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Controlled-release coevaporates of dipyridamole prepared with acrylic polymers

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Summary

The objective of this study was to obtain controlled-release dosage forms of dipyridamole chosen as a model drug practically insoluble above pH 5. The coevaporates were prepared by the solvent method using enteric and insoluble acrylic polymers as well as their mixtures in different proportions. The in vitro dissolution test results were determined by the USP XXII paddle method at different pH values during a period of 8 h. These results showed that the progressive pH-dependent release of dipyridamole could only be achieved by blending enteric and insoluble polymers. To overcome the difficulty in maintaining sink conditions with the paddle method, the dissolution profiles of some of the formulations were investigated using the open flow-through cell method.

Introduction

Dipyridamole (DIP) is a poorly water-soluble organic base which is used as a coronary vasodilator for its ability to prolong a shortened platelet survival, thus preventing thromboembolic complications. The solubility of this drug is highly pH dependent, being very soluble in acidic media and practically insoluble above pH 5 (Chiou and Riegelman, 1971; Hasegawa et al., 1986). This is the reason why it shows irregular and incomplete absorption from the gastro-intestinal tract. Accordingly, the intrinsic dissolution rates (0.01 mg/cm^2 per min at pH 5) confirm this bioavailability problem.

In this study, the solid dispersion technique was applied to prepare controlled-release dosage forms of DIP using enteric and insoluble acrylic polymers. The solvent method is used to prepare coevaporates of DIP with Eudragit® S, L, L 100–55, RL and RS. When the active substance is absorbed throughout the gastro-intestinal tract, whatever the dosage form, it should be necessary to increase the drug release as the form progresses through the intestine, so as to compensate for the decrease in absorption which generally occurs in the colon. With the conventional sustained-release dosage forms, the opposite is likely to happen; when the dosage form reaches the colon, the last phase of the release prevails and is generally characterized by a slow and continuous decrease (Moës, 1989).

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In order to achieve this goal, insoluble and enteric acrylic polymers were blended in different proportions and used as carriers.

Only the in vitro dissolution of the amorphous coevaporates was determined by the USP XXII paddle method at different pH values during a period of 8 h. The results showed that it was practically impossible to maintain sink conditions above pH 5, therefore, for this reason the dissolution profiles of some of the formulations were investigated using the open flow-through cell method.

Materials and Methods

Materials

Dipyridamole (Office Chimique, Lot 89f26–184, USP XXII)

Eudragit® S, L, L 100–55, RL, RS (Röhm Pharma, Darmstadt, Germany), ethanol, dichloromethane, chloroform and methanol (Merck, Analytical Grade) were used as received.

Methods

Preparation of DIP / Eudragit® coevaporates

DIP and Eudragit® S, L, L 100–55, RL, RS were dissolved in a suitable ratio in a solvent mixture comprising ethanol/ dichloromethane (1 : 1) and then the solvent was removed under vacuum in a rotary evaporator at 45°C. The residue was pulverized, dried for 48 h under vacuum at room temperature and stored in a dessicator protected from light. The different particle size fractions were obtained by sieving (Model 42 Rhewum). The same fraction size (0.1–0.2 mm) was used for all tests.

Preparation of physical mixtures

DIP and the polymers were weighed accurately in a 2 : 8 ratio and then mixed thoroughly by light trituration in a mortar.

Analysis of the samples

Samples were analyzed for dipyridamole content at 283 nm by UV spectroscopy (Hitachi spectrophotometer model 100–60) after dissolution and suitable dilutions in dichloromethane.

In vitro release tests

USP XXII paddle method The experiment was carried out at 37.0 ± 0.1°C in the USP XII No. 2 dissolution apparatus at a stirring rate of 60 rpm. The dissolution medium was a phosphate buffer with the following composition: acetic acid (0.05 M), potassium dihydrogen phosphate (0.05 M) and Tween 20 (0.05%).

