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RESEARCH PAPER

Solid Dispersions of Diflunisal–PVP: Polymorphic and Amorphous States of the Drug

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ABSTRACT

Coprecipitates of diflunisal and polyvinylpyrrolidone (PVP K15, K30, and K90) and physical mixtures were studied using x-ray diffraction analysis, infrared (IR) spectroscopy, differential scanning calorimetry (DSC), and hot-stage microscopy. X-ray diffraction results revealed an almost amorphous state, even in coprecipitates with a high content of drug, next to 70%, which was independent of the polymer molecular weight. The IR spectra of 70:30 drug–PVP solid dispersions suggest the formation of diflunisal–PVP hydrogen bonds. For 70:30 drug–polymer ratio, the physical mixture showed linear dissolution kinetics of free crystals, but the corresponding coprecipitates exhibit two different dissolution processes. When the 25:75 drug–polymer dispersion is analyzed by hot-stage microscopy, only solid plates of PVP are observed; the absence of drug particles may be due to a molecular dispersion of the drug into the polymer. Moreover, polymorphic changes of diflunisal were detected in the solid dispersions in comparison with the corresponding physical mixtures, which are always formed by polymorph II. At high concentrations of drug (75:25 and 80:20), x-ray diffraction patterns of solid dispersions showed the partial recrystallization of the drug, displaying the main diffraction peaks of polymorph I when ethanol was used as coprecipitation solvent, whereas diflunisal form IV was obtained in chloroform.

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Key Words: *Amorphous state; Diflunisal; Dissolution rate; Polymorphic forms; Polyvinylpyrrolidone; Solid dispersions*

INTRODUCTION

Diflunisal is a salicylic acid derivative with analgesic and anti-inflammatory activity. It has been studied in osteoarthritis, pain resulting from musculoskeletal sprains and strains, and in minor surgery and cancer (1).

Diflunisal is poorly soluble in water and therefore its bioavailability is expected to be dissolution-limited. One of the ways used to increase the dissolution rate of drugs is its dispersion in a water-soluble carrier such as polyvinylpyrrolidone (PVP). Polyvinylpyrrolidone has been demonstrated to retard and inhibit the crystallization of drugs, giving amorphous solid dispersions with increased drug dissolution rates and solubility (2–7). The drug–PVP ratio from which an amorphous state of drug is obtained depends on both the drug nature and PVP molecular weight. Likewise, the properties of solid dispersions are dependent on the polymer content. In addition to these facts, diflunisal is a polymorphic drug that exhibits four distinct crystalline forms (8). While the solid dispersions are prepared, changes in the starting drug crystalline phase could occur, but there are only scanty publications about this topic. In this regard, several crystalline phases of diflunisal have been detected in drug–PEG 4000 solid dispersions (9).

The mechanisms by which solid dispersions enhance drug dissolution are frequently difficult to explain. The enhancement of drug dissolution has been attributed to different facts, such as the formation of a high-energy complex (10,11), the molecular dispersion of the drug in the polymer matrix (12), and the ability of the drug to form hydrogen bonding with the pyrrolidone moiety of the polymer (13–15).

In order to study the characteristics of the dispersed systems and relate them to the dissolution properties, solid dispersions and physical mixtures of diflunisal at different molecular weights of PVP were prepared.

The solid-state characterization was studied by combining the infrared (IR) spectroscopy and x-ray diffraction data with the results of thermal analysis [differential scanning calorimetry (DSC)] and thermomicroscopic observation. Dissolution profiles of almost amorphous coprecipitates in comparison with those of the corresponding physical mixtures were investigated by the rotating disc method, which has already been extensively described (16). The effect of the molecular weight of PVP on the dissolution rate has also been proved.

MATERIALS AND METHODS

Materials

Diflunisal was kindly supplied by Merck S.A. (Spain). Polyvinylpyrrolidone (Gaf Corporation) having an average molecular weight of 10,000 (PVP K15), 38,000 (PVP K30), and 630,000 (PVP K90) was used as received.

All chemicals used: ethanol, chloroform (Scharlau S.A.), KH_2PO_4, and Na_2HPO_4 (Merck S.A.) were of analytical grade. Double-distilled water was used thoughout the study.

