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COMMUNICATION

Solubilization and Interaction of Sulindac with Polyvinylpyrrolidone K30 in the Solid State and in Aqueous Solution

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ABSTRACT

In this report the interactions of sulindac with polyvinylpyrrolidone K30 (PVP K30), both in the solid state and in aqueous solution, have been investigated. Solid dispersions of sulindac with PVP K30 were prepared by the solvent method in ethanol from various drug-to-polymer weight ratios. X-ray powder diffraction and differential scanning calorimetry have shown that PVP inhibits the crystallization of sulindac. The stabilization of the noncrystalline state of sulindac was shown by x-ray diffractometry after a 1-year storage. There was a considerable increase in the release rate of the drug when the polymer content was increased and the intrinsic dissolution rate values of these systems were calculated. From the UV spectra a bathochromic shift and a well-defined isosbestic point were observed at pH 2 and 6, which confirmed an interaction between the drug and the polymer in solution. Moreover, the apparent solubility of sulindac has been modified as a function of the polymer concentrations. The binding process between the drug and PVP was exothermic from the stability constant values at 25, 30, and 37°C at pH 2.

INTRODUCTION

Dissolution rate enhancement is one of the most commonly used approaches to improve the bioavailability of drugs the absorption of which is dissolution rate limited. Solid dispersions of drugs in macromolecules such as polyvinylpyrrolidone (PVP) have been extensively used to enhance the dissolution characteristics of these sparingly soluble drugs. This enhancement has been attributed to the formation of a coacervate and also to a molecular dispersion of the drug in the polymer matrix. Moreover, this increase in the dissolution

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rate can be a result of the formation of a soluble complex between the drