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RESEARCH PAPER

Polymers with pH-Dependent Solubility: Possibility of Use in the Formulation of Gastroresistant and Controlled-Release Matrix Tablets

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ABSTRACT

Polymers usually utilized for gastroresistant film coating of tablets or pellets such as cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), and Eudragit L and S were used in the preparation of drug/polymer matrix tablets. These tablets were prepared either by direct compression of both powders or by the formulation of microspheres that were then compressed. The microspheres were characterized by scanning electron microscopy (SEM), differential scanning calorimetry (DSC), and X-ray diffractometry analyses. Dissolution studies were finally carried out to verify if the tablets possessed gastroresistant or controlled-release characteristics. Except for Eudragit L, the polymers can be used under certain conditions in the formulation of modified-release tablets.

Key Words: *CAP; CAT; Controlled release; Eudragit; Gastroresistance.*

INTRODUCTION

Enteric polymers like cellulose acetate phthalate (CAP), cellulose acetate trimellitate (CAT), hydroxypropylmethylcellulose phthalate (HPMCP), and Eudragit L and S are usually used in the film-coating processes of solid dosage forms such as tablets or pellets when the dosage unit has to pass the stomach without disintegrating and releasing the drug (1). More recently, these polymers have been used as coating materials in the preparation of microcapsules (2–9) and microspheres (10,11) or solid dispersions (12–14) and coprecipitates (15,16) to

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be transformed into tablets for controlling drug release (17,18). This last use could represent a new field of application of these polymers. In fact, at pH values higher than their pK_a, they could behave as hydrocolloids and so be used the same as classic hydrocolloids in the formulation of hydrophilic matrix tablets for drug controlled release (10–28).

Because there are few papers (17,18) on the possible use of enteric polymers as hydrocolloids and the real capability of controlling drug release has not been defined, we tried to obtain matrix enteric polymer/drug tablets to verify this possibility. The easiest way to make these tablets is the direct compression of the physical mixture of polymer and drug powders, but in this case, an intimate mixture between the two molecules could not be obtained. On the other hand, all methods usually used in the preparation of microspheres allow the recovery of small matrix particles when the drug is uniformly and finely dispersed in the polymer chains. The compression of these types of particles (microspheres) should give better results in drug release control than direct compression.

For this reason, we prepared tablets either by direct compression or through the intermediate formulation of microspheres, using paracetamol as the model drug and enteric polymers as the matrix-forming material.

In vitro dissolution studies were performed to find out if these tablets possess gastroresistant or controlled-release characteristics.

MATERIALS AND METHODS

Preparation of Tablets by Direct Compression

Cellulose acetate phthalate (CAP; Eastman Fine Chemicals, Zürich, Switzerland), cellulose acetate trimellitate (CAT; Eastman), hydroxypropylmethylcellulose phthalate (HPMCP; Eastman), and Eudragit L and S (Röhm Pharma, Weiterstadt, Germany) were in turn mixed in a laboratory V-shape mixer (Laboratori Mag, Garbagnate Milanese, Italy) for 10 min with paracetamol using the following drug/polymer w/w ratios: 2:1, 1:1, 1:2, 1:4, and 1:8.

The addition of other excipients (such as the lubricant) was avoided to study the effect on the drug release characteristics due only to the type and amount of polymer.

All the mixtures prepared as described above were compressed directly with a 15-station rotary press (Kilian, Koln-Niehl, Germany) to obtain 250 mg tablets of 4, 8, and 12 Kp hardness.

Preparation of Microspheres

Microspheres of paracetamol/CAP, paracetamol/CAT, paracetamol/HPMCP, paracetamol/Eudragit L100, and paracetamol/Eudragit S100 in the ratios (w/w) 2:1, 1:1, 1:2, 1:4, and 1:8 were prepared by dissolving drug and polymer in the least volume of 0.05 N NH_4OH necessary to obtain a solution. These solutions were then spray-dried (Büchi Mini Spray-Dryer B-191, Flawil, Switzerland) under the following conditions: inlet temperature 150°C, outlet temperature 90°C, feed rate 10 ml/min, pressure 5 bar, and throughput of drying air 35 m^3/hr. All the powders recovered were stored under vacuum 2 days before being transformed to tablets.

Characterization of Microspheres

All the powders were assayed spectrophotometrically (Cary 1E UV-Vis, Varian, Leini, Italy) at 257 nm in 0.05 N NH_4OH (Carlo Erba, Milan, Italy) to be sure that no loss of drug or variation in the composition occurred during preparation.

Scanning electron microscopy (SEM) analysis was carried out with a Stereoscan 360 (Cambridge Instruments, Ltd., Cambridge, UK) on all series of microspheres to obtain a visual image and to evaluate particle size, shape, and surface.

Differential scanning calorimetry (DSC) was performed on the powders with a Perkin-Elmer DSC-2C differential scanning calorimeter connected to a personal computer data station. Each sample (10 mg of powder in aluminum pans) was heated at a heating rate of 5°C/min between 27°C and 227°C.

X-ray diffractograms of the prepared powders and of pure drug and polymers were carried out with a Philips PW 1730 X-ray generator using CuK_α radiation and a goniometer camera.

Preparation of Tablets by Microsphere Compression

All the series of microspheres prepared as above described were directly compressed with a 15-station rotary press to obtain 250-mg tablets of 4, 8, and 12 Kp hardness. Also, in this case, the addition of other excipients (such as the lubricant) was avoided to study the effect on the drug release characteristics due only to the structure and composition of the microspheres.

Dissolution Studies

The dissolution studies were performed in triplicate with an Erweka DT6 dissolution test using the paddle method at a rotation speed of 75 rpm (USP 23 apparatus 2). One tablet of each series was put into a vessel with 1000 ml 0.1 N of HCl. At 10-min intervals, 3 ml of water were withdrawn, passed through a 0.45-μm membrane filter (Millipore), and assayed spectrophotometrically with a Cary 1E UV-Vis spectrophotometer (Varian) at 257 nm to measure the concentration of drug present in the solution. The initial volume of the vessel was maintained by adding 3 ml of 0.1 N HCl after each sampling.

After 2 hr, the tablet was recovered and immediately put into 1000 ml of phosphate buffer (pH 7). At 10-min intervals, 3 ml of water were withdrawn, passed through a 0.45-μm membrane filter, and assayed spectrophotometrically at 257 nm for 6 hr. The initial volume of the vessel was maintained by adding 3 ml of phosphate buffer after each sampling.

RESULTS AND DISCUSSION

Characterization of Microspheres

The UV analyses performed on the prepared powders in all cases showed a 100% drug content according to the theoretical composition.

Figures 1 and 2 show the SEM images of the microspheres with paracetamol/CAP 2:1 and 1:8, respectively. Both powders (but also the intermediate ratios not shown) presented 30–80-μm particles that were not spherical and were formed by clusters of smaller microspheres (0.5–4 μm). These small microparticles indeed were not spherical in the 2:1 ratio, probably because of the considerable amount of paracetamol present in the powder, which tended to crystallize.

Figures 3 and 4 show the SEM images of the microspheres with paracetamol/CAT 2:1 and 1:8, respectively. In this case, the powders presented a particle size ranging between 15 and 100 μm, and the particles were formed by clusters of smaller microspheres (0.5–4 μm), except for ratios having the highest content of paracetamol (2:1 and 1:1), for which drug crystals were visible and the microparticles forming the clusters were not spherical.

Paracetamol/HPMCP microspheres are very similar to those shown, and their photos are not included here.

Figures 5 and 6 show the SEM images of the microspheres of paracetamol/Eudragit S 2:1 and 1:8, respectively. The particles of all the powders were formed by clusters of smaller microspheres, but while those with more paracetamol present small drug crystals on the surface and microspheres with dimension that ranged between 10 and 100 μm, those containing more Eudragit S were smaller (10–15 μm), and most of them were formed by clusters of ring-shaped microspheres.

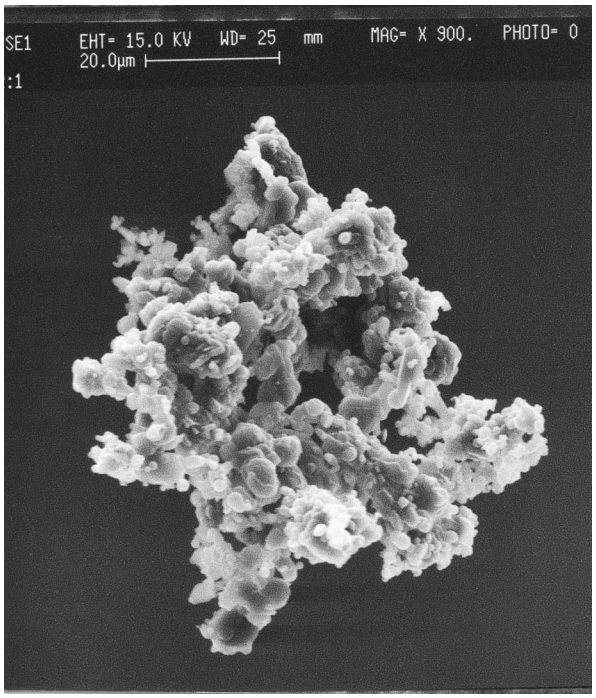

Figure 1. SEM image of paracetamol/CAP 2:1 microspheres.

In practice, form, dimension, and surface of paracetamol/polymer particles did not depend on the type, but only on the ratio of the polymer used.

Figure 7 shows the DSC plots of paracetamol/CAP microspheres. The paracetamol melting peak, which is visible in the pure drug thermogram, decreases gradually in intensity as the amount of polymer in the powder increases and disappears in the 1:2 ratio. This could induce the belief that paracetamol possesses a high solid solubility in this polymer (33%), but X-ray diffractograms do not confirm this interpretation. DSC curves of microspheres containing the other polymers gave very similar results and for this reason are not shown here.

Figures 8 and 9 show the diffractograms of paracetamol/CAP and paracetamol/Eudragit S microspheres, respectively. Diffractograms of paracetamol/CAT and paracetamol/HPMCP microspheres were prac-

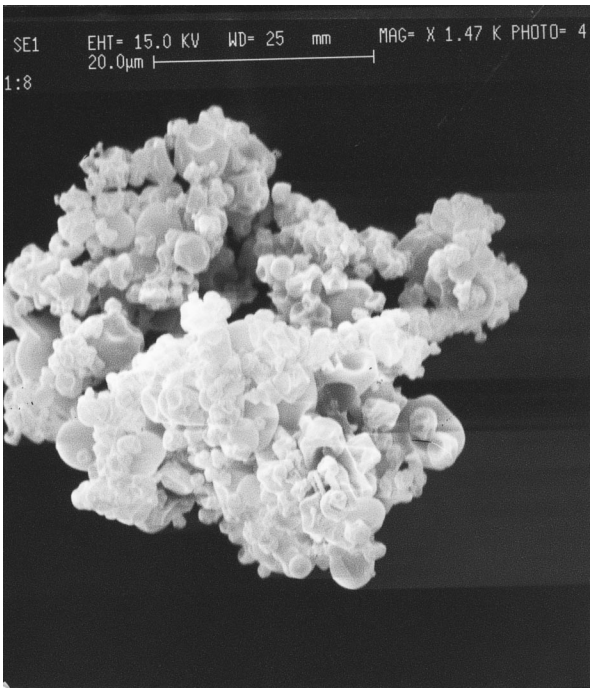

Figure 2. SEM image of paracetamol/CAP 1:8 microspheres.

