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COMPRESSION OF INDOMETHACIN COPRECIPITATES WITH POLYMER MIXTURES: EFFECT OF PREPARATION METHODOLOGY

Anees A. Karnachi[1], Rene A. De Hon[2] and Mansoor A. Khan[1,3]
[1] Department of Pharmaceutics and Medicinal Chemistry
School of Pharmacy, [2] Department of Geosciences
Northeast Louisiana University
Monroe, Louisiana 71209

ABSTRACT

The objective of this study was to prepare, characterize, formulate and compare coprecipitates, solid dispersions and physical mixtures of indomethacin with Eudragit polymer mixtures, RS100 and L100. Coprecipitates, solid dispersions (melting-solvent method) and physical mixtures were prepared with a drug : polymer ratio of 12.6 : 1.0 respectively. Biconvex tablets of 7 mm diameter were compressed. Response variables studied were cumulative percent released and T_{50}. Dissolution was performed by exposing the tablets to SGF (pH 1.2) for 1 hour followed by pH 7.2 phosphate buffer for 24 hours. T_{50} values obtained were 7.5 hours for coprecipitates, 4.5 hours for solid dispersions and 17 hours for physical mixtures. The drug loading for all the three formulations did not show significant difference. The formulations were characterized by X-ray diffraction (qualitative and quantitative) and IR. IR data did not indicate any significant difference between the pure drug and the formulations.

[3] To whom all correspondence should be directed.

However, significant differences were seen in X-ray diffractograms. The crystallinity did not change for physical mixtures, was reduced for coprecipitates and solid dispersions. Also the diffraction patterns for solid dispersions and coprecipitates were similar. The coprecipitates and physical mixture followed the Higuchi's square-root-of-time equation suggesting a matrix effect. These results suggest that compression of coprecipitates offer most efficient release as compared to solid dispersions and physical mixtures.

INTRODUCTION

Indomethacin is an anti-inflammatory drug used in the treatment of rheumatoid arthritis. However, its use is frequently limited because of significant gastrointestinal side effects. Alvan et al have reported that a high initial plasma concentration after oral administration of indomethacin produces adverse reactions (1). Administration of indomethacin controlled release capsules produced longer, smoother plasma levels as compared to conventional capsules that produced strong peaks and troughs (2). Tablet dosage forms have been reported to possess less tendency to adhere to the oesophagus (3). Since indomethacin causes oesophageal ulceration, gelatin capsules are not the best choices of solid dosage forms (4). Hence the present investigation was directed towards the development of sustained release tablets of indomethacin by compressing its coprecipitates with a mixture of Eudragit polymers, RS 100 and L100. Coprecipitation technique reported by Simonelli et al and Khan et al was used to prepare indomethacin micromatrices (5,6). Coprecipitates of poorly water soluble drugs with polymers have been extensively studied to improve their dissolution and availability (5,7). However, the recent trend is to modify this technique to sustain the release of therapeutic agents (6,8,9). The method of coprecipitation involves the solubilization of drug and polymer mixtures in an organic solvent and adding a non-solvent with agitation. The product obtained is filtered and dried. Coprecipitates of ibuprofen using different acrylate polymers have been prepared and characterized (10). In the present study indomethacin was chosen as a model drug as it has a short half-life, gastrointestinal effects, is soluble in alcohol and practically insoluble in water. Eudragit RS100 and L100 were used as they yield micromatrices without any need of additives (6). The objective of the present investigation was to prepare, characterize, formulate, and compare coprecipitates, solid dispersions, and physical mixtures of indomethacin with the polymer mixtures, Eudragit RS100 and L100.

MATERIALS AND METHODS

Indomethacin was purchased from Spectrum chemicals, and Eudragit RS100 and L100 were gifts from Rohm Pharma (Weiterstadt, Germany). Alcohol USP. and other chemicals were used as received. Water used was deionized and distilled.

