Preparation of Controlled-Release Coevaporates of Dipyridamole by Loading Neutral Pellets in a Fluidized-Bed Coating System

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Purpose. The purpose of this study was to demonstrate that it is possible to prepare controlled-release drug-polymer coevaporates on an industrial scale, omitting the recovery problems and the milling and sieving processes encountered when coevaporates are prepared by the conventional solvent-evaporation technique. ***Methods.*** Controlled-release coevaporates were prepared by spraying organic solutions of dipyridamole-Eudragit® blends onto neutral pellets using the fluidized-bed coating method. Enteric acrylic polymers Eudragit® L100-55, L, and S were used as dispersing agents and drug/polymer ratio 2:8 was selected for all formulations. Polarized light microscopy, X-ray diffraction spectroscopy, and differential scanning calorimetry were used to determine whether the drug was amorphous or crystalline in the coating films. Moreover, *in vitro* dissolution tests were performed on the dipyridamole coated pellets in test media simulating the pH variations in the GI tract and the results were compared to the release data obtained from coevaporates prepared by the conventional solvent-evaporation method. ***Results.*** All the results clearly indicate that dipyridamole is amorphous in the coating films deposited on neutral pellets as well as in coevaporate particles obtained by the conventional solvent-evaporation method. When the release patterns of the dipyridamole coated pellets are compared to those of the drug coevaporate particles prepared with the same enteric acrylic polymers, the results show similar dissolution trends. ***Conclusions.*** The results obtained indicate that pelletization can be considered as a method of choice for pilot plant and/or full-scale production of controlled-release dosage forms based on the formation of amorphous solid dispersions.

KEY WORDS: pellet loading; coevaporate; dipyridamole; Eudragits®; controlled-release; fluidized-bed.

INTRODUCTION

The solid dispersion technique can be used either to enhance the dissolution rate of poorly water-soluble drugs by using water-soluble inert carriers such as polyethylene glycols (1) and polyvinylpyrrolidone (2) or to prepare controlled-release dosage forms using water insoluble and/or enteric polymers as dispersing agents like Eudragits® RL, RS, L 100-55, L, S, and carboxymethylcellulose (3-5). The results of these studies showed that it was possible to prepare controlled-release dosage forms of drugs with bioavailability problems like nifedipine and dipyridamole (6,7).

In a previous investigation, dipyridamole, which is a poorly water soluble weak organic base, was used as a model drug showing irregular and incomplete absorption from the gastrointestinal tract because its solubility is strongly dependent on pH variations. The solvent-evaporation method was used to prepare coevaporates for this drug with Eudragits® RL, RS, L 100-55, L, and S.

The results showed that when using blends of polymers, ratios of Eudragits® S/L, S/L 100-55, and RS/S/L could be optimized to modulate the drug release profiles (8). However, the preparation of coevaporates by the solvent-evaporation technique proved not to be a very practical method for manufacturing these dosage forms at an industrial scale. Indeed, the dried products are difficult to recover from the evaporation tanks and further, have to be ground to a powder which, in turn, has to be sieved for selecting fraction sizes according to the desired drug release profiles.

On the other hand, drug layering by spraying a solution or suspension containing suitable binders, onto non-pareil seeds is one of the techniques of pelletization commonly performed on an industrial scale, using different fluidized-bed modes (9).

Different viscosity grades of water-soluble or water-insoluble polymers were used in order to design drug-coated granules with modified-release properties (10,11). Therefore, in this study, it is proposed to prepare drug-loaded core formulations where the coevaporate of dipyridamole is formed on the surface of neutral pellets in such a manner that the recovery problems and the subsequent milling and sieving processes could be omitted in an industrial manufacturing procedure.

For this purpose, organic solutions of dipyridamole-Eudragit® blends were applied onto pellets using the fluidized-bed coating method. The enteric acrylic polymers Eudragit® L 100-55, L, and S were used for coating, and the physical structure of dipyridamole in the coating films was determined.

In vitro dissolution tests were performed on the dipyridamole coated pellets and the results were compared to the release data obtained from coevaporates prepared by the conventional solvent-evaporation method.