Sample Preparation

Solid dispersions were prepared by coprecipitation. The required amounts of diflunisal and PVP were separately dissolved in a minimum volume of ethanol or chloroform at room temperature and both solutions were mixed with constant stirring. Then the solvent was eliminated under vacuum in a rotary evaporator at 40°C. The samples were dried over P_2O_5 in a desiccator at room temperature. The dispersions were prepared at 80:20, 75:25, 70:30, and 25:75 drug–polymer ratios from ethanol and at 80:20 ratio from chloroform.

For comparison purposes, physical mixtures were prepared by simple mixing of the drug and polymers in the same weight ratios as solid dispersions.

Characterization

X-ray Powder Diffractometry

X-ray patterns were obtained with a Siemens Kristalloflex 810 diffractometer system with Cu Kα radiation over the interval 2–22°/2θ. The measurement conditions were as follows: target, Cu; filter,

Ni; voltage, 40 kV; current, 20 mA; time constant, 4 sec; scanning speed, 1°/min. The samples were slightly ground and packed into the aluminum sample container.

Infrared Spectroscopy

Infrared spectra were recorded on a double-beam Perkin-Elmer 681 IR spectrophotometer by the conventional KBr pellet method.

Differential Scanning Calorimetry

The thermograms of the samples were recorded on a Setaram DSC-92 differential scanning calorimeter, calibrated with naphthalene, indium, and zinc at a heating rate of 5 K/min. The thermal behavior was studied by heating about 5 mg of the sample at a scan rate of 5 K/min in a covered sample pan under nitrogen gas flow, and the investigation was carried out over the temperature range 30–240°C. Measurements were made in triplicate.

Hot-Stage Microscopy

An Olympus BH-2 thermomicroscope connected to a Mettler FP 80 temperature controller was used for the microscopic investigation. The samples were heated at a rate of 10 K/min and the temperature interval examined was between 25 and 300°C.

Dissolution Studies

Dissolution rates were determined according to the disc method described by Wood et al. (16). The dissolution experiments were carried out in a USP 23-NF18 (17) dissolution apparatus (Dissolutest 07170025). Every experiment was conducted under the following conditions: 900 mL of 0.067 M aqueous phosphate buffer solution (pH 5.0) as a dissolution medium, maintained at 37±0.1°C and 100 rpm stirrer speed. A hydraulic press was used to prepare 13-mm compressed discs similar to those used for IR spectroscopy by the conventional procedure; about 50–60 mg of the samples under test was used in each case. Once the assay was started, 5 mL of solution was taken at appropriate time intervals and the volume was kept constant by adding the same amount of fresh dissolution medium. The samples were filtered through a 0.8-mm membrane filter and the diflunisal concentration was determined by spectrophotometry at 251 nm, a Hewlett Packard 8452A diode array spectrophotometer, after suitable dilution with buffer solution. The presence of PVP in the systems did not affect the determination of diflunisal by this method.

The total amount of drug was determined using an accumulative correction from the removed samples. Dissolution runs for all samples were performed at least six times and the mean values of the dissolved drug were reported.

RESULTS AND DISCUSSION

Solid dispersions of diflunisal with PVP K15, K30, and K90 were examined by x-ray diffraction analysis, IR spectroscopy, DSC, and hot-stage microscopy and compared with the corresponding physical mixtures in the same molar ratio, in order to determine the characteristics of the binary systems. For each technique only one example, either PVP K30 (RX and IR) or PVP K15 (DSC), has been shown as the results for different polymer molecular weights were very similar.

X-ray diffractometry was the main technique used in the characterization of diflunisal solid forms. X-ray diffraction patterns of PVP K30 solid dispersions prepared using ethanol as solvent and that of the 70:30 physical mixture are shown in Fig. 1. For comparative purposes (8), the diffraction spectra of polymorphs I and II are shown in Fig. 1 and that of polymorph IV in Fig. 2.

The diffraction patterns of the 70:30 physical mixtures show the main diffraction peaks of diflunisal form II, whereas those corresponding to the 70:30 solid dispersions exhibit the absence of reflections but very weak diffraction peaks are observed as well, which can be related to a very low drug crystallinity. The dispersions with PVP K15 and PVP K90 also show a similar absence of reflections in the 70:30 ratio. The formation of these almost amorphous dispersions can be associated with certain intermolecular interactions between diflunisal and PVP, as well as with the high viscosity of the solution that retarded or inhibited the drug recrystallization during the coevaporation process.