12 N HCl was added to adjust the initial pH to 1.3. At predetermined intervals 4 N NaOH was added with an automatic burette (Radiometer ABU80) connected to an automatic titrator (Radiometer TTT8O) and a pH Meter (Radiometer pHM 82) in order to carry out variation of the pH programmed as follows: 0–1.0 h, pH 1.3; 1.0–1.5 h, pH 5.0; 1.5–4.5 h, pH 6.3; 4.5–7.5 h, pH 6.9.

A sample equivalent to 25 mg of dipyridamole was introduced in a lock-cap gelatine capsule maintained in the dissolution medium (900 ml at t_0) by a helicoidal stainless-steel wire. At predetermined intervals the test solution was filtered automatically and assayed spectrophotometrically at 283 nm (Philips PU 8605/60 Tablet Dissolution Monitoring System).

Open flow-through cell method (Sotax) A flow-through apparatus (Sotax AG, Switzerland) with cells of 12 mm diameter were used in these experiments. This apparatus has been described by several authors (Posti and Speiser, 1980; Möller, 1983; Langenbucher et al., 1989). The flow rate was fixed at 16 ml/min. The phosphate buffer mentioned above was used and at the predetermined intervals the pH was adjusted to the required value with a pH meter (Radiometer pHM 82). The total testing time was 7.5 h. A sample equivalent to 75 mg dipyridamole was introduced in a lock-cap gelatine capsule which was placed in the dissolution medium at t_0. The capsules were positioned directly onto a bed of 2.5 g of glass beads just filling the conical part at the bottom of each cell. In order to avoid floating, the capsules were fixed below an inverted wire hook to force their immersion in the fluid. At predetermined intervals sampling was performed by collecting the clear eluate leaving the