Preparation of Coprecipitates

Preliminary screening experiments carried out in our laboratory have shown that Indomethacin and Eudragit RS100 and L100 in the ratio of 12.6 : 1, form coprecipitates having good flow properties, percent loading and prolonged release of drug. Hence this ratio was used for formulating coprecipitates, solid dispersions, and physical mixtures (refer Table I). Indomethacin (12.6 g), Eudragit RS100 (0.5215 g) and L100 (0.478 g) were dissolved in 315 mL alcohol USP at 40°C. The solution was cooled to room temperature. To the alcoholic solution, 875 mL water (reduced to pH 1.2 with 1N HCl at 4°C) was added at 233 mL/min under stirring (522 rpm) for 30 minutes using Caframo stirrer (type RZR50). The formulation and process conditions are summarized in Table I. The resultant coprecipitates in the form of micromatrices, were filtered using Whatman #4 qualitative filter paper, collected and air dried for 48 hours. The micromatrices were passed through #20 mesh and stored in amber bottles.

Preparation of Solid Dispersion

Solid dispersions were prepared using the solvent evaporation method. Indomethacin (12.6 g) and the polymers Eudragit RS100 (0.5215 g) and L100 (0.478 g) were dissolved in 315 mL alcohol USP at 40°C. The alcoholic solution was then poured in a glass tray and air dried for 48 hours. The sample was passed through #20 mesh and stored in amber bottles.

Preparation of Physical Mixtures

The polymers were ground by using mortar and pestle. Indomethacin (12.6 g) was mixed manually with the ground polymers Eudragit RS100 (0.5215 g) and L100 (0.478 g) in a plastic bag and was stored in amber bottles.

Preparation of Tablets

Micromatrices corresponding to 75 mg in weight of Indomethacin were mixed with Lactose (56.8 %), Talc (2% w/w) and Magnesium stearate

TABLE I

Formulation and process conditions.

Drug/polymer ratio	12.6 : 1
Eudragit RS100/L100 ratio	1.09 : 1
Alcohol/Water ratio	0.36 : 1
Water addition rate	233 mL/min
Agitation speed (rpm)	522 rpm

(1% w/w). Weighed quantities of the mixture were individually poured into a die of 7mm in diameter and compressed using a Carver press at a pressure of 1370 lbs. The same procedure was used for solid dispersions and physical mixtures as well.

Drug Loading Efficiency

Accurately weighed sample of micromatrices (50 mg) were dissolved in alcohol USP. and assayed spectrophotometrically for the content of indomethacin at 317 nm. A calibration curve was used based on standard solutions in alcohol USP. [slope = 0.019, and intercept = - 0.0011]. The polymers Eudragit RS100 and L100 did not interfere with the assay at this wavelength. The indomethacin concentration was calculated and expressed as percent drug loading efficiency.

Infrared Spectroscopy

Infrared spectra of all the formulations prepared were determined using model MX-S (Nicolet Analytical Instruments) from KBr pellets. The scanning range used was 4000 to 400 cm^{-1}.

Qualitative and Quantitative X-Ray Diffraction Study

Qualitative and quantitative X-Ray diffraction studies were performed using a Philips X-ray diffractometer model PW 1840. The finely ground

samples were scanned from 10^0 2θ to 40^0 2θ the region where major peaks were observed. Measurements were carried out using 40 KV voltage and 35 mA current. The scan rate was one second per step . Diffraction of indomethacin was used as the reference for qualitative studies. In quantitative determinations sodium chloride was used as the internal standard and the peak height ratio (I/Io) of indomethacin to internal standard for all the samples were performed. The degree of crystallinity was estimated from a standard plot of I/Io versus the indomethacin concentration in polymer mixtures.

Dissolution Studies

Dissolution experiments were performed using the USP basket method. The tablets were exposed to pH 1.2 for one hour followed by changing the medium to pH 7.2. The study was then carried out for 24 hours. Tablets of micromatrices, solid dispersions and physical mixtures were placed in the baskets individually. The dissolution medium was maintained at a temperature of $37^0C \pm 1^0C$ The stirring speed used was 100 rpm. Samples (5 mL) were withdrawn at fixed time intervals and analyzed spectrophotometrically at 318 nm. After each sampling, equivalent amount of buffer was added as replacement. From the absorbance values, the cumulative percentage of indomethacin released was calculated. All the experiments were performed in triplicate.