The spectra of the PVP K15, K30, and K90 solid dispersions in 80:20 ratio show the crystallization of the drug and display the main reflections of polymorph I. Figure 1 exhibits those corresponding to PVP K30. Likewise, the 75:25 drug–polymer coprecipitates also displayed the patterns of form I,

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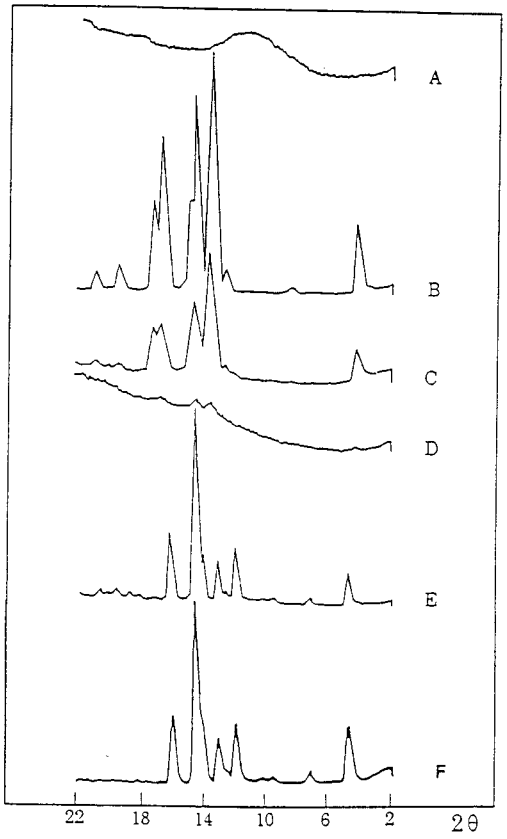

Figure 1. X-ray diffraction patterns. (A) PVP K30, (B) diflunisal form I, (C) coprecipitate 80:20, (D) coprecipitate 70:30, (E) physical mixture 70:30, and (F) diflunisal form II.

although a marked decrease of the drug crystallinity was observed in diflunisal–PVP K90 coprecipitates.

The polymer causes the isolation of a different polymorph (form I) during the coevaporation process since form III is obtained by recrystallization in pure ethanol (8). Moreover, the x-ray diffraction patterns of 80:20 solid dispersions prepared using chloroform as solvent show the main peaks of polymorph IV (Fig. 2), probably due to a rapid precipitation rate of the drug. Likewise, Martínez-Ohárriz et al. (9) obtained form IV in solid dispersions of diflunisal–PEG 4000 prepared using chloroform as solvent.

Therefore, the differences between the x-ray patterns of solid dispersions and physical mixtures are caused by both the amorphous state of diflunisal and the polymorphic transitions.

The IR spectra of PVP K30, starting drug (form II), 70:30 drug–PVP physical mixture, 70:30 and 80:20 solid dispersions obtained in ethanol and

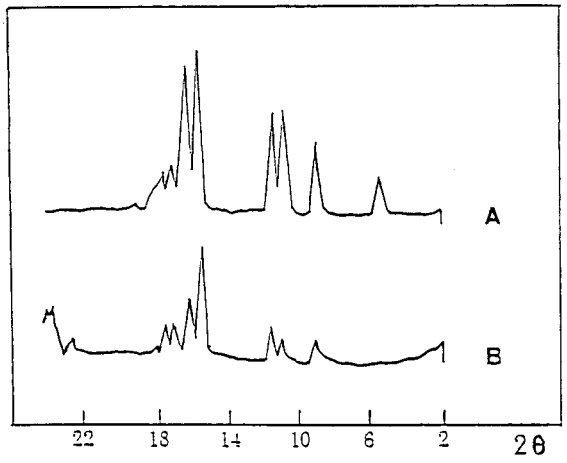

Figure 2. X-ray diffraction patterns. (A) Diflunisal form IV and (B) coprecipitate 80:20 drug–polymer, using chloroform.

polymorph I are shown in Fig. 3. For comparison purposes, the IR spectra of the 70:30 and 80:20 solid dispersions and physical mixtures were expanded in the 1700–1300 cm^{-1} range (Fig. 4).