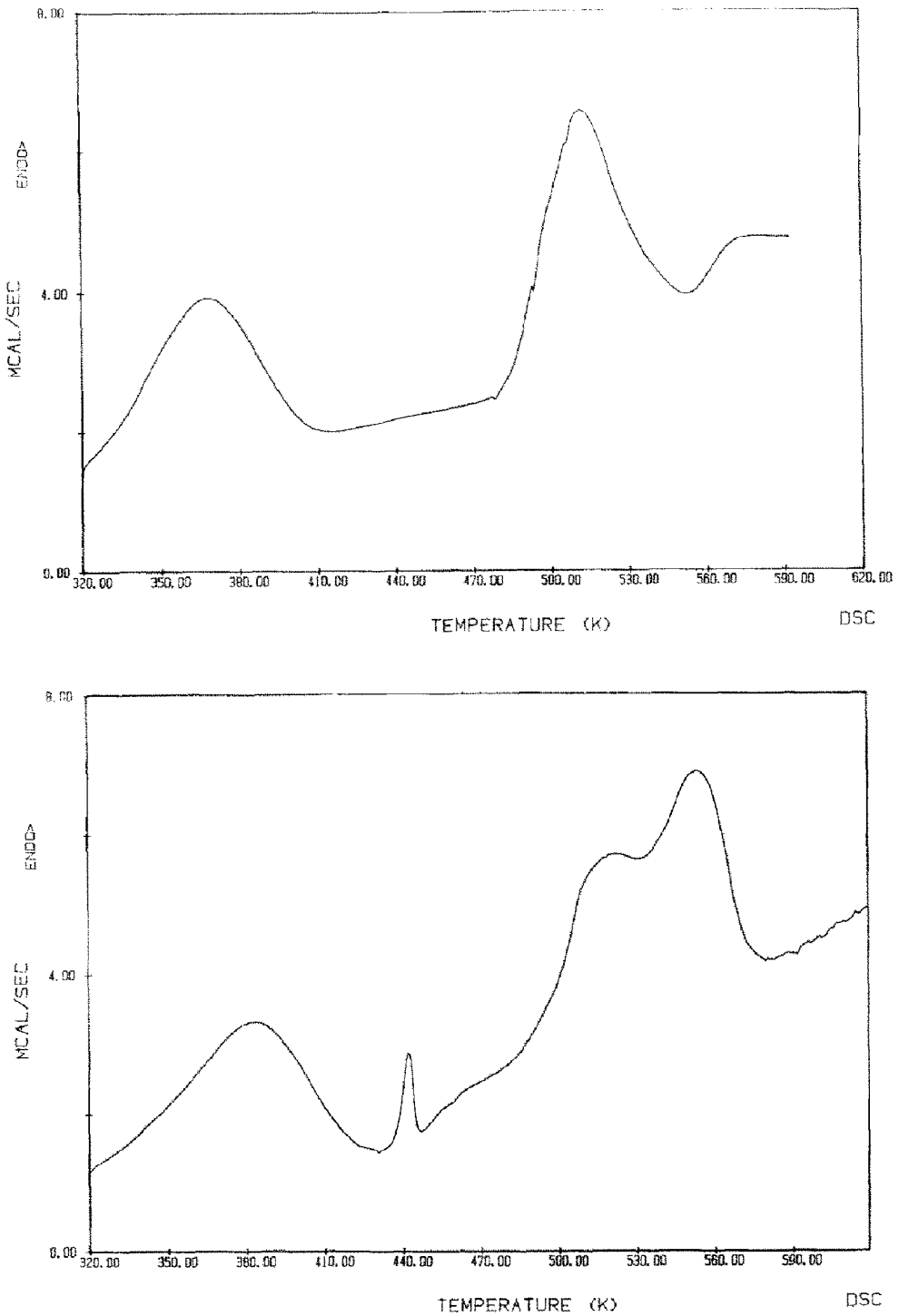

Fig. 1. DSC thermograms of: (1) coevaporate (2:8); (2) physical mixture (2:8); (3) coevaporate (2:8) after annealing.

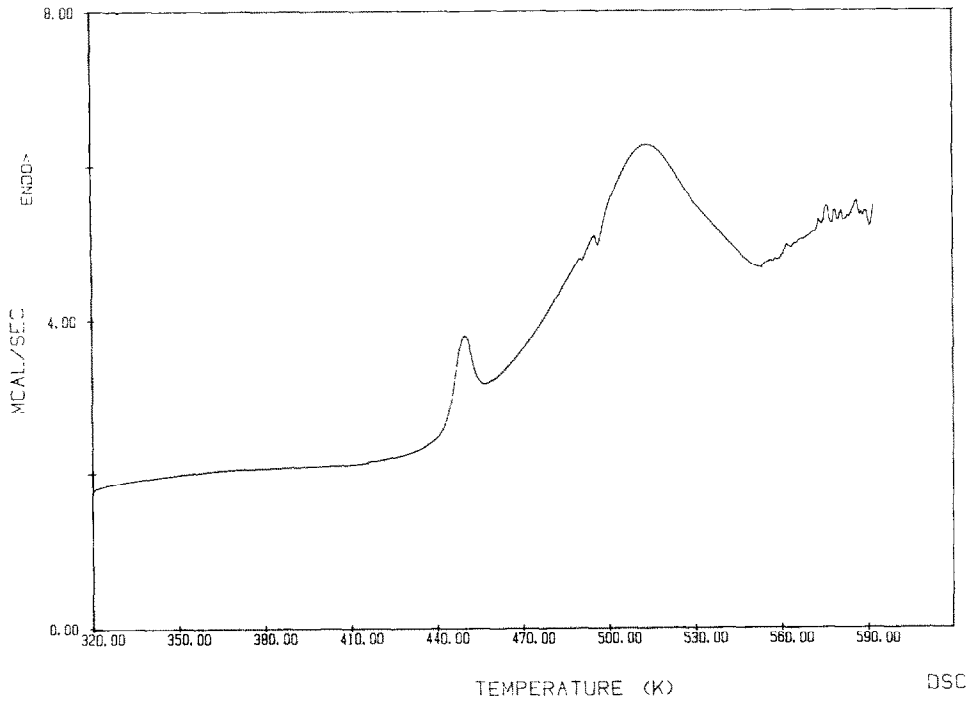

Fig. 1 (continued).

filter head without aliquoting so that the eluate was homogeneous in concentration which was measured spectrophotometrically at 283 nm (Hitachi Spectrophotometer model 100–60, Tokyo, Japan).