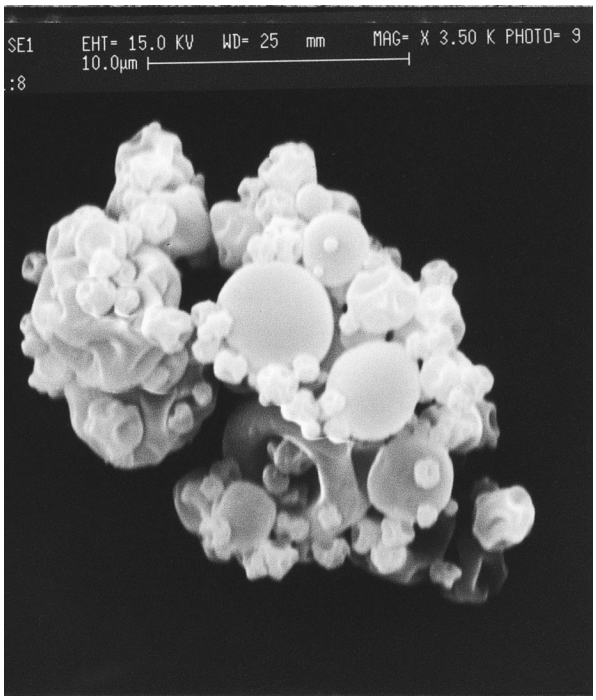

Figure 4. SEM image of paracetamol/CAT 1:8 microspheres.

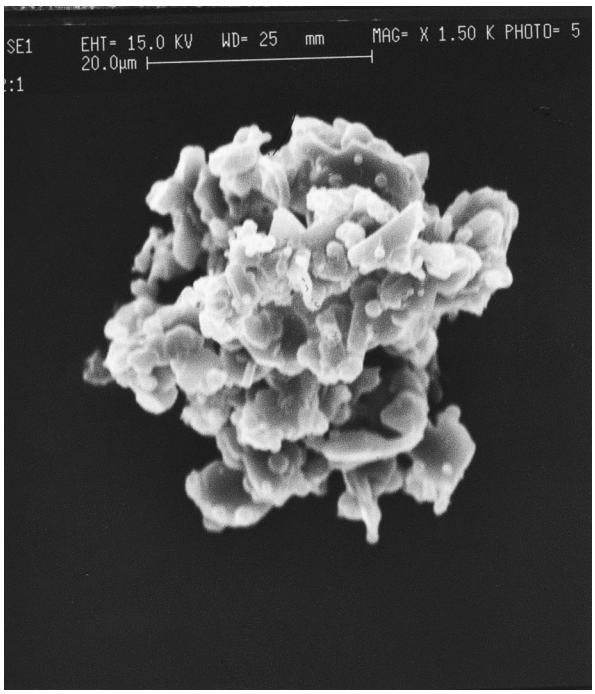

Figure 3. SEM image of paracetamol/CAT 2:1 microspheres.

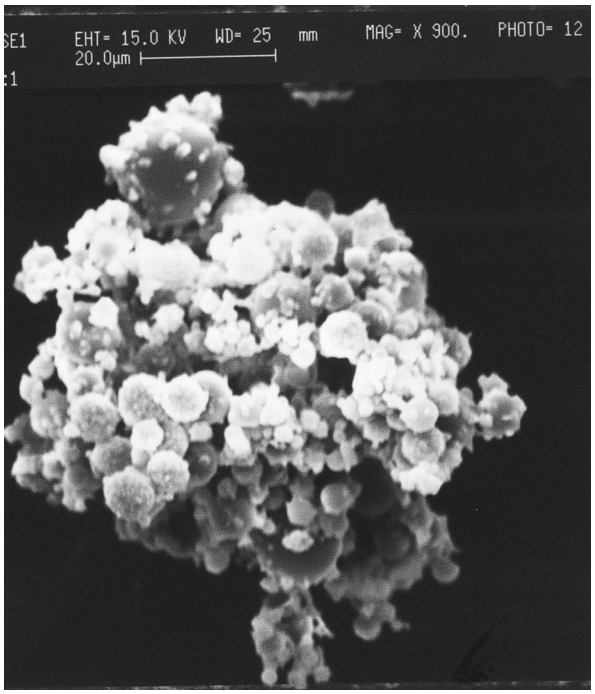

Figure 5. SEM image of paracetamol/Eudragit S 2:1 microspheres.