It is apparent that some of the IR absorption peaks in 70:30 coprecipitates were different from those of the corresponding physical mixtures. The spectra of the physical mixtures are the weighted average of those of the single components, whereas those of the solid dispersions exhibit marked variations in some bands (broadenings and intensity reductions) which can be interpreted assuming a change in the hydrogen bonds of the drug due to the interaction with PVP.

In the region 4000–2000 cm^{-1} the drug exhibits a broad band at about 3200–2800 cm^{-1} due to the stretching of the carboxylic O-H group which is subjected to intermolecular hydrogen bonding. The aromatic C-H stretch interferes with the O-H band and a broad multiplet at about 2800–2600 cm^{-1}, which is attributed to the C-H stretch, is also observed (18). In the same region, the polymers show two broad bands, the first centered at 3500 cm^{-1} which could be attributed to the presence of traces of moisture and the second at about 2800 cm^{-1} related to the aliphatic C-H stretch (14).

In the carbonyl frequency region, the drug shows a strong band at 1690 cm^{-1} associated with the CO stretch in the carboxylic group, while the polymer gives a broad strong band (1660 cm^{-1}) due to the CO stretch in the cyclic amide. The broadening of

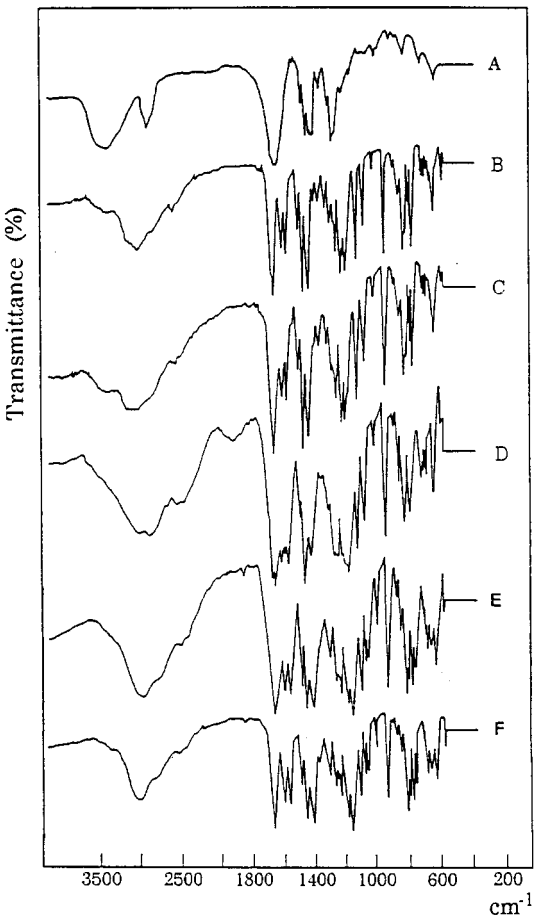

Figure 3. Infrared spectra. (A) PVP K30, (B) diflunisal form II, (C) physical mixture 70:30, (D) coprecipitate 70:30, (E) coprecipitate 80:20, and (F) diflunisal form I.

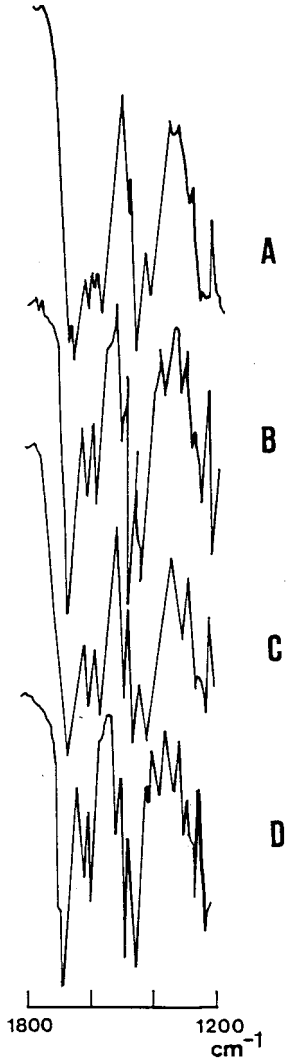

Figure 4. Infrared spectra. (A) Coprecipitate 70:30, (B) physical mixture 70:30, (C) coprecipitate 80:20, and (D) physical mixture 80:20.

the band corresponding to the diflunisal carbonyl group (1690 cm^{-1}) in the 70:30 solid dispersions suggests the formation of intermolecular hydrogen bonding diflunisal–PVP which does not exist in the physical mixtures. In the same way, from spectroscopic studies, El-Hinnawi and Najib (14) reported that ibuprofen interacts with PVP mainly through hydrogen bonding between the carboxylic group and the nitrogen of the pyrrolidone ring.