X-ray analysis

Powder X-ray diffractometry was carried out with a Philips X-ray Diffractometer, CuKα radiation (40 kV, 16 mA, slit 1°–1°).

DSC

Thermal analysis was performed on the drug, drug-polymer physical mixture and the coevaporates using a Perkin-Elmer 2C differential scanning calorimeter equipped with a computerized data station (Perkin Elmer Corp., Norwalk, CT). Aluminium pans and lids were used for all samples. Temperature calibrations were performed using indium as a standard. All samples were run at a scanning rate of 20°C/min using nitrogen as effluent gas. The determinations of transition temperature were carried out by a computerized procedure. An annealing procedure was also carried out by placing the solid dispersions in an oven at a fixed temperature for a given period of time (130°C during 48 h) before performing the thermal analysis (Shefter and Cheng, 1980; Benoit et al., 1983; Porter and Ridgway, 1983).

Results and Discussion

Investigation of the physical nature of the coevaporates

The coevaporate systems were generally yellow, the intensity of the colour depending on the nature and the quantity of polymer present in the mixture. When a dense yellow precipitate was observed it was due to the recrystallisation of dipyridamole. In this study, only the amorphous solid dispersions (2 parts DIP and 8 parts of polymer) were selected for further investigation.

Microscopy (polarized light)

When the coevaporate was amorphous, there was no reflection of light with different colours, indicating the absence of crystallinity.

X-ray diffraction

The X-ray diffraction patterns of these coevaporate systems were examined and compared with those of the pure substance and their physical mixtures. When the X-ray diffraction patterns showed no diffraction peaks attributed to dipyridamole, this implied the absence of apparent crystallinity for DIP in the coevaporate systems. As the DIP content increased the coevaporates were no longer amorphous and presented definite diffraction peaks.

DSC

Both the drug and the physical mixture exhibit a sharp endothermic peak around 163°C, corresponding to the melting point of dipyridamole, thus indicating that the latter is in its crystalline form. However, in the thermogram of the solid dispersions there was no sharp peak at 163°C, confirming that the drug was indeed amorphous in the solid dispersions. Furthermore, an annealing experiment was carried out in order to differentiate between a solid-state solution or a molecular dispersion of the drug in the polymer. After annealing, the characteristic peak of the melting point of dipyridamole at 163°C reappeared. This showed that by increasing the temperature above the glass transition temperature of the polymer, the mobility of the polymeric chain was increased, thus enabling the drug to diffuse in the polymer and then crystallize. This was evidence that dipyridamole did not form a solid solution with Eudragit® S, but instead formed a molecular dispersion. The thermograms of the coevaporate (2:8), physical mixture and coevaporate after annealing are presented in Fig. 1.