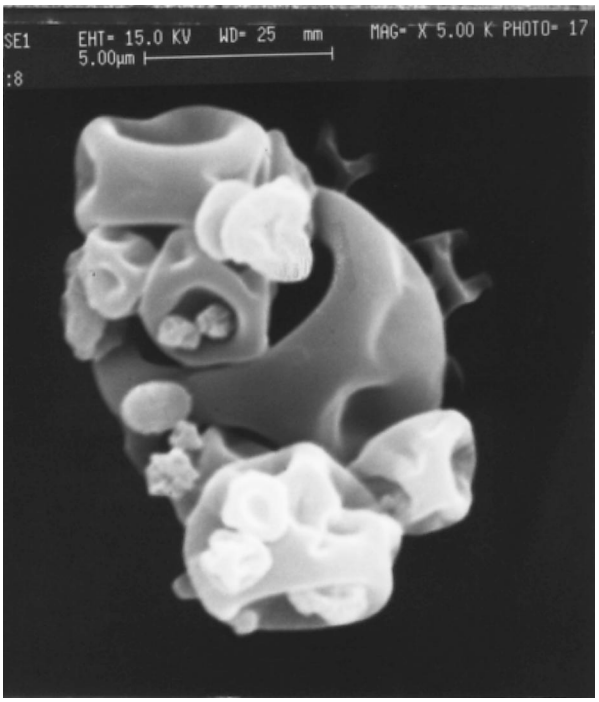

Figure 6. SEM image of paracetamol/Eudragit S 1:8 microspheres.

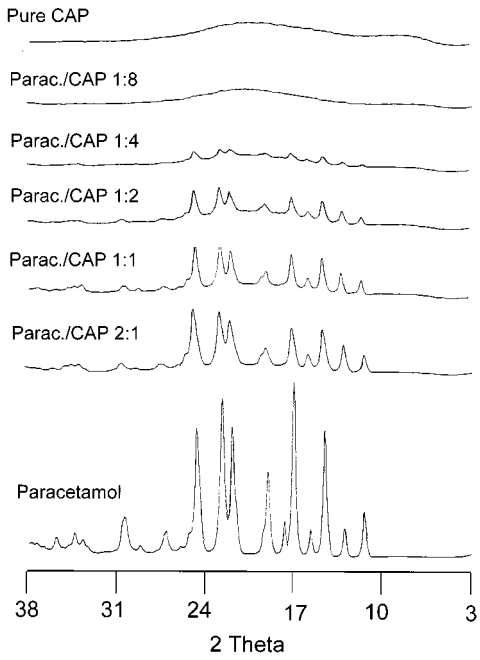

Figure 8. X-ray diffractometry plots of paracetamol/CAP microspheres.

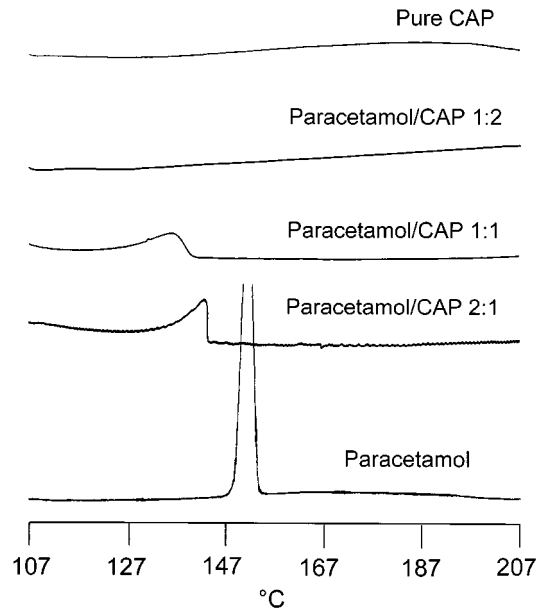

Figure 7. DSC plots of paracetamol/CAP microspheres.