In the low-frequency region (1500–600 cm^{-1}) the bands observed in the 70:30 coprecipitates belong to both the polymer and the drug, but some bands of diflunisal have either disappeared or reduced their intensity significantly. For example, the C-F stretching vibrations of diflunisal (1410–1310 cm^{-1}) have disappeared in the 70:30 solid dispersions; this can be interpreted assuming an interaction between the drug and PVP. It is worth noting the strong reduction of intensity in the aromatic C-C stretching bands (1550–1450 cm^{-1}) and in the phenolic O-H group (1300 cm^{-1}) that might be due to the vibrational restrictions imposed upon complexation. The solid dispersions and physical mixtures exhibit slightly different IR spectra in the fingerprint region as well. All these results might indicate that a significant change in the total symmetry of the drug molecule in the solid polymer matrix has occurred in the coprecipitates.

In accordance with the x-ray diffraction results, the IR spectra of coprecipitates whose diflunisal content is about 80% are very similar to that of polymorph I (Fig. 5).

In order to get further evidence of the possible interaction of the drug with PVP and to get an insight into the structure of these binary systems, DSC studies of diflunisal–PVP solid dispersions prepared in ethanol and physical mixtures were performed.

The results obtained for PVP K15, K30, and K90 systems are similar, so only the thermograms obtained for PVP K15 are shown in Fig. 6 as an example. The DSC curves of starting drug (form II) and polymer are included for reference. The diflunisal curve shows an endothermic peak at 210°C that corresponds to its melting (8). The thermal behavior of the polymers of PVP is that expected for hygroscopic, amorphous substances, with a large endothermal effect in the 90–140°C range due to polymer dehydration (4).

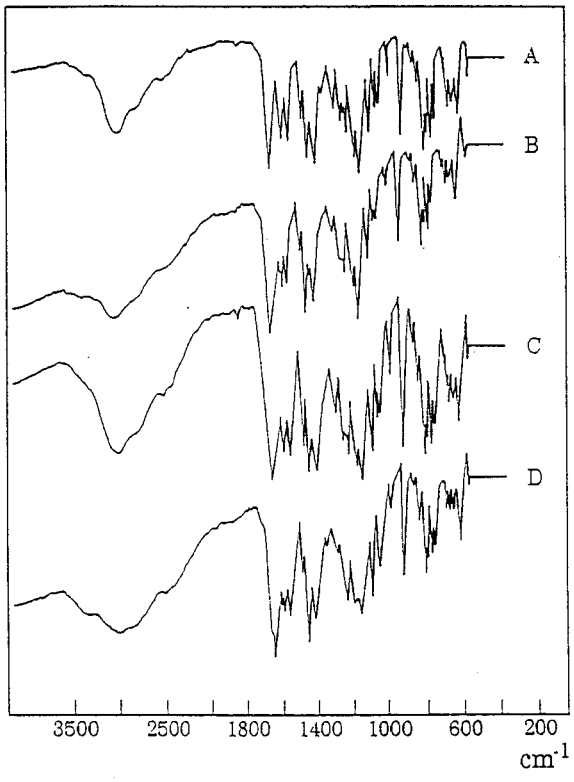

Figure 5. Infrared spectra. (A) Diflunisal form I and coprecipitates (B) diflunisal–PVP K15, (C) PVP K30, and (D) PVP K90, 80:20 drug–polymer.

The DSC of some physical mixtures (80:20 drug–PVP) show an endothermic peak near 200°C, which is related to the melting of the drug. This peak shifts slightly to higher temperature if the molecular weight of PVP increases. The apparent failure of diflunisal to melt in the 70:30 physical mixtures might be explained by the dissolution of the drug in the softened matrix of PVP. In the same way, Bettinetti and Mura (4) did not observe the melting of naproxen in physical mixtures containing crystalline drug due to the formation of microaggregates of the drug within the polymer matrix.

