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THE RELEASE RATE OF INDOMETHACIN FROM SOLID DISPERSIONS WITH EUDRAGIT E

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ABSTRACT

The coprecipitates were prepared by a solvent technique using Eudragit E as carrier and indomethacin as a model drug.

X-Ray diffractometry, differential scanning calorimetry (DSC) and wettability tests were employed to investigate the physical state of the studied formulations. Up to 50% of indomethacin can be dispersed in an amorphous state in Eudragit E.

The influence of the pH on the in vitro release of solid dispersions has been evaluated. Because of the good solubility of Eudragit E at pH 1.2 a fast dissolution rate of the drug was observed while a marked delay was noticed at pH 7.5 where the polymer is only permeable to water. At pH 5.8 the kinetics of drug release can be modulated by the drug/polymer ratio. The dissolution rate of the drug can be increased by decreasing its amount in the coevaporate.

INTRODUCTION

Solid dispersions, obtained by a solvent method, are used to modify the dissolution rate of drugs using polymeric carriers as dispersing agents (1,2).

More recently an interest was shown in the study of solid dispersions using various types of polymethacrylates.

Coevaporates of indomethacin with Eudragit RS and RL resulted in a dispersed and amorphous state of the drug up to 30% and 20% w/w respectively. The release profiles of the drug can be fitted to the square-root of time model. Formulations with Eudragit RS give slower rates than those prepared with Eudragit RL (3). Coacervates containing aspirin and Eudragit L 100 in a 3:2 w/w ratio show a low dissolution in simulated gastric juice (pH 1.2): only 1% was released after 1 h with a lag-time of 45 minutes. In a neutral medium (pH 7.5) aspirin dissolved more rapidly than drug alone: 54% after 1 h (4). An in vivo sustained release action of coevaporates of clonidine prepared with Eudragit E 30 D was described (5). Hasegawa et al. (6) prepared coevaporates of various drug using Eudragit L and S. Indomethacin dispersed in a 1:3 w/w ratio to polymer was present in an amorphous form and its dissolution behaviour showed a supersaturation phenomena at pH 6.8 and no dissolution at pH 1.2. Finally Abd El-Fattah et al. (7) obtained sustained release of pheniramine aminosalicylate using coevaporates with Eudragit S, L, RS and RL. Eudragit S 100 was shown the most suitable polymer to reduce the release rate.

In this paper powders of coevaporates of indomethacin with Eudragit E were investigated.

Indomethacin is a poorly soluble, non-steroidal antiinflammatory drug containing an acidic function with a pK_a=4.5 (8). Eudragit E is a cationic copolymer of dimethylaminoethyl methacrylate and neutral methyl and butyl

methacrylic acid esters. This polymer is soluble up to pH 5 and above this pH value is capable of swelling and permeable to water.

Our aim was to enhance the dissolution rate of poor water soluble drugs and evaluate the effect of various parameters (drug to polymer ratio, pH) on the release profiles of those coprecipitates.

EXPERIMENTAL

MATERIALS

Indomethacin (Sigma Chemicals), Eudragit E 100 (Röhm-Pharma) were recrystallized from ethanol and used as controls. Solvents and buffers were of analytical grade.

METHODS

Preparation of indomethacin/Eudragit E 100 coevaporates

Indomethacin (1 g) and Eudragit E 100 (1-9 g) were dissolved in 120-250 ml of ethanol, then the solvent was removed under reduced pressure in a rotary evaporator at 50±1 °C. Further drying was carried out for 5 days under vacuum at room temperature. The residue was ground and the 75-250 μm particle size fraction was obtained by sieving.

Preparation of the physical mixtures

The samples were prepared by simple mixing of the powdered drug and Eudragit E possessing the same particle size range.

Analysis of drug content

UV assays

Samples were assayed for indomethacin content by dissolving a weighed amount of the solid dispersion in ethanol. The drug was determined spectrophotometrically at 320 nm (Perkin Elmer spectrophotometer, Mod. 559).