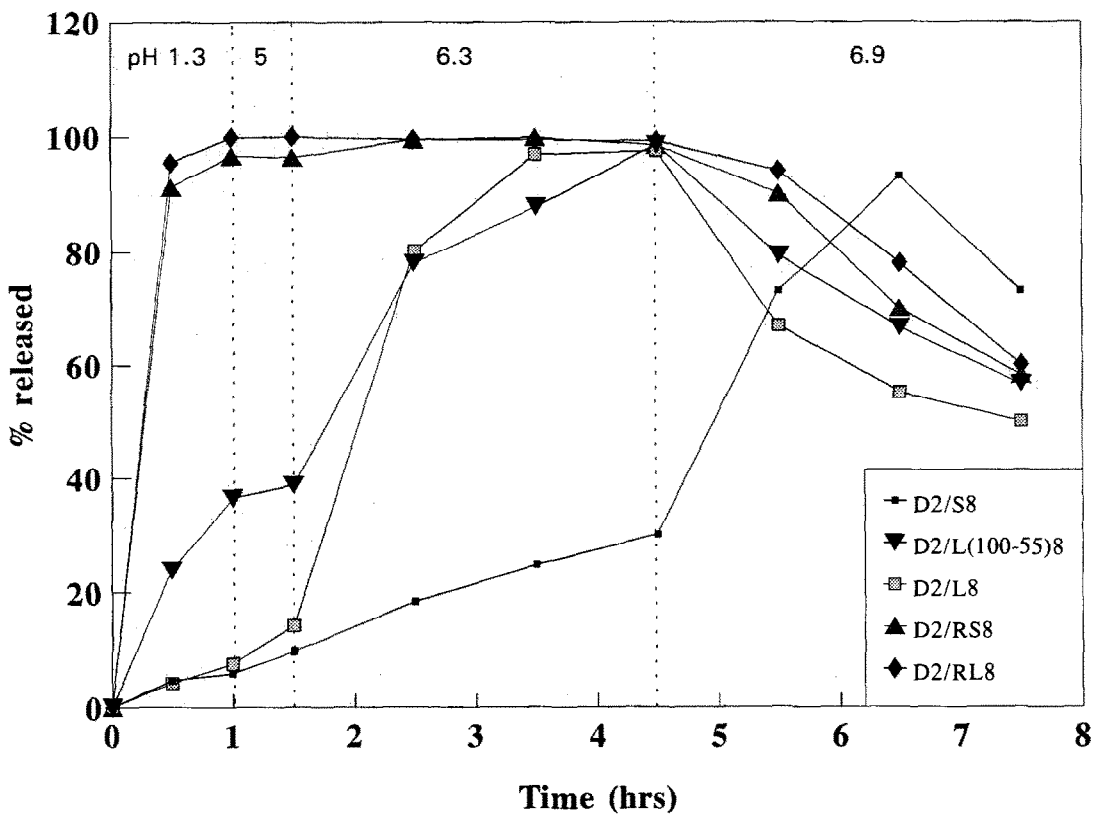

Fig. 2. Influence of the nature of the polymer on the percentage of DIP released as a function of time.

In vitro release studies

USP XXII paddle method

These studies allowed the identification of the different parameters influencing the drug-release from the coevaporates

Nature of the polymer

The enteric acrylic polymers used to prepare coevaporates with dipyridamole were Eudragit® S, L, L 100–55, which are soluble at pH 7, 6 and 5.5, respectively. Accordingly, the dissolution profiles obtained for each coevaporate were different. The release profiles from coevaporates DIP/S, DIP/L and DIP/L 100–55 are plotted in Fig. 2 in comparison with the dissolution curves of the coevaporates DIP/RL and DIP/RS.

These dissolution profiles clearly indicate that it is possible to decrease to a great extent the dissolution of dipyridamole in acidic media and to enhance its release at higher pH when enteric polymers are used. This effect depends very much on the pH of polymer dissolution. It should be noted that in all cases, the drug crystallized from supersaturated solutions.

On the other hand, the results of the dissolution tests of the coevaporates prepared with insoluble acrylic polymers Eudragit® RL and RS showed that these polymers have no effect on the drug-release profiles. This difference between the drug release profiles is caused by an interaction between Eudragit® S and dipyridamole (Beten et al., 1992).