RESULTS AND DISCUSSION

The IR spectra of the drug and the physical mixtures showed characteristic absorption for the C=O group (carboxylic acid) at 1713 cm^{-1} and C=O group (amide) at 1692 cm^{-1}. Strong broad absorptions in the range of 3000 to 2500 cm^{-1} were observed for O-H stretching vibrations (carboxylic acid group). For the coprecipitates and solid dispersions, the characteristic peaks overlap, which indicates that there is no strong interaction between indomethacin and the polymers, Eudragit RS100 and Eudragit L100. X-Ray diffraction patterns are shown in figures 1 and 2. Both polymers Eudragit RS100 and L100 used are amorphous in nature. Comparison of the X-ray diffraction patterns of indomethacin, coprecipitates, solid dispersions and physical mixtures showed a significant reduction in the crystallinity of coprecipitates and solid dispersions. This could be due to retardation of indomethacin crystallization by the polymers. Hitoshi Sekikawa et al, have

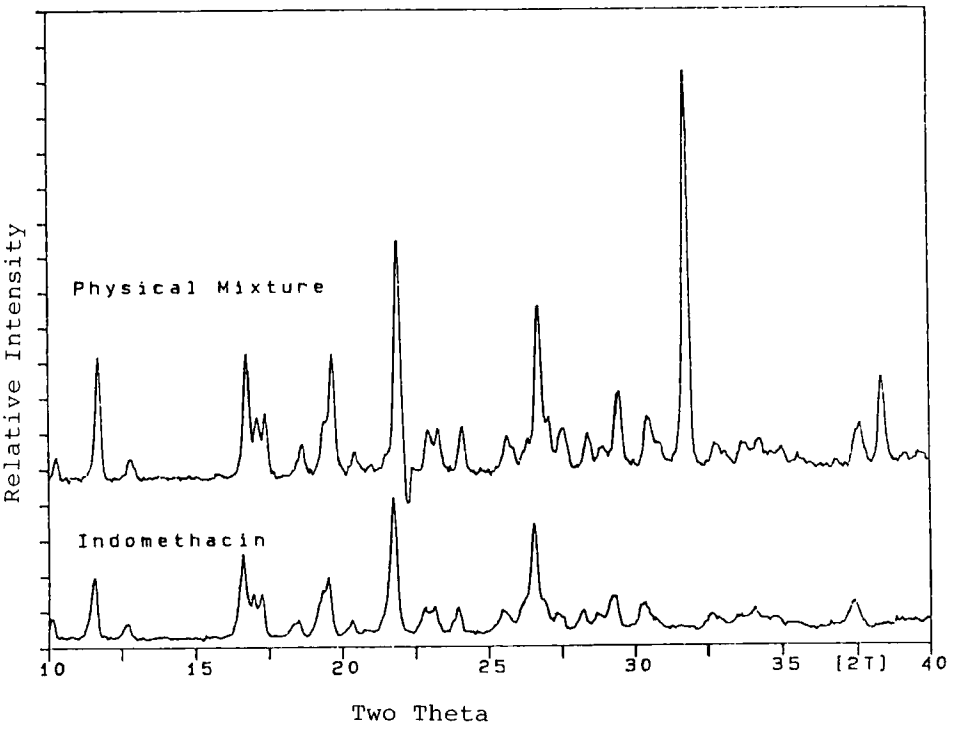


FIGURE 1.
X-ray diffraction patterns of Indomethacin and Physical mixture.