Stability assay

This procedure was carried out in a liquid chromatograph (Perkin Elmer, series 4) equipped with an injector (Rheodyne, mod. 7125) with a 20 µl loop, and a variable wavelength UV detector. Samples were chromatographed using an analytical Lichrosorb RP 18 column (Perkin Elmer) of 250 mm length, 4.6 mm internal diameter and 10 µm particle size. The mobile phase was prepared with 55/45% (v/v) of acetonitrile and 0.01 M potassium dihydrogen ortophosphate, adjusted to pH 2.4. The UV detector was set at 320 nm, flow rate of 1.5 ml/min, sensitivity 0.02 a.u.f.s. (9). Ethanolic solutions of solid dispersions containing 1.5 mg/100 ml of indomethacin were prepared. Aliquots of 20 µl of each solution were injected.

Differential Scanning Calorimetry (DSC)

Thermal analyses were carried out using a differential scanning calorimeter (Mettler DSC 20, TA 3000). Samples were placed in aluminium pans and heated at a scanning rate of 10 °C/min.

X-ray diffractometry

The solid was exposed to Cu K_α radiation with a Siemens wide angle diffractometer over a range of 2θ angles from 4 to 30 degrees.

Wettability test

Wettability of powders and coprecipitates was evaluated by direct measurement of contact angles with a wettability tester (Lorentzen-Wettre, Sweden). Drops of distilled water were placed on the compact surface by a microsiringe. The contact angle values were derived from the height and the length of the drop image. At least 6 determinations were carried out for each sample.

Solubility measurements

The solubility of indomethacin dispersed in the polymer was measured by introducing an excess amount of the solid dispersion in a USP XXII vessel containing 900 ml of pH 1.2 solution at 37±0.1 °C under continuous stirring with paddle. The solution was filtered and pumped directly to a spectrophotometer cell; the absorbance values were recorded at 320 nm.

In vitro release

The USP XXII rotating paddle apparatus (Erweka, mod. DT-1, West Germany) was used with a stirring rate of 100 rpm and maintained at 37±0.1 °C. The dissolution media were pH 1.2 (simulated gastric juice without pepsin), 5.8 (phosphate buffer), and 7.5 (simulated intestinal juice without pancreatin). The coevaporate powder, containing the equivalent of 40 mg of drug, was added over the surface of 900 ml dissolution medium. The aqueous solution was filtered and continuously pumped to a flow cell in a spectrophotometer and absorbance values were recorded at 320 nm. The polymer did not interfere with the UV analysis of the drug. The results were averaged from at least triplicate experiments and standard deviations were within 5 percent of mean value.

RESULTS AND DISCUSSION

Physicochemical properties of indomethacin in solid dispersions

The content of the drug formulated in solid dispersions was checked by HPLC. A retention time of 8 minutes for indomethacin was determined. A quantitative recovery was obtained and no additional peak was detected. These data indicated that indomethacin was not decomposed by the technological process.

The physical state of indomethacin in coevaporates was assessed by DSC and powder X-ray diffraction. The X-ray diffraction patterns of coevaporates

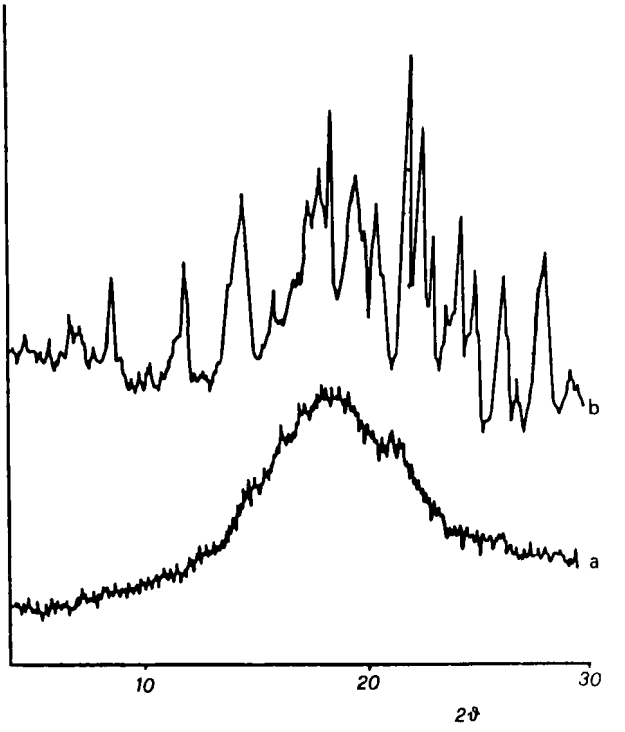

FIGURE 1

X-ray diffraction patterns of 1:1 indomethacin/Eudragit E.
a) solid dispersion; b) physical mixture.

indomethacin/Eudragit E 100 1:1 and 1:9 show no defined peaks attributed to indomethacin; this implies the absence of apparent crystallinity of the drug in the solid dispersion. However in the physical mixture typical peak of indomethacin are present, so confirming the satisfactory sensitivity of the method (Figure 1).

