoprofen with acrylic polymers (Eudragit RL/RS), with a coacervation process, obtaining microcapsules which are then formulated into tablets and capsules; Kawashima et al. describe spherical matrices containing ibuprofen (microsponges), prepared with acrylic polymers and using a solvent diffusion method (8).

Cellulose acetate trimellitate (CAT) is a relatively new enteric polymer (9) that is gaining more and more importance in the pharmaceutical field for the coating of solid oral dosage forms or granules, besides its homologues, the well-known cellulose acetate phthalate (CAP) and hydroxypropylmethylcellulose phthalate (HPMCP).

This polymer is characterized by a cellulose backbone, with 25 to 33 % w/w of trymellityl content and the acetyl content between 18 and 26 % w/w (10). In aqueous medium CAP dissolves at a pH of about 6.5, while CAT dissolves at a pH of about 5.5. In the preparation of solid oral dosage forms, CAP and CAT can be blended together, in order to achieve release profiles between that which would result from each of the pure polymer coatings (10).

Several reports recently describe microencapsulation techniques that use CAP as polymer. These procedures involve non-aqueous (11-13) and aqueous phases (14), using coacervation processes, or some of them involve a sort of precipitation method (15).

Furthermore, until now there are relatively few reports concerning CAT and its pharmaceutical applications, particularly in the field of the preparation of microparticulate delivery systems. Sanghvi and Nairn (16, 17) describe the preparation of CAT microspheres with an emulsification method, using light and heavy mineral oil as external phase, and the solvent mixture acetone:ethanol as internal phase.

A spray drying technique has been previously set up for the preparation of albumin or polylactide microspheres (18, 19), and in previous reports (20, 21) we described the preparation, through a spray drying technique, of ketoprofen loaded microspheres, using mixtures of cellulose acetate butyrate and ε-polycaprolactone.

The present report describes a spray drying technique to formulate NSAIDs into microparticulate delivery systems containing CAT as polymer and using a spray drying technique. Indomethacin and ketoprofen, belonging to the class of acidic non-steroidal anti-inflammatory drugs, were chosen as model.

MATERIALS AND METHODS

Materials

Cellulose acetate trimellitate (CAT) (Eastman® Kodak.C-A-T; Eastman Chemical Products Inc., Kingsport, TN, USA); Indomethacin (Ind), [1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid (Mw = 357.8; Mp = 158-162°C; Res Pharma, Trezzo sull'Adda, Milano, Italy);

Ketoprofen (Ket), 2-(3-Benzoylphenyl)propionic acid (Mw = 254.29; Mp = 93-95°C; Società Italiana Medicinali, Scandicci, Firenze, Italy).

Microsphere Preparation

The compositions of the different batches of spray dried microspheres are reported in Table 1.

Organic solutions of the polymer (1% w/v) were prepared at room temperature in the solvent mixture acetone:ethanol 3:1 v/v. The NSAID (Ind or Ket) was dissolved in the prepared solution of the polymer, in different weight ratios (1 %, 0.33 %, 0.25 % w/v), in order to obtain a final solution of polymer and drug, that was then sprayed through the nozzle (0.7 mm diameter) of a spray dryer (co-current flow type), model Mini Büchi 190 (Büchi Laboratoriums - Technik AG, Flawil, Switzerland).

The conditions of the spray drying process were both in the case of the preparation of Ind loaded microspheres, and in the case of the preparation of Ket loaded microspheres, the following: inlet air temperature 58-59°C; outlet temperature 45-46°C; spray flow rate about 8-10 ml/min. The total quantity of drug and polymer used for the preparation of each batch was 5 g.

Solid microparticles were collected into the final bottom vessel of the spray drying apparatus, and then harvested and kept under vacuum for 24 h.

The yields of production of the different batches prepared are reported in Table 2.

Microsphere Characterization

Evaluation of Drug Content and Encapsulation Efficiency

Samples of each batch of microspheres corresponding to about 20 mg of drug, were dissolved in USP phosphate buffer (pH 6.8) and the drug content was determined using a UV spectrophotometer (Spectracomp 602, Advanced Products, Milano, Italy) and with a 1 cm cell, at the wavelength of 320 nm for Ind and of 262 nm for Ket.