MATERIALS AND METHODS

Materials

Two batches of neutral pellets, 75% sugar and 25% maize starch (Werner's® Fine Dragées, Tornesch, Germany), in the size range of 0.50-0.60 mm or 1.00-1.18 mm, and glass beads were used as core materials. In order to reduce specific surface area variations, batches of pellets with narrow sieve fractions were selected (min. 90% of granules within the specified size ranges). Dipyridamole (Office chimique, USP XXII) was used as the model drug. Eudragit® L 100-55, L, and S (Röhm Pharma, Darmstadt, Germany) were selected as the anionic polymers. Ethanol and dichloromethane (Merck, Analytical Grade) were used for the preparation of the drug-polymer solutions.

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Pellet Loading

Batches of about 800 g of neutral pellets were transferred in a fluidized-bed coating apparatus (Uniglatt, Glatt GmbH, Germany), equipped with a bottom spray coating process in a Würster column (12) and coated with the different formulations until the desired quantity of drug was deposited.

The inlet and outlet temperatures of the drying air during the coating procedure were respectively 30 ± 1°C and 28 ± 1°C. Coating solutions were pumped at a flow rate of 10 ml/min and the pneumatic spraying pressure was 1 bar. The total spraying time was approximately 4 hours. The coated pellets were dried in the same apparatus for 10 minutes at the same working temperatures. The coating conditions were kept almost identical throughout the study. Dipyridamole and Eudragit® L 100–55, L, and S were dissolved in a suitable ratio in the solvent mixture ethanol/dichloromethane (1:1). The total solid content of solutions was 10% w/w.

The pellets were sprayed with the following drug-polymer solutions: D/S (2:8), D/L (2:8), D/L 100–55 (2:8), and D/S/L 100–55 (2:6:2). For each batch of coated pellets, the dipyridamole content was determined by UV spectroscopy (Hitachi spectrophotometer, model 100–60) at 283 nm, after dissolution and suitable dilutions in dichloromethane. The total drug loading was fixed at 5% w/w, while the drug/polymer ratio 2:8 was selected for all formulations.

Dissolution Studies

In vitro dissolution tests were performed using the USP dissolution apparatus no. 2 (paddle) at 37.0 ± 0.1°C with a stirring rate of 60 rpm. The dissolution medium was a phosphate-acetate buffer (0.05 M) containing 0.05% w/w Polysorbate 20. The initial volume and pH of the dissolution media were respectively 900 ml and 1.3. At predetermined intervals, 4 N NaOH solution was added with an automatic burette (Radiometer ABU80) connected to an automatic titrator (Radiometer TTT80) 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; 1.5–4.5 h, pH 6.3; 4.5–7.5 h, pH 6.9.

Samples of loaded pellets (n = 5), equivalent to 25 mg of dipyridamole, were placed in the dissolution medium. Samples were withdrawn continuously from the dissolution media by a peristaltic pump (Gilson minipuls 2, Villiers-Le-Bel, France) and passed after filtration through a multi-cell Philips 8620 series spectrophotometer and assayed at 283 nm at preselected time intervals. All these operations were controlled by the Philips PU 8605/60 Tablet Dissolution Monitoring System. The drug loading determined for each individual batch of coated pellets was used as the value representing 100% of the drug released.

Determination of the Physical Structure of Dipyridamole

Preparation of Physical Mixtures

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

X-ray Analysis

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

Differential Scanning Calorimetry

Thermal analysis was performed on the pure drug, the drug-polymer physical mixtures, and the drug-polymer films using a DSC-7 Differential Scanning Calorimeter / TAC-7 thermal analysis controller with an intracooler-2 cooling system for subambient determinations (Perkin Elmer Corp., Norwalk, CT).

Aluminium pans and lids were used for all samples. Temperature calibrations were performed using cyclohexane and indium as standards. The determinations of transition temperatures were carried out by a computerized procedure. All samples were run at a scanning rate of 10°C/min using nitrogen as effluent gas. The samples of drug-polymer films were obtained by scratching films off the surface of loaded pellets or glass beads with a scalpel.

RESULTS AND DISCUSSION

The physical state of dipyridamole in the drug-Eudragit® films was first investigated using the three following methods.

Microscopy (Polarized Light)

When dipyridamole was in its amorphous state in the films, there was no reflection of light with different colors, thus, indicating the lack of crystallinity.

X-ray Diffraction

The X-ray diffraction spectra of dipyridamole-Eudragit® films were examined and compared to those of the pure substance and physical mixtures. The powder X-ray diffraction patterns showed no diffraction peak attributable to dipyridamole in the different drug-Eudragit® films indicating the lack of apparent crystallinity of the drug in the sprayed films.