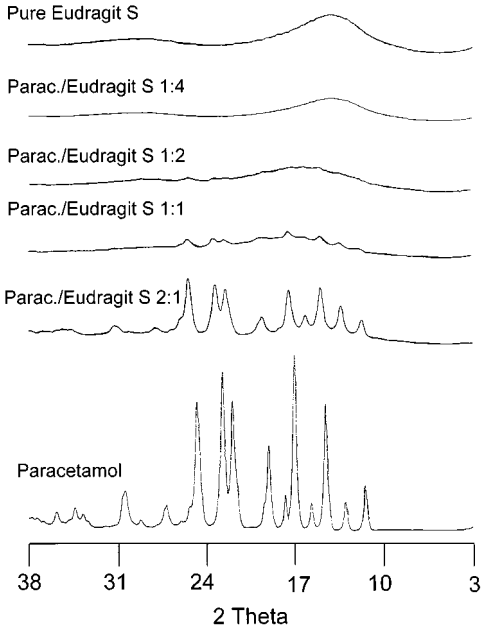

Figure 9. X-ray diffractometry plots of paracetamol/Eudragit S microspheres.

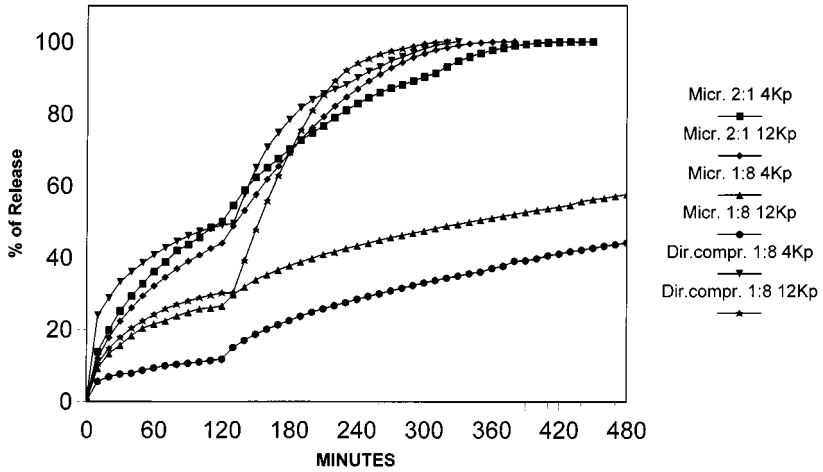

Figure 10. Dissolution profiles of 2:1 and 1:8 paracetamol/CAP tablets.

tically identical to that of paracetamol/CAP, and for this reason are not shown. In the same manner, diffractograms of paracetamol/Eudragit L microspheres were identical to that of paracetamol/Eudragit S, so they also are not shown.

Because all these polymers are amorphous, the presence of drug peaks (and therefore the presence of paracetamol crystals) in the powders should be easily detected. Diffractograms of powders containing CAP, CAT, or HPMCP show the classical drug peak intensity reduction until the peaks disappear in the 1:8 drug/polymer w/w ratio. This means that the solid solubility of paracetamol in these polymers is approximately 11–12% and not 33%.

Also, diffractograms of powders containing Eudragit L or Eudragit S show the same classical drug peak intensity reduction, but its disappearance occurs at the 1:4 drug/polymer weight/weight ratio. So, paracetamol seems to possess a better solid solubility in Eudragit L and Eudragit S (20% approximately) than in the studied cellulose derivative polymers.

Dissolution Studies

Figures 10–14 show the dissolution profiles of 2:1 and 1:8 (w/w) paracetamol/CAP, paracetamol/CAT, paracetamol/HPMCP, paracetamol/Eudragit L100, and paracetamol/Eudragit S100 tablets, respectively, pre-

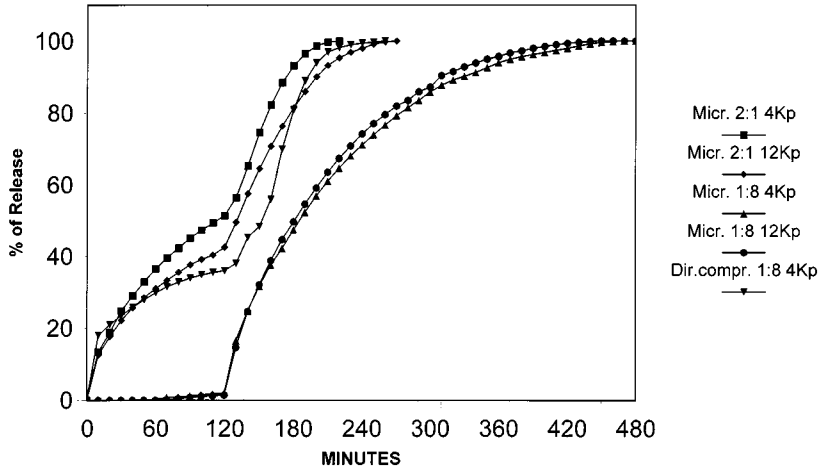

Figure 11. Dissolution profiles of 2:1 and 1:8 paracetamol/CAT tablets.