DSC curves of recrystallized indomethacin, powdered polymer and 1:1 indomethacin/Eudragit E 100 coprecipitate are reported in Figure 2. Indomethacin melting peak is at 159.5 °C, while the polymer shows a transition peak at 55 °C. The DSC curves of the solid dispersion denotes the disappearance of the endothermic melting peak of indomethacin compared to the identical physical

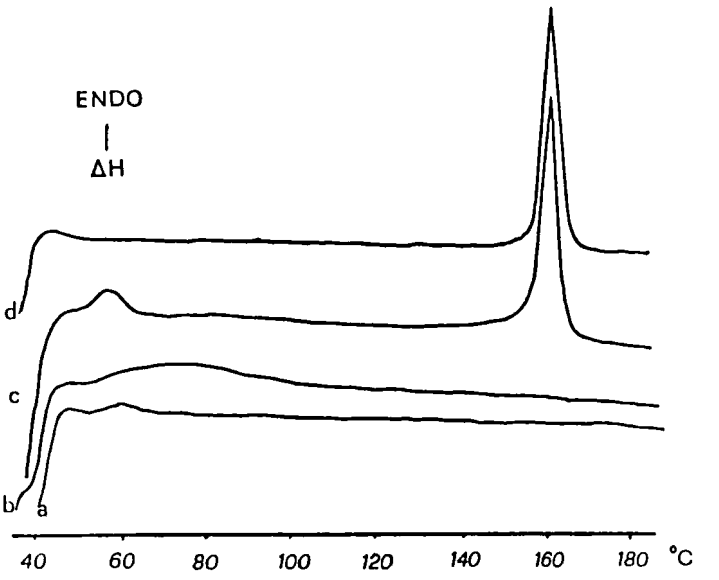

FIGURE 2

DSC curves.
a) Eudragit E; b) 1:1 coprecipitate; c) 1:1 physical mixture; d) indomethacin.

mixture. The results can be correlated to an amorphous state of the drug present in the 1:1 solid dispersion (Figure 2).

Since the wettability in water of both indomethacin and polymer is very low (contact angle values 74° and 86° respectively), the solid dispersions 1:1 and 1:9 (contact angle values 72° and 93° respectively) are hydrophobic too. The reported values have a standard deviations within 5% therefore the differences of wettability among those samples can be considered to be not significant.

Solubility behaviour

In an acidic medium (pH 1.2) the solubility of the drug, recrystallized from ethanol, is very low (2 μg/ml) while a 14 or 17 fold increase was observed with a 1:1 or 1:9 w/w solid dispersions at this pH. These supersaturation phenomena are

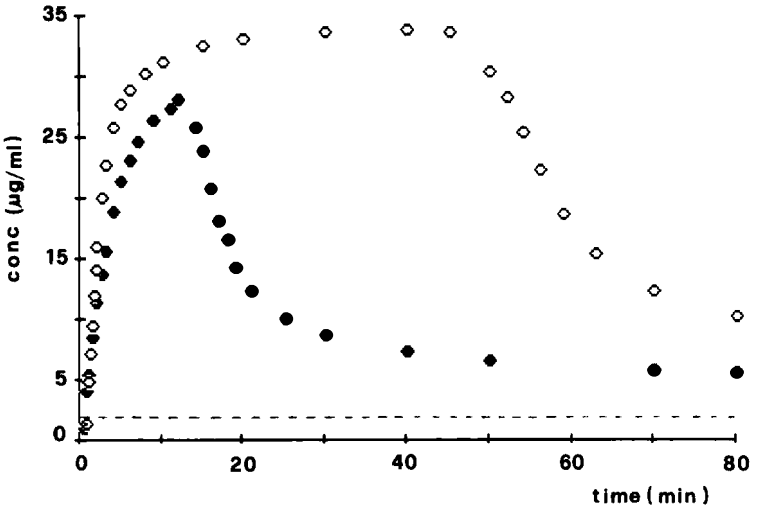

FIGURE 3

Solubility of indomethacin from solid dispersions at 37°C, pH 1.2
● 1:1;◇1:9; compared with recrystallized indomethacin (---).

noticed after 15 minutes followed by a gradual reprecipitation of the drug (Figure 3). Those data can be correlated to the above shown amorphous state of the drug present in the solid dispersions.