reported the inhibitory effect of polyvinylpyrrolidone on the crystallization of sulfonamide solid dispersions (11). The solid dispersions were prepared by dissolving the drug and polymer in alcohol and evaporating off the solvent from the solution. As the evaporation continues, the concentration of the drug in solution increases, exceeds its solubility and a supersaturated solution is formed. The polymer loses its solvent with the drug and since the concentration of the polymer is high enough to retard the crystallization, the drug comes out of the solution in a non crystalline form. The solvent evaporates at a faster rate which does not provide sufficient time for the drug molecules to come closer in an ordered manner to form crystal lattices. Solid dispersions thus formed, exhibit reduced crystallinity. In the case of coprecipitates, drug and polymers precipitate out initially to form a film on the outer surface of the coacervate droplet. This film later solidifies on drying

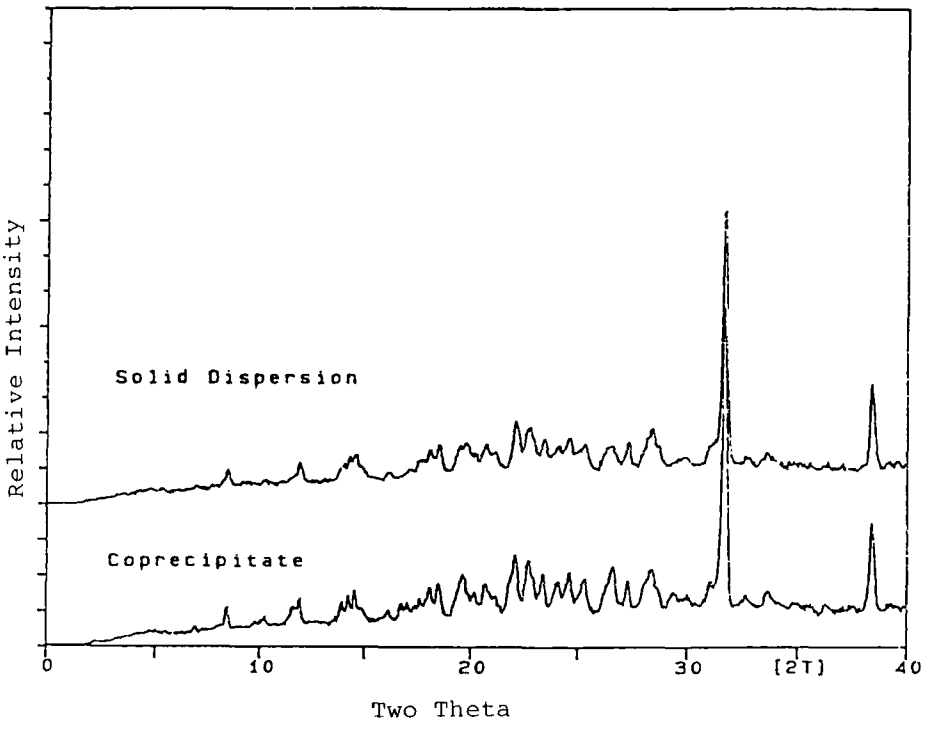


FIGURE 2.
X-ray diffraction patterns of Coprecipitates and Solid dispersion.

due to the diffusion of ethanol out of the droplet to produce a polymer matrix surrounding the drug (6,9). Hence the X-ray diffraction patterns show reduced crystallinity for indomethacin coprecipitates. To study the relationship between the drug content and crystallinity quantitatively, a standard curve was plotted for peak intensity ratio of the drug (I) to internal standard (Io) versus the drug concentration. Sodium chloride was used as the internal standard. Physical mixtures of the drug and polymer with the internal standard were run and the peak intensity, the angle 2θ and the "d" values were obtained. A linear relationship of I/Io was observed with increasing drug concentrations. Two peaks at 11^0 2θ and 21^0 2θ were chosen for quantification since they responded most sensitively to the changes in drug concentration. As shown in figure 2, there is a significant reduction in the crystallinity of solid dispersions and coprecipitates. Table II gives the I/Io values obtained.