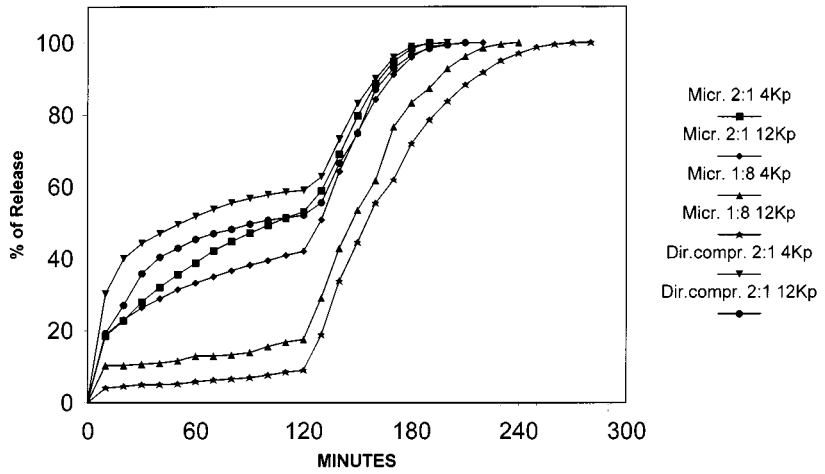

Figure 12. Dissolution profiles of 2:1 and 1:8 paracetamol/HPMCP tablets.

pared either by microsphere compression or by direct compression. In the last case, since only a few types of drug/polymer mixtures could be transformed into tablets because of their poor compressibility, fewer dissolution curves for these tablets are presented. Standard deviation bars are omitted to avoid overlapping.

Dissolution curves of microspheres are not shown because paracetamol release is too fast to make the use of the microspheres in powder form possible.

From these five figures, one can immediately realize that tablets obtained by direct compression always release the drug quicker than tablets obtained by microsphere compression, either in 0.1 N HCl or in phosphate buffer, pointing out the effectiveness of the intermediate spray-drying step in the formulation of modified-release matrix tablets.

CAP (Fig. 10) is the only polymer able to control drug release in a quasi-linear way if a high polymer/drug ratio (8:1 w/w) is used in the preparation of microspheres, particularly in phosphate buffer medium. If after 120 min, the pH of the dissolution medium is changed, the release kinetics remain substantially unmodified. This means that CAP, even if it is classified as an enteric polymer, also could be used for the formulation of controlled-release matrix tablets, provided microspheres are used in tablet preparation.

On the other hand, when there is a large polymer excess in the tablet composition (1:8 drug/polymer ratio),

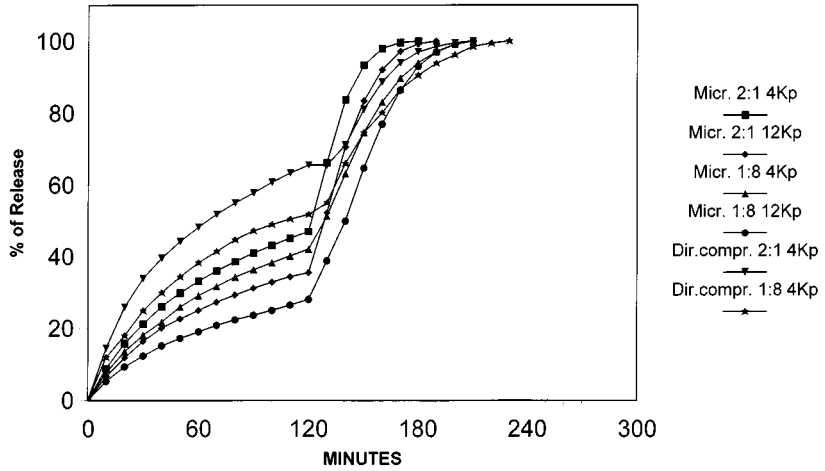

Figure 13. Dissolution profiles of 2:1 and 1:8 paracetamol/Eudragit L tablets.