In vitro release

The release of indomethacin from solid dispersions were evaluated at pH 1.2, 5.8 and 7.5 because the solubility of indomethacin is very dependent on pH variations. In fact at pH 1.2 a solubility value of 2 µg/ml was determined, while at pH 5.6 and 7.2 values of 30 µg/ml (8) and 1600 µg/ml (10) were reported respectively. Moreover the polymer is soluble up to a pH 5 while above this pH value it is capable of swelling and permeable to water. Figure 4 shows the release profiles of the drug from 1:9 and 1:1 coprecipitates. Values of t_{50} (time necessary to obtain 50% of the drug content in solution) of 110 and 70 seconds are observed

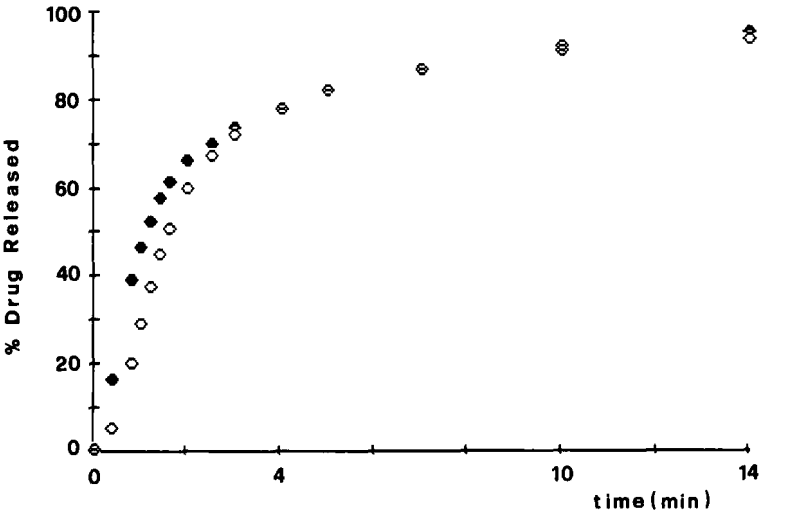

FIGURE 4

Dissolution profiles of solid dispersions at pH 1.2 and 37°C.
◆ 1:1; ◇1:9.

respectively. This rapid release of the drug can be attributed to the amorphous state of the drug and to the solubility of the polymer to this pH value.

At pH 7.5 indomethacin dissolved very rapidly (t_{50}=105 seconds). Furthermore a commercial product which contains the drug and lactose as main component in the 1:6 w/w, shows the same release profile. The coacervated system delayed and decreased the dissolution of the indomethacin in the simulated intestinal fluid. After 7 hours 10% of the drug was released from 1:9 coacervate and 40% from 1:1. The addition of 0.05% w/w polysorbate 80 in the dissolution medium, in order to evidence wettability problems, resulted in a drug release of 24% from 1:9 coprecipitate and 71% from 1:1 after 7 hours (Figure 5). This enhancement can be attributed to the low wettability of solid dispersions.