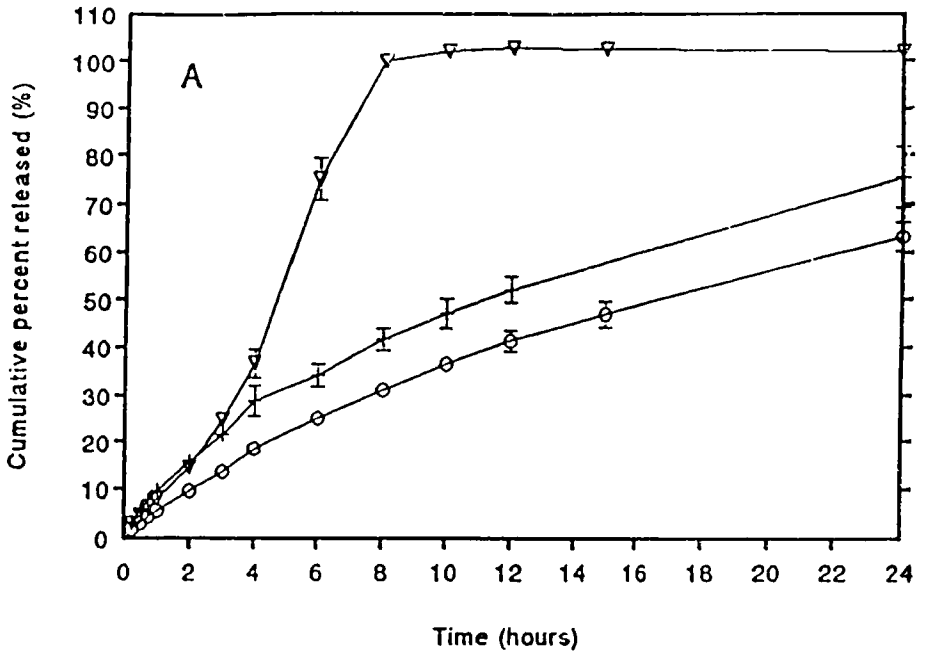
TABLE II

SAMPLE	I/Io		2θ		"d" values	
	P1	P3	P1	P3	P1	P3
PURE DRUG	0.54	0.95	11.7	21.8	7.55	4.07
PHY MIX	0.32	0.60	11.7	21.9	7.54	4.05
SOLID DISP	0.14	0.26	11.88	22.07	7.44	4.02
COPPT	0.13	0.26	11.88	22.12	7.44	4.01

Peak 1 is abbreviated P1, peak 3 is abbreviated P3, Coprecipitate is abbreviated as Coppt.

Table II shows that the I/Io ratio of peak # 1 (P1) and peak # 3 (P3) for physical mixtures are 0.32 and 0.60 respectively, for solid dispersions are 0.14 and 0.26, for coprecipitates are 0.13 and 0.26 as compared to 0.54 and 0.95 for pure drug. This shows that the peak intensity of solid dispersions and coprecipitates are considerably reduced as compared to pure drug and physical mixtures. Thus for coprecipitates and solid dispersions there is a reduction of crystallinity. The "d" values (Bragg spacings) are similar for the pure drug and the three formulations which demonstrates evidence that there is no interaction between indomethacin and the polymers, Eudragit RS100 and L100. In summary the IR and X-ray diffraction data does not indicate a strong interaction between drug and the polymer but only the extent of crystallinity is reduced.

The UV scan of indomethacin demonstrated a maxima at 318 nm and was used to determine indomethacin dissolution in pH 1.2 and pH 7.2 media. Indomethacin is a weakly acidic drug with a pKa of 4.5. Hence an increase in dissolution at 7.2 pH is expected and is demonstrated in figure 3A . The T_{50} values calculated from the graphs in figure 3A were 7.5 hours for coprecipitates, 4.5 hours for solid dispersions and 17 hours for physical mixtures. The release from solid dispersions after 8 hours was about 99.84 percent. In order to quantify these effects the goodness of fit of the release data was tested with the Higuchi's square-root-of-time equation (12). The plot of cumulative percent released versus square root of time (figure 3B) is linear for the coprecipitates and physical mixtures, whereas in the case of solid dispersions, it is not linear. This indicates that there is a matrix