The obtained results are reported in Table 2 as drug content and encapsulation efficiency, which was calculated from the ratio of actual to theoretical drug content, and expressed as a percentage.

TABLE 1
Compositions of Spray Dried Microspheres

Microsphere	% CAT	% Ind	% Ket
CAT:Ind 1:1	50.0	50.0	-
CAT:Ind 2:1	66.66	33.33	-
CAT:Ind 3:1	75.0	25.0	-
CAT:Ket 1:1	50.0	-	50.0
CAT:Ket 2:1	66.66	-	33.33
CAT:Ket 3:1	75.0	-	25.0

TABLE 2
Yields of Spray Dried Microspheres

Microsphere	% Theor. drug content	% Actual drug content	% Encaps. efficiency	% Yield of production
CAT:Ind 1:1	50.0	47.81	95.62	49.5
CAT:Ind 2:1	33.33	32.22	96.66	48.7
CAT:Ind 3:1	25.0	24.56	98.24	49.1
CAT:Ket 1:1	50.0	49.01	98.02	50.4
CAT:Ket 2:1	33.33	31.94	95.82	51.3
CAT:Ket 3:1	25.0	23.99	95.96	52.3

Scanning Electron Microscopy (SEM)

Scanning electron microscopy was carried out on samples of all batches of microspheres prepared, by using a Jeol JXA 840A (Jeol Italia S.p.A., Pieve Emanuele, Milano, I) at 15.0 kV acceleration voltage, with $1*10^{-9}$ probe current.

The samples were analysed after gold sputtering (about 25 μm gold film thickness).

Particle Size Analyses

Particle size distributions of the spray dried microspheres were analysed by light blockage method with a HIAC/ROYCO model 9064 (Pacific Scientific, Silver Spring, Maryland, USA), equipped with a light scattering/light blockage Micro CT-05 sensor.

Small amounts (about 2 mg) of microspheres were suspended in 100 ml of bi-distilled filtered water (0.22 μm, Millipore S.p.A., Italia, Milano, Italy) and sonicated for about 2 min. The analyses were carried out under continous stirring at 50 size levels, in the 0.53 - 100 μm size range. Results are the average of five withdrawals (10 ml each) for each sample tested, and they are expressed as undersize cumulative particle size distributions by volume.

In vitro Drug Release Tests

The *in vitro* drug release tests of the spray dried microspheres containing the NSAIDs were carried out using a flow-through cell technique (22).

The apparatus is constituted by recycling flow-through cells (Dissotest Sotax CE6, Sotax Ltd, Basel, Switzerland), having an internal diameter of 22.6 mm, containing as fluid inlet a bed of glass beads with 1 mm diameter, and connected to a pump (Sotax CY 6D Piston Pump, Sotax Ltd, Basel, Switzerland). Two flow rates were selected for the *in vitro* release experiments: 45 ml/min and 16 ml/min.

The test was carried out using a pH change method (USP Method A for Enteric Coated Articles): for the first two hours of the test, 750 ml of HCl (pH 1.0) were used, and then 250 ml of 0.20 M tribasic sodium phosphate solution were added, in order to obtain a final pH of 6.8 in a total volume of 1000 ml. The dissolution medium (37°C) was placed in an external vessel, connected with the cell through the pump.

Samples of spray dried microspheres corresponding to about 20 mg of drug (Ind or Ket) were placed in the cells for the release tests. The drug released/dissolved was assessed with UV determination in the case of Ind, while through HPLC analysis with UV detector, in the case of Ket, owing to the interference of CAT in the absorbance of Ket at 262 nm.

The HPLC determinations for Ket were carried out (Varian HPLC 9050, Varian S.p.A., Cernusco S/N, Milano, Italy), with a partially modified method, previously utilized for ibuprofen (23). The determination was performed using the reverse-phase column MicroPak SP-C18-5J, and a mobil phase of 60/40 v/v acetonitrile/phosphate buffer pH 2.8 (0.012 M sodium phosphate buffer and 0.021 M sodium perchlorate). A flow rate of 1.2 ml/min, a detector wavelength of 262 nm (UV-Vis detector Varian 9050), and an injection volume of 10 μm were used.