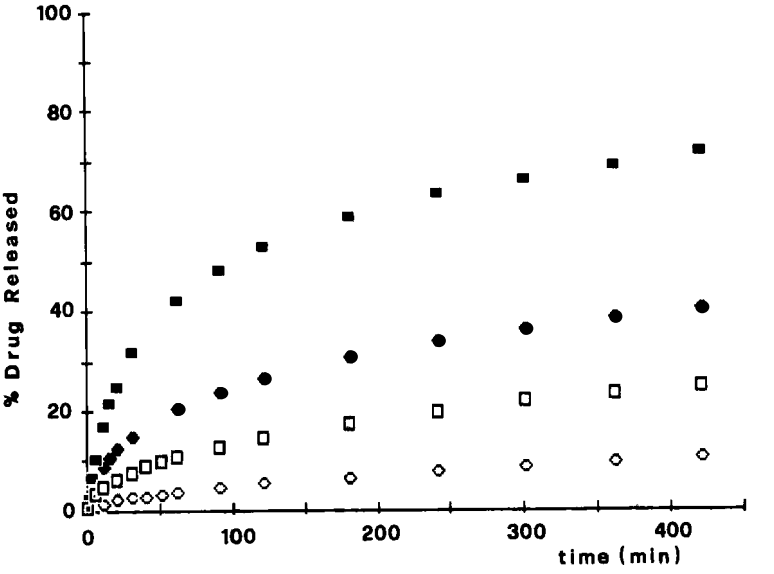

FIGURE 5

Dissolution profiles of solid dispersions at pH 7.5 and 37 °C.
in absence of polysorbate 80: ◆1:1; ◇1:9
in presence of polysorbate 80: ■1:1; □1:9.

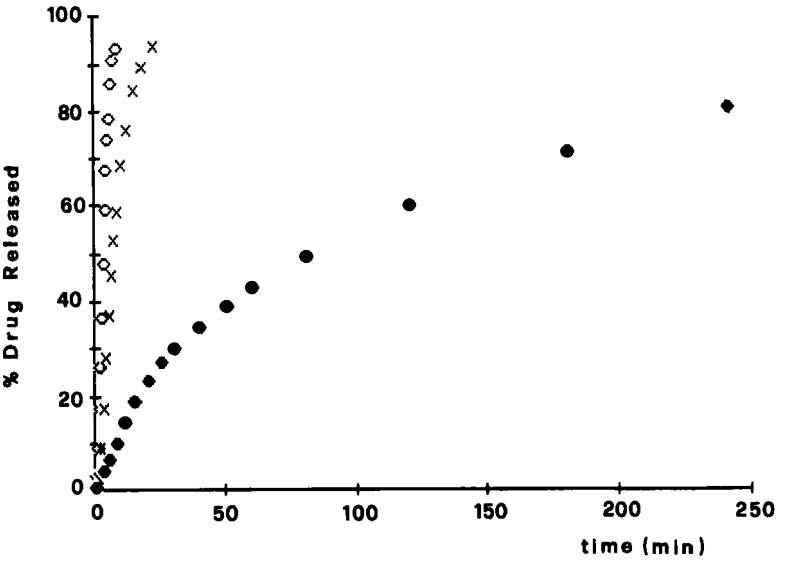

FIGURE 6

Dissolution profiles of solid dispersions at pH 5.8 and 37 °C.
◆1:1; X 4:6 (3:7 is superimposed); ◇1:9 (2:8 is superimposed)

The lower dissolution rates of the drug in the coprecipitate compared to the recrystallized indomethacin can be associated to the insolubility of the polymer at this pH value. Furthermore an higher polymer content resulted in coacervates with lower amount of drug released. The mechanism the drug release depends on the penetration of the dissolution medium into the coacervate, the dissolution and subsequent diffusion of the drug through the polymeric matrix and hence the diffusional process within the drug polymer system is the main release factor as already shown (7).

The pH of 5.8 was selected because it is similar to the duodenum medium. The release profiles of 1:9, 4:6 and 1:1 coprecipitates are reported in Figure 6.

A marked delay of the dissolution of the drug is noticed in 1:1 coprecipitate (t_{50}=85 min). On the other hand 1:9 solid dispersion provided a faster release than recrystallized indomethacin. A t_{50} value of 190 seconds was calculated compared to a t_{50} of 35 minutes for the drug and to a t_{50} of 330 seconds for the commercial product. Figure 6 also shows that changing the drug-polymer ratio of coevaporates the kinetics of release from those solid dispersions can be modulated. Increasing the polymer content (1:1, 4:6, 3:7, 2:8, 1:9), improved the release rate of the drug. This relation is not in accordance to the results obtained at pH 7.5. Further investigations are in progress in order to elucidate this anomalous behaviour.

CONCLUSIONS

At pH 1.2 an increase of the solubility of indomethacin can be achieved via solid dispersion of the drug in different ratios with Eudragit E. The loading ratio of the drug in the polymer affects the dissolution rate of indomethacin at pH 5.8. Finally at pH 7.5 a marked delay of the release rate is observed.

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