In accordance with the DSC traces, the thermomicroscopic analysis of the physical mixtures displays crystals of diflunisal and dark plates of PVP. During the heating, once the glass transition temperature of PVP is reached, the dark plates turn

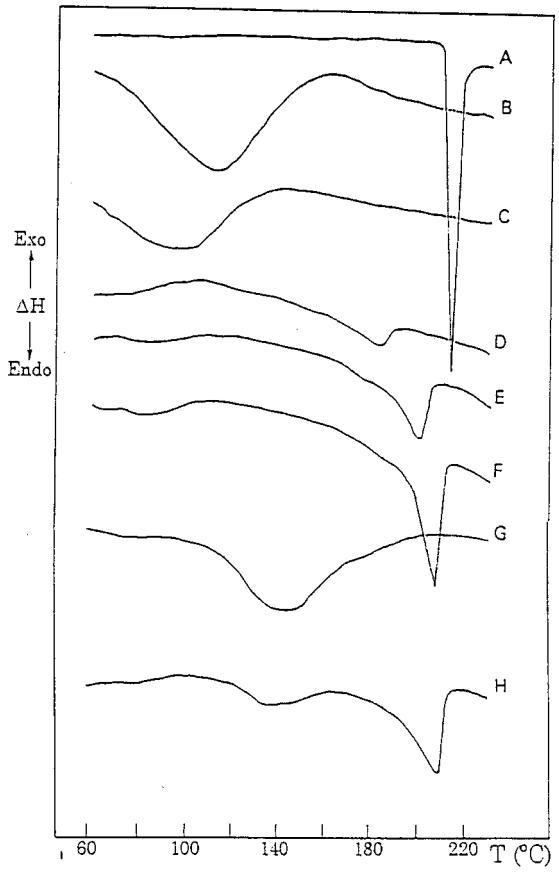

Figure 6. Differential scanning calorimetry curves. (A) Diflunisal, (B) PVP K15, coprecipitates (C) 25:75, (D) 70:30, (E) 75:25, (F) 80:20, and physical mixtures (G) 70:30, (H) 80:20, drug–polymer.

into a highly viscous fluid and in the 130–140°C range the dissolution of the drug in the polymer is observed. Furthermore, in mixtures whose PVP content is 20%, the remaining crystals of diflunisal experience changes in their form, size, and arrangement at about 180°C, which evidence the polymorphic transition from phase II to polymorph I, as reported by Martínez-Ohárriz et al. (8). After that, the new crystals melt.

With regard to the DSC studies of solid dispersions, the curves of some coprecipitates (25:75 drug–PVP) are similar to those of pure PVP. As the proportion of diflunisal increases (70:30), polymer dehydration is not detected but only the melting peak of the drug. This endothermic effect shifts towards lower temperatures if the content of the drug decreases.

Hot-stage microscopy makes clear that solid dispersions whose PVP content is 75% are only formed by solid plates of PVP in which diflunisal is dissolved. Drug crystals were not observed during the heating but only the glass transition of the polymer. These results point out the formation of a molecular dispersion and thus prove the drug–PVP solid-state interactions. However, if the drug content is increased up to 80%, crystals of drug are observed which are thinner and larger than those appearing in physical mixtures. In coprecipitates with a 70:30 drug–PVP ratio there are only small crystals of drug incorporated into the PVP matrix. When these systems are heated, both an increase of crystal size and drug crystallization in the rim of PVP plates are detected; finally, the melting of the drug is seen at about 190°C. The increase in crystal size during the heating is attributed to the opening of diflunisal–PVP intermolecular bindings.

The high stability of the solid dispersions could also be explained by the strong intermolecular interaction between both components. Thus, the coprecipitates (70:30 drug–PVP) stored for four years in a desiccator at room temperature have displayed x-ray diffraction patterns like those of the practically amorphous phases. Similarly, the stability of naproxen–PVP solid dispersion was related to interactions between both components (3).