Differential Scanning Calorimetry

The thermograms of the pure drug, Eudragit® S, the drug-Eudragit® S (2:8) physical mixture, and the drug-Eudragit® S (2:8) sprayed film are respectively presented in Figure 1. 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. No endothermic peak appeared for sprayed films.

All these results clearly indicate that dipyridamole is amorphous in the coating layers deposited on neutral pellets as well as in coevaporate particles obtained by the conventional solvent-evaporation method.

In Vitro Release Studies

The enteric acrylic polymers used to prepare polymeric coating solutions and coevaporates with dipyridamole were Eudragits® L 100–55, L, and S which start to solubilize at

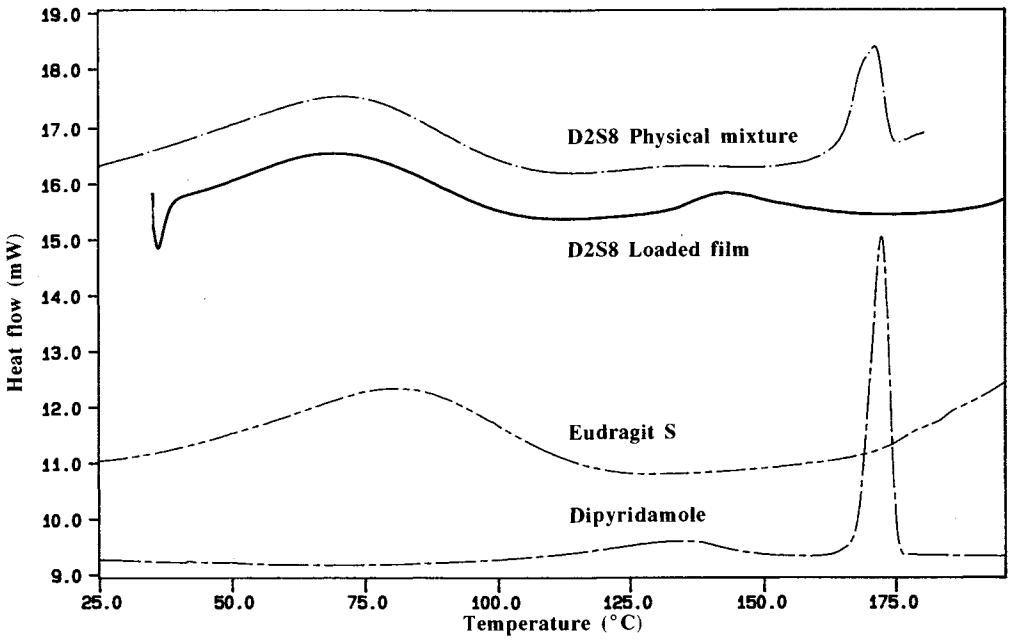

Fig. 1. DSC thermograms of dipyridamole, Eudragit S, D2S8 loaded film, and D2S8 physical mixture.

pH 5.5, 6, and 7 respectively. On the contrary, dipyridamole is very soluble in acidic media and practically insoluble above pH 6 (solubility, at 37°C, ranges between 36.5 mg/ml at pH 1 and 0.02 mg/ml at pH 7).

The formulation of drug-enteric polymer solid dispersions aims to decrease as far as possible the dissolution rate of dipyridamole in acidic media while enhancing it at higher pH values despite the low solubility of the drug above pH 6.

The drug release profiles from 0.5–0.6 mm pellets with Eudragits® L 100–55, L, and S are plotted in Figure 2.

These dissolution profiles show that it is possible to inhibit, to a great extent, the dissolution of dipyridamole in acidic media, and to enhance its release at higher pHs, the results depending very much on the pH of dissolution of the polymer used. These release profiles had been explained previously by an interaction existing between dipyridamole and anionic acrylic polymers (13).

When the release patterns of the dipyridamole coated pellets are compared to those of the drug coevaporate particles prepared with the same enteric acrylic polymers, the results show similar dissolution trends. It should be noticed that in all cases, the drug crystallizes slowly from the supersaturated solutions.

This phenomenon is not likely to occur *in vivo* because sink conditions prevail thanks to the absorption process.

In order to achieve controlled drug release throughout the entire gastrointestinal tract, the enteric polymers were blended in different proportions. The dissolution profiles of 0.5 and 1.0 mm pellets coated with the D/S/L 100–55 (2:6:2) formulation are given in Figure 3 in comparison with those of

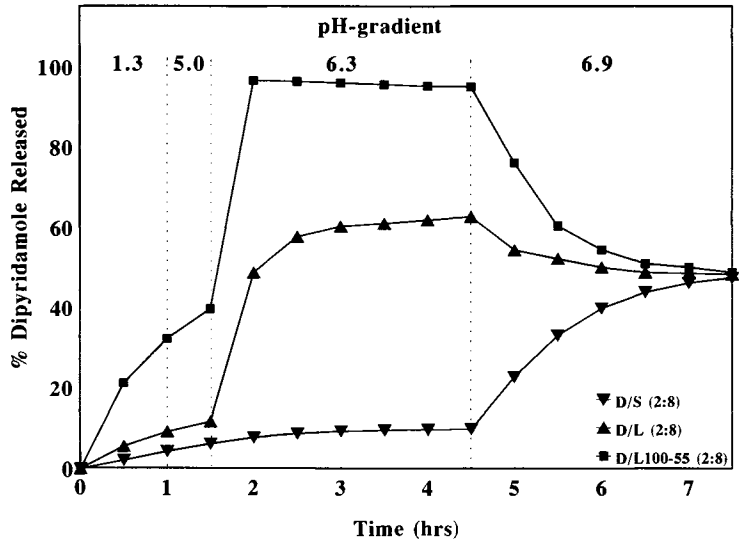

Fig. 2. Dipyridamole release profiles from 0.5–0.6 mm pellets loaded with drug/polymers (2:8) mixtures: D/S, D/L, D/L 100–55.

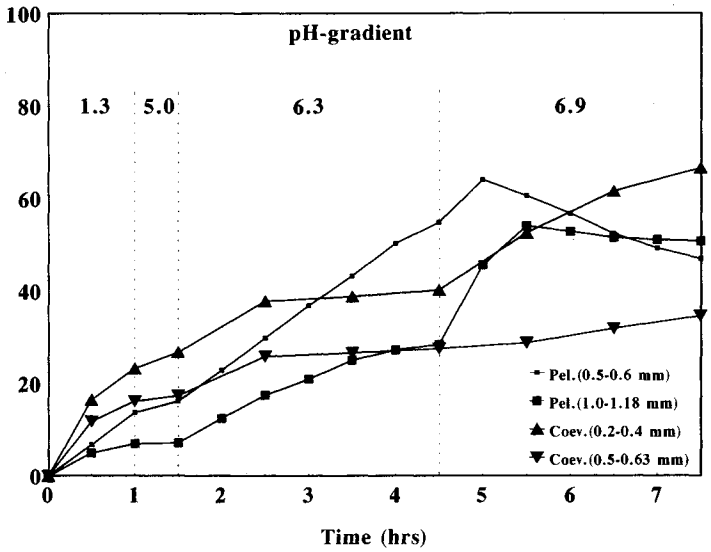

Fig. 3. Comparison between the dissolution profiles of loaded pellets (0.5 and 1.0 mm) and coevaporate particles (0.20–0.40 and 0.50–0.63 mm fraction sizes) for the D/S/L 100–55 (2:6:2) formulation.

coevaporate particles (fraction sizes 0.20-0.40 mm and 0.50-0.63 mm) prepared with the same polymeric blend. Again, the delivery systems are characterized by similar dissolution trends despite profile differences most probably due to specific surface area differences existing between the two types of dosage forms.

It can be observed also that the drug release rate from pellets can be decreased by increasing the pellet size as well as increasing the particle size of conventional coevaporates.

In conclusion, we can assert that it is possible to prepare controlled-release dosage forms of amorphous dipyridamole by loading neutral pellets of known size with drug - enteric polymer organic solutions sprayed in a fluidized-bed coating device. Dipyridamole is distributed under its amorphous form into the polymeric network, and the *in vitro* drug release profiles from the coated pellets are similar to those obtained from coevaporates prepared by the solvent-evaporation technique.

As the latter has many disadvantages compared to that forming the coevaporates directly on the pellet surface, the results obtained in this study indicate that pelletization should be considered as a method of choice for the manufacture of controlled-release dosage forms based on the formation of amorphous solid dispersions. Furthermore, if necessary, the use of pellets also offers the possibility of placing an ultimate selected overcoating, free of drug, for an accurate monitoring of drug release rates.

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