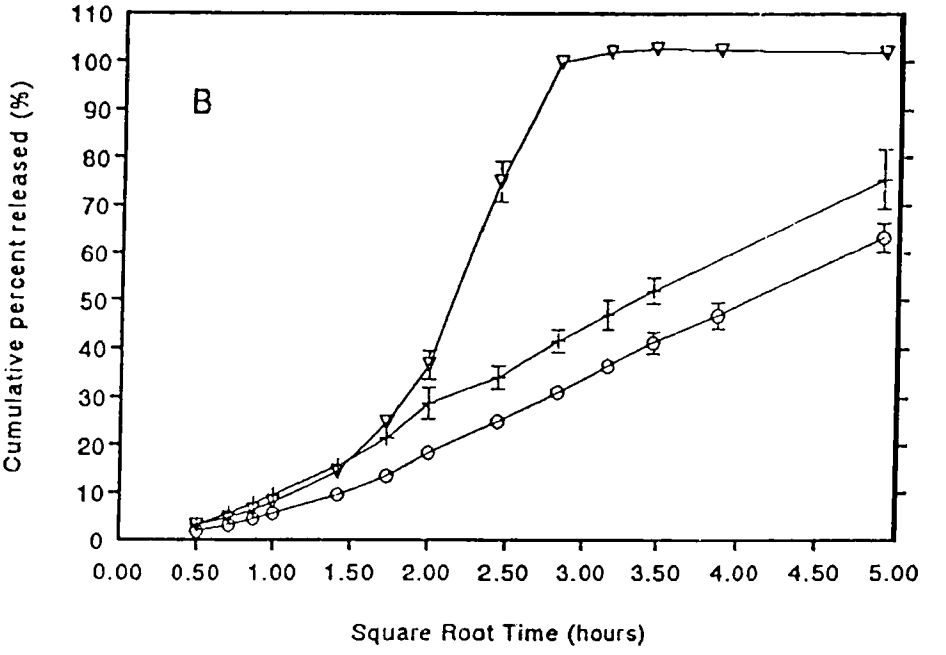


FIGURE 3.

Dissolution profiles of Indomethacin tablets prepared from Coprecipitates (+), Solid dispersions (▽), and Physical mixtures (o). (A) Cumulative percent released versus time. (B) Cumulative percent released versus square root-of-time.

formation in the case of coprecipitates and physical mixtures and not in solid dispersions. Also the carrier of indomethacin comprises of two polymers with different pore formation and swelling properties, due to different cation content. This may affect the permeability and transfer of the drug from the micromatrices. A reasonable explanation for the release could be the precipitation of drug in the precipitated polymers which retards the release of drug in the case of coprecipitates. The controlling mechanism could be the swelling and slow erosion of the matrix and the simultaneous diffusion of drug molecules through the matrix. The rapid release of indomethacin from solid dispersions can be attributed to the amorphous state of the drug and to the solubility of the polymers at alkaline pH. The slow release of drug in the case of physical mixtures could be due to a compact formed during compression, which results in a reduced porosity of the tablet and also, as shown in figure 3B, there is a possibility of a matrix effect.

CONCLUSIONS

Coprecipitates in the form of micromatrices, solid dispersions and physical mixtures were prepared using Eudragit polymers and characterized. These coprecipitates can be useful for preparing indomethacin sustained release tablets. The method of preparation of coprecipitates is simple, practical, minimizes the use of toxic organic solvents and allows for the production of tablets. The effect of preparation methodology on the degree of crystallinity indicated that the crystallinity is low in solid dispersions and coprecipitates as compared to the physical mixtures. Further, the dissolution from solid dispersions was considerably faster than the coprecipitates and physical mixtures. Further studies are needed to understand and identify the variables which would provide the least crystalline reversion upon storage . If crystalline reversion is controlled, numerous therapeutic agents can be formulated as extended release dosage forms.

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