RESULTS AND DISCUSSION

Spray drying of organic solutions containg the NSAID and the polymer in different weight ratios, is a simple and suitable technique to obtain drug loaded microparticles.

As shown by Table 2, the encapsulation efficiencies of the different batches are always very high (95-98 %). The yields of production, which are expressed as the weight percentage of the final product harvested, with respect to the initial amount of polymer and drug sprayed , are about 50 %.

These latter values are relatively good, particularly in relation of the low quantity of materials used for the preparation of each batch of microspheres. The main reason that can explain the relatively low yields obtained is the loss of the smallest and lightest particles through the exhaust of the spray dryer apparatus.

Photomicrographs of spray dried microspheres are given in figs.1a-c (microparticles containing Ind) and in figs.2a-c (microparticles containing Ket), in the three different polymer:drug ratios (respectively 1:1, 2:1 and 3:1).

Figs.1 show that for the microparticles containing Ind, no remarkable morphological differences are evident in the cases of the microspheres prepared with the different polymer:drug ratios. All the three batches are characterized by microspheres having a quite small size (less then 6-8 μm); furthermore all the microparticles seem to be

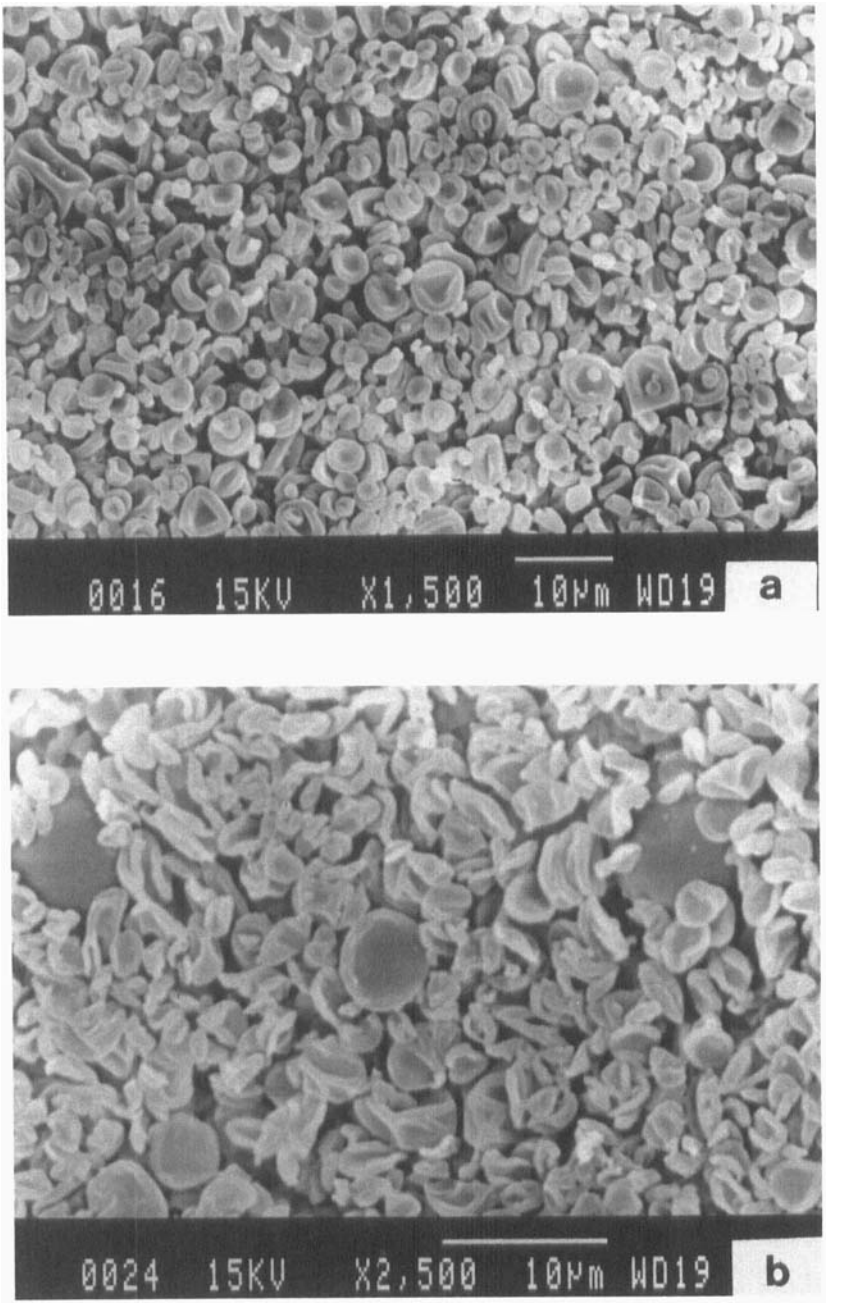

FIGURE 1

Photomicrographs of spray dried microspheres: (a) CAT:Ind 1:1 (1500x); (b) CAT:Ind 2:1 (2500x); (c) CAT:Ind 3:1 (3000x).

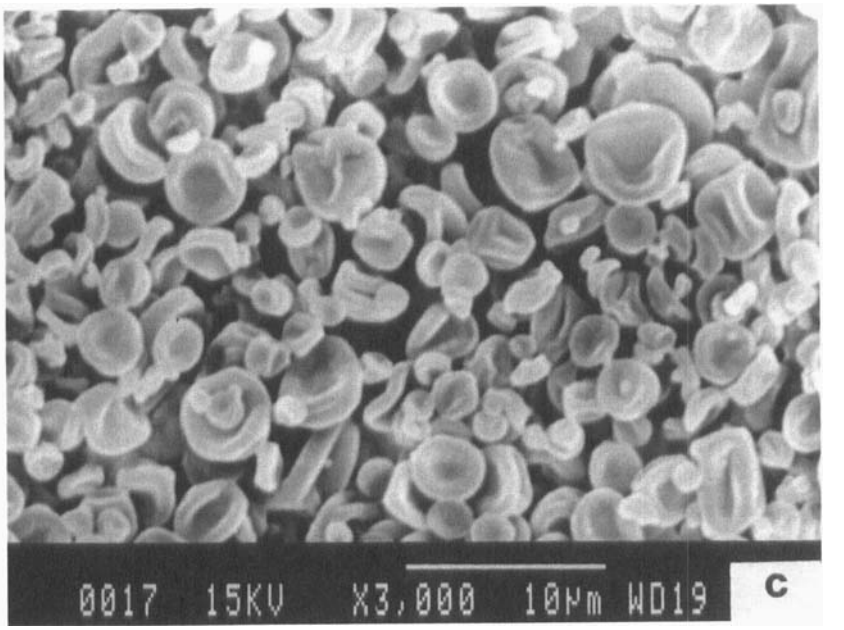

FIGURE 1. Continued

partially and/or totally collapsed and from this results their particular lens-shape.

No free indomethacin crystals appear in all the different preparations, characterized by the three different drug/polymer ratios.

The collapse of the original spherical structure of the microspheres could be due to the presence in the organic solution to be sprayed (and owing to the solubility characteristics of the polymer) of a remarkable quantity of a volatile solvent such as acetone (75 % v/v of the solvent mixture).

Considering the microparticles containing Ket as drug, also in these cases the three batches are characterized by similar morphology, as shown by figs.2.

In fact there are always microparticles of irregular shape, much more irregular than the microspheres containing Ind, and also in this