Influence of blending enteric and insoluble acrylic polymers

The objective of blending these acrylic polymers in different proportions was to achieve con-

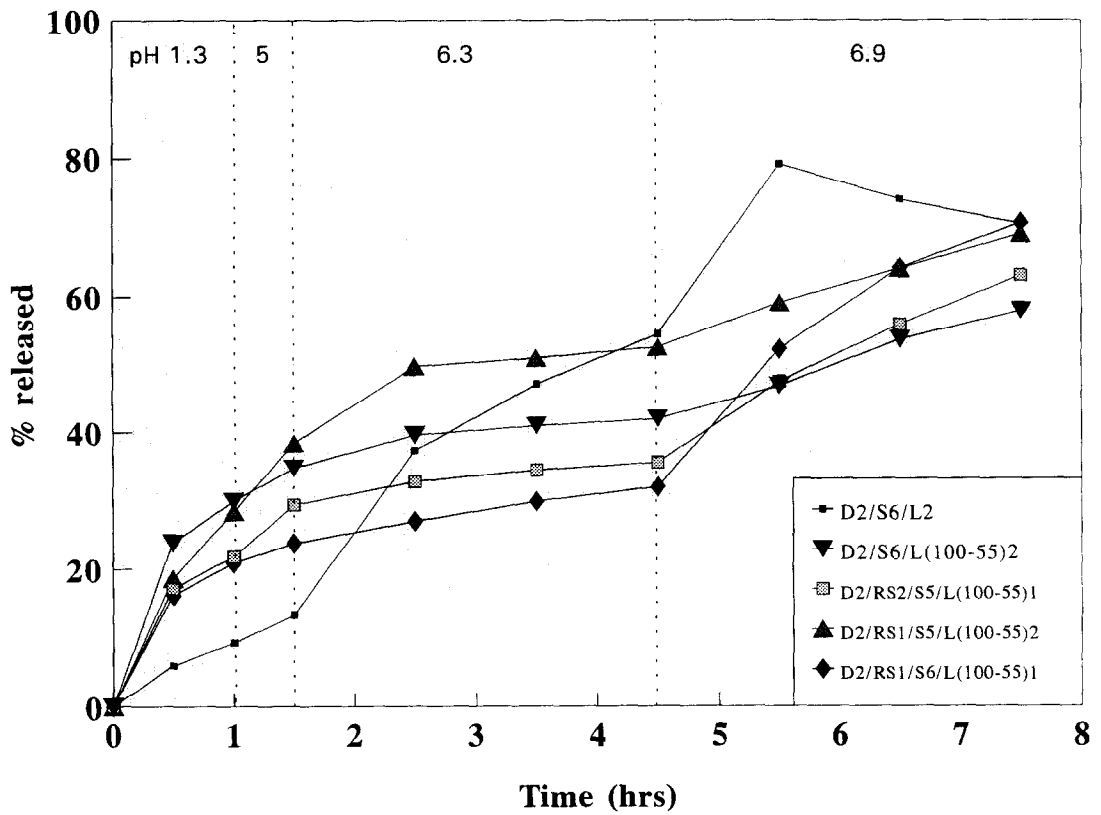

Fig. 3. Influence of blending acrylic polymers in different proportions on the drug release as a function of time.

trolled-drug release throughout the entire gastro-intestinal tract. The dissolution profiles of some of these coevaporates are shown in Fig. 3. These results show that the drug release can be modified by changing the amount of enteric polymer present in the coevaporate system. Thus, if the quantity of Eudragit® S is increased, the release of drug is very much inhibited in acidic media whereas once the pH of polymer dissolution is reached, drug release is enhanced to a great extent despite the low solubility of dipyridamole at this particular pH value.

Effect of the particle size

The release profiles of DIP from different size fractions of the coprecipitate DIP/S/L 100–55 (2:6:2) are plotted in Fig. 4. As can be seen from these results, the drug-release rate can be reduced by increasing the particle size. The influence of particle size on drug release was taken into consideration and the fraction of size 0.1–0.2 mm was used for all formulations.