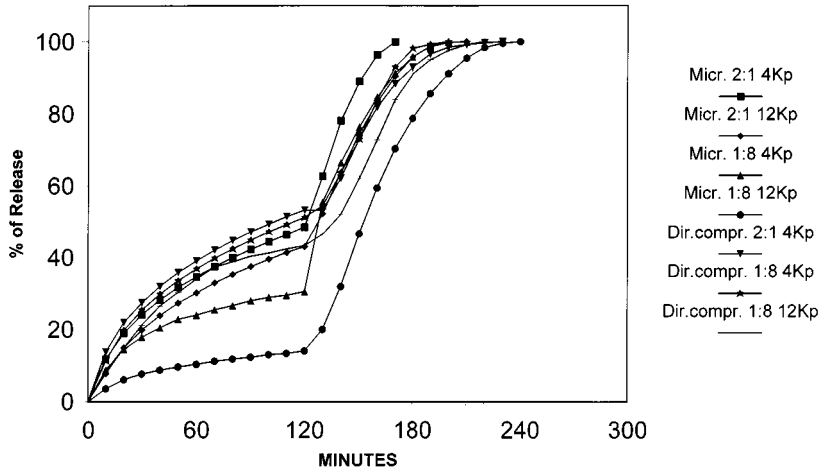

Figure 14. Dissolution profiles of 2:1 and 1:8 paracetamol/Eudragit S tablets.

CAT (Fig. 11) is very effective in avoiding paracetamol release in 0.1 N HCl from tablets obtained by microsphere compression and, at the same time, presents acceptable sustained release of drug in phosphate buffer, even if the kinetics are not linear.

Also, HPMCP and Eudragit S (Figs. 12 and 14), when used in the 1:8 drug/polymer ratio, show an appreciable variation of drug release kinetics from tablets obtained by microsphere compression when, after 120 min, the dissolution medium changes from 0.1 N HCl to phosphate buffer (pH 6.8). This release is slow in the first 120 min and increases remarkably in phosphate buffer, making possible potential use in the formulation of gastroresistant matrix tablets.

Tablets containing Eudragit L (Fig. 13) are not able to slow paracetamol release even in 0.1 N HCl. Therefore, this polymer is not indicated for gastroresistant or controlled-release matrix tablets.

CONCLUSION

Microspheres of the five polymers with paracetamol can be formed easily by spray-drying. Their diameters ranged between 10 and 100 μm, and they were formed by clusters of smaller microspheres (0.5–4 μm).

Solid solubility of paracetamol was less than 11% in CAP, CAT, and HPMCP and less than 20% in Eudragits L and S.

The powders of microspheres could be compressed easily into tablets, whereas physical mixtures of paracetamol/polymer very often were not compressible. This particular behavior of the compression of the microspheres will be studied in more detail.

Except for Eudragit L, the other gastroresistant polymers can also be used for the formulation of modified-release matrix tablets if elevated amounts are present in the matrix tablets obtained by compression of previously prepared microspheres.

Among these polymers, there were some differences concerning the paracetamol dissolution from tablets. HPMCP and Eudragit S could be used in the formulation of gastroresistant matrix tablets when the drug contained in the tablets does not possess a water solubility higher than that of paracetamol. CAT was the only polymer able to avoid drug release in 0.1 N HCl and had remarkable kinetics variation in phosphate buffer. Finally, changing the medium from 0.1 N HCl to phosphate buffer, CAP did not change the drug release kinetics, which remained gradual and quasi linear for the entire 480 min.

So, CAP can be used for the formulation of controlled-release matrix tablets provided an intermediate spray-drying step is added to the formulation.

ACKNOWLEDGMENT

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