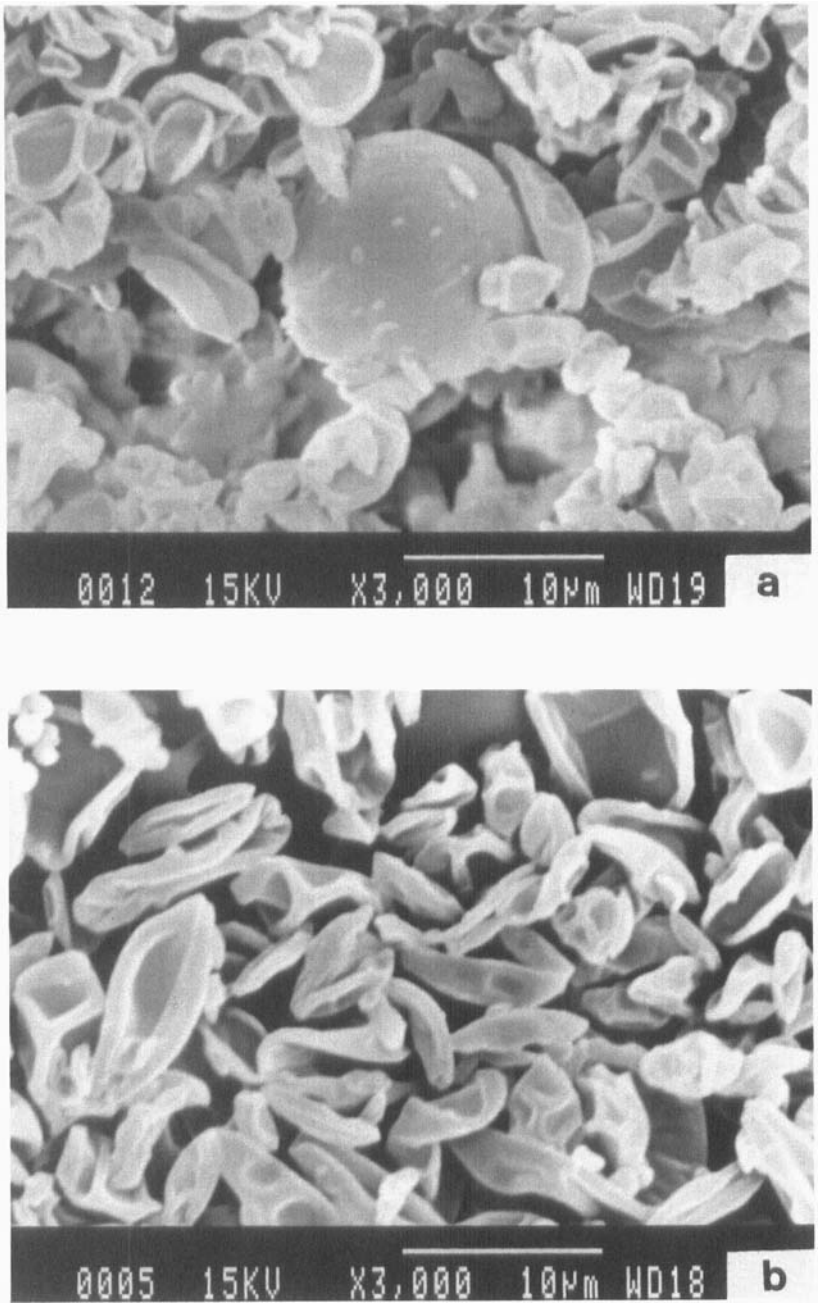

FIGURE 2

Photomicrographs of spray dried microspheres: (a) CAT:Ket 1:1 (3000x); (b) CAT:Ket 2:1 (3000x); (c) CAT:Ket 3:1 (3000x).

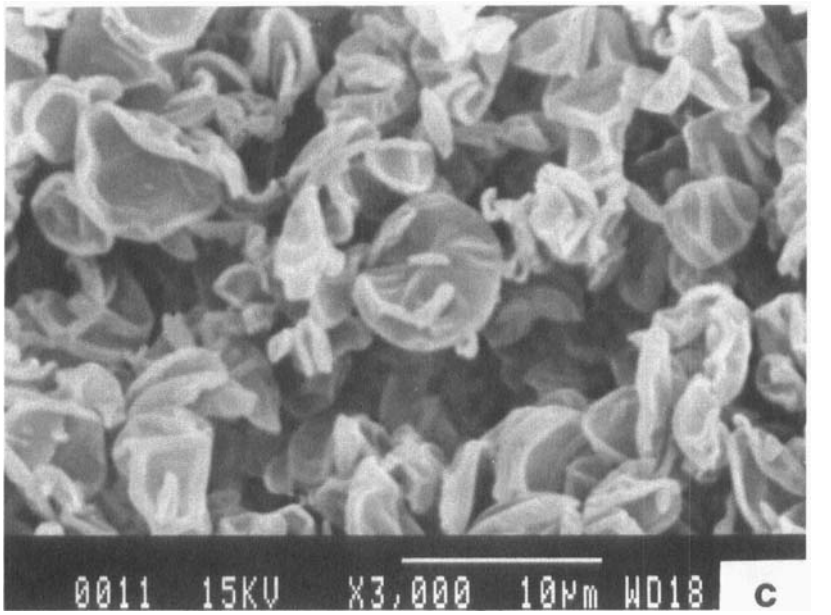

FIGURE 2. Continued

case the structures seem to be collapsed. Furthermore, the microparticles containing Ket are characterized by larger sizes (about 10 µm), and in the case of the preparaton CAT:Ket 1:1, also by the presence of some spherical particles of bigger size (more than 10 µm).