Open flow-through cell method (Sotax)

Because the solubility of dipyridamole is very much pH dependent, it is practically impossible to maintain sink conditions using the USP XXII paddle method once pH 6 is reached. When the open flow-through cell method is used, the unlimited supply of the dissolution fluid maintains sink conditions irrespective of the solubility of dipyridamole.

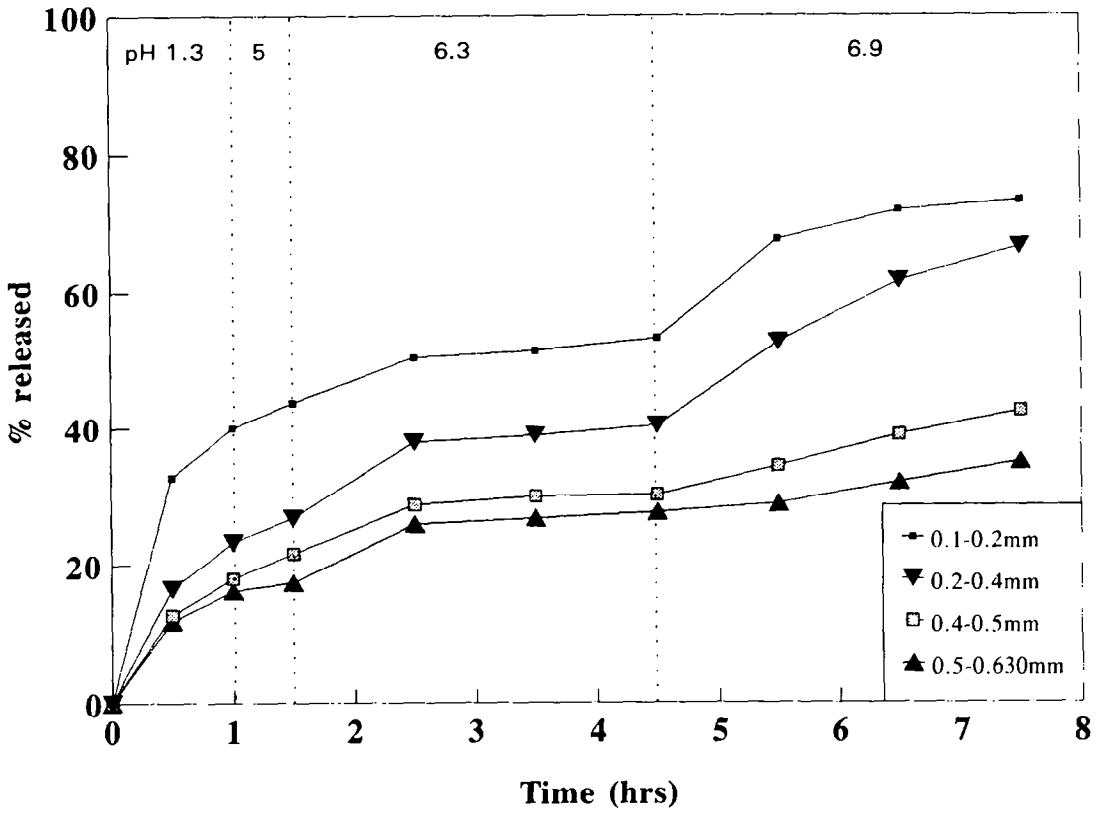

Fig. 4. Influence of the particle size of the coevaporate DIP/S/L 100-55 (2:6:2) on the percentage of DIP released as a function of time.