Diflunisal yields a slow dissolution rate with only 14.9 mg (form I) or 15.6 mg (polymorph II) of drug dissolved in 180 min because its hydrophobic nature caused an impermeable barrier around the dissolving drug particles (8). The different solid structure between the 70:30 coprecipitates and the corresponding physical mixtures is also noted in the dissolution assays of these systems. The dissolution tests of the 70:30 solid dispersions and physical mixtures diflunisal–PVP K15, K30, and K90 obtained by the rotating disc method are shown in Fig. 7. The straight profiles of the physical mixtures are similar to those of pure drug, in accordance with the dissolution of diflunisal crystals under the solubilizing effect of the polymer. The small differences in the dissolution rate among these systems could be attributed to slight changes of the drug wettability together with the PVP viscosity. The dissolution rate of diflunisal in solid dispersions was

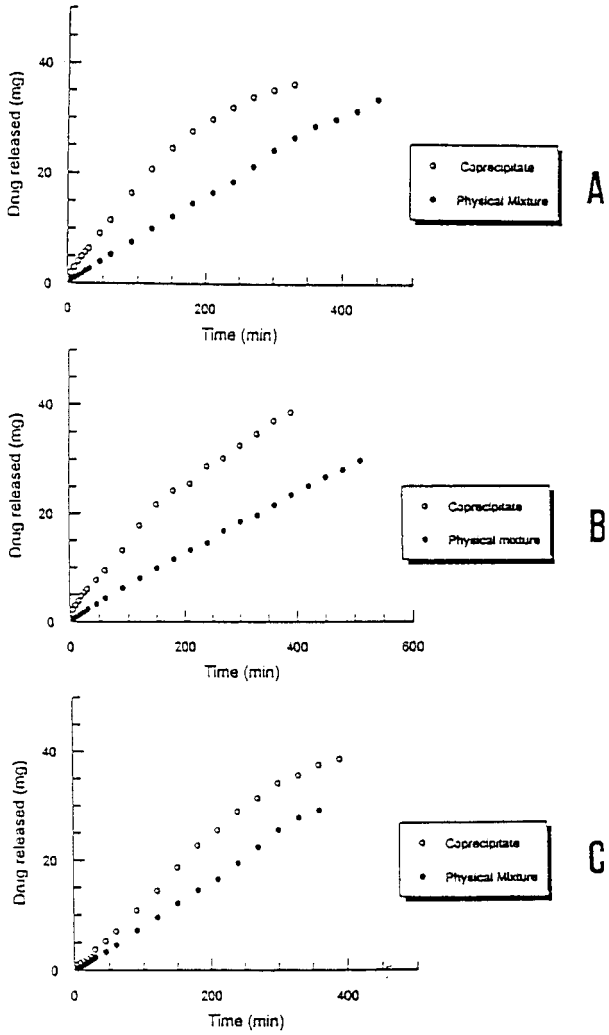

Figure 7. Dissolution profiles of coprecipitates and physical mixtures 70:30 drug–PVP. (A) K15, (B) K30, and (C) K90.

strongly dependent on the drug–PVP concentration ratio (6). For 50:50 drug–polymer systems, 42 mg of drug was dissolved in only 25 min.

In all cases, the 70:30 solid dispersions exhibited faster dissolution rates than their corresponding physical mixtures, although these differences depend on the molecular weight of the polymer. The dissolution patterns of the coprecipitates exhibit two linear portions with different slopes, which are more similar if the molecular weight of the polymer increases. These results suggest two different mechanisms of dissolution of solid dispersions. As it has been pointed out through thermal methods, the 70:30 coprecipitates are formed by both a molecular dispersion and small size crystals that are incorporated into the PVP matrix. Due to that, the dissolution rate values of the first linear interval decrease if the viscosity of the polymer increases; likewise, the slopes of the last portion of the dissolution curves are similar to those of the corresponding physical mixtures.

Using drug–polymer ratio 70:30, the physical mixtures show dissolution kinetics in which free crystals of diflunisal are dissolved, but the curves of the coprecipitates are in accordance with the previous dissolution of the solid solution followed by that of the small crystals. The increase in dissolution rate of coprecipitates has widely been attributed to the interaction between drug and polymer (13–15,19,20).

In conclusion, the present study has shown that, on using complementary techniques, the characteristics of diflunisal–PVP solid dispersions are dependent on both polymer content and coprecipitation solvent. When the drug crystallizes in the 80:20 solid dispersions, form I was obtained in ethanol but polymorph IV was formed in chloroform. The lowest amount of polymer needed to obtain an amorphous solid dispersion was 30%, which was independent of the molecular weight of PVP. Infrared analysis indicated different intermolecular hydrogen bonding interactions between diflunisal and PVP in the solid dispersions. The 70:30 amorphous dispersion displayed faster dissolution rates than the corresponding physical mixtures, resulting from the drug–polymer interactions.

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