As in the previous cases, no ketoprofen crystals are present in each of the three different batches of microspheres.

Cumulative particle size distributions by volume are shown in fig.3 for the microspheres containing Ind, and in fig.4 for the microspheres containing Ket.

Fig.3 shows that the microspheres containing Ind are characterized by particle size distributions very similar, independently of their compositions (different polymer:drug weight ratios), and averagely 60 % of microparticles are smaller than 6-10 µm.

Fig.4 shows a different situation, because the preparation CAT:Ket 1:1 is characterized by a particle size distribution quite different with

respect to the other two preparation, CAT:Ket 2:1 and 3:1; in fact while these two latter preparations, averagely 60 % of microparticles are smaller than about 20 μm, while in the case of CAT:Ket 1:1 they are averagely smaller than about 30 μm.

Fig.5 and fig.6 show the drug release profiles obtained with the in vitro release tests (pH change method and with a flow rate of 45 ml/min), respectively in the cases of the microspheres containing Ind (fig.5), and in the cases of the microparticles containing Ket (fig.6).

The microspheres containing Ind are characterized by an initial drug release which corresponds to about 10-15 % in the first 30 minutes of the test, followed by a slow release of the drug from the microparticles: at the end of the first two hours 15-20 % of drug is detectable in the medium. This behaviour could be due to the fact that part of the drug is embedded just at the surface of the microparticles (about 10-15 %), while the main part is embedded into the polymeric network.

When the pH is raised to 6.8, by the addition of the phosphate buffer, the amount of drug released/dissolved increases very quickly, reaching the maximum (100 % of drug release) in about one hour.

This typical delayed release behaviour is due to the pH-dependent solubility of CAT polymer, which dissolves at pH 5.5. At the pH of 6.8 the microspheres dissolve very quickly in the dissolution medium, thus leading to the prompt release of the drug.

Similarly, delayed drug releases are obtained in the cases of the microparticles containing Ket, and with the three different polymer:drug ratios: also here a sudden release appears in the neutral phase.

The only difference remarkable in the comparison of the microparticles containing the two different drugs, is that CAT polymer seems to better control the release of Ind in the acidic medium (about 20 % of drug released after two hours), with respect to the control of the release of Ket (about 40 % after the same time). This latter result was obtained even lowering the rate of the flow through the diffusion cells, from 45 ml/min to 16 ml/min (data not reported).

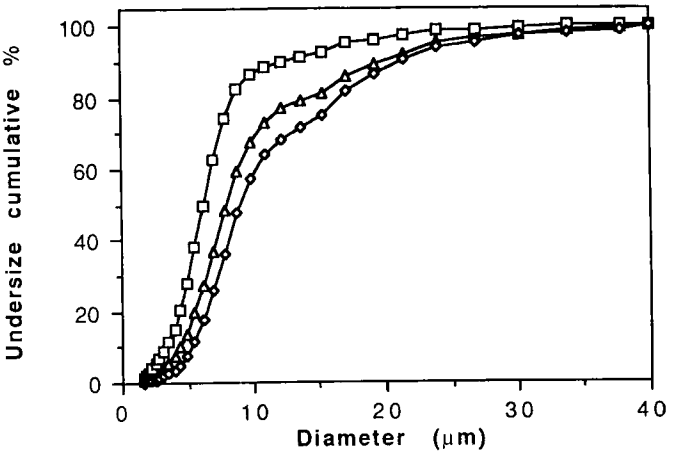

FIGURE 3

Undersize cumulative particle size distributions by volume of (Δ) CAT:Ind 1:1; (□) CAT:Ind 2:1; (◊) CAT:Ind 3:1.

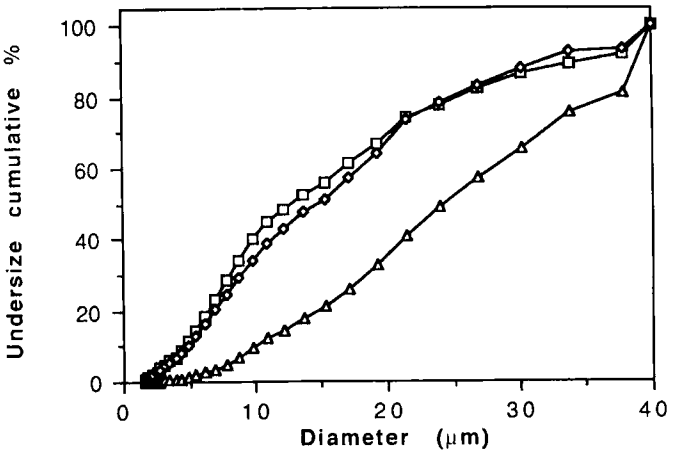

FIGURE 4

Undersize cumulative particle size distributions by volume of (Δ) CAT:Ket 1:1; (□) CAT:Ket 2:1; (◊) CAT:Ket 3:1.

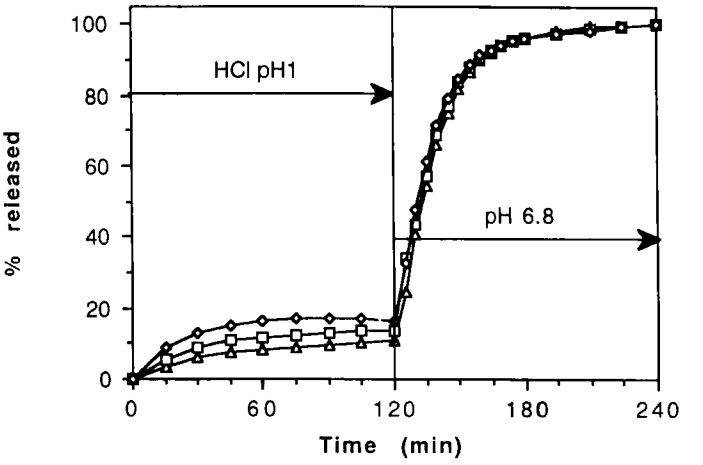

FIGURE 5

In vitro release profiles (pH change method) of (Δ) CAT:Ind 1:1; (□) CAT:Ind 2:1; (◊) CAT:Ind 3:1.

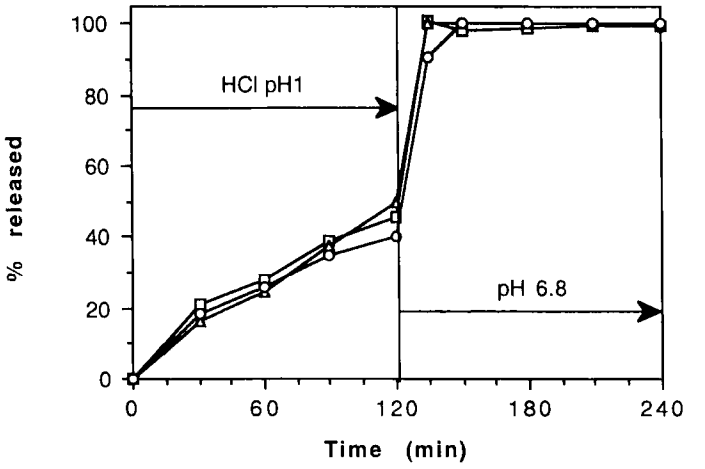

FIGURE 6

In vitro release profiles (pH change method) of (Δ) CAT:Ket 1:1; (□) CAT:Ket 2:1; (◊) CAT:Ket 3:1.

CONCLUSIONS

Spray drying is a simple technique for the preparation of drug loaded microparticles. The use of Cellulose Acetate Trimellitate as polymer is suitable for the formulation of NSAIDs such as indomethacin and ketoprofen.

All the tests were carried out using the flow-through cell apparatus, because this method gives advantages in comparison with other *in vitro* tests, particularly in the case of microparticulate delivery systems.

The microparticulate delivery systems here described is proposed for the design of oral dosage forms.

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