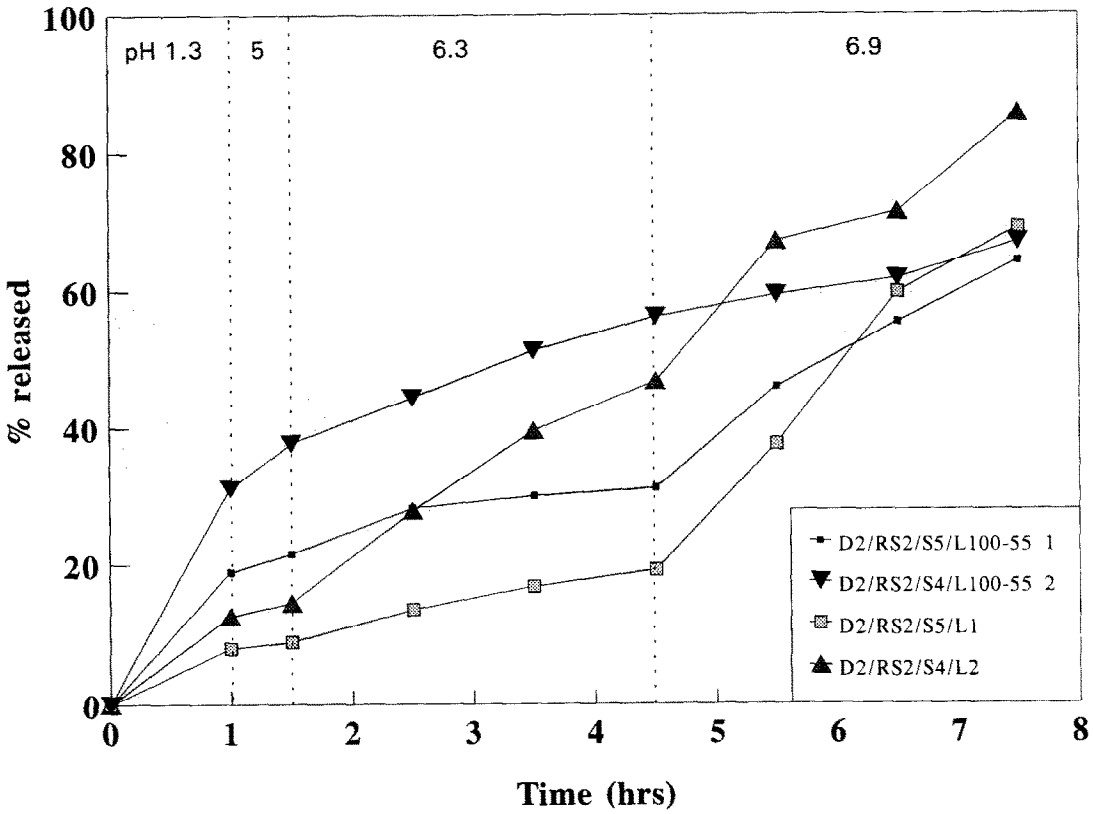

Fig. 5. Percentage of dipyridamole released as a function of time using the open flow-through cell method at a flow rate of 16 ml/min. Cell diameter = 12 mm.

Conclusions

Controlled-release dosage forms of dipyridamole could be prepared by blending enteric and insoluble acrylic polymers. The results of the annealing experiments showed that dipyridamole formed a molecular dispersion with Eudragit® S. The dissolution profiles of coevaporates prepared with Eudragit® S, L, L 100–55, showed that it is possible to inhibit to a great extent the dissolution of dipyridamole in acidic medium and to enhance it in fluid media of higher pH values despite its low solubility at these pH values. In contrast, Eudragit® RL and RS had no effect whatsoever on drug release. On the other hand, it was shown that the S/L, S/L 100–55, RS/S/L and RS/S/L 100–55 ratios could be optimized to modulate the release profile of dipyridamole. As an example, the dissolution profile of the D2/RS2/S4/L2 coevaporate shown in Fig. 5 indicates that zero-order release is practically achieved with a release rate of 11.4%/h (r = 0.9961). It is also worth noting that the drug release rate is highly dependent on the particle size of the coevaporates. Therefore, this parameter must be kept under control during the manufacturing process. In vivo studies are now being undertaken to evaluate the behaviour of coevaporate particles during gastric emptying and to estimate their mean gastric residence time in fasting and fed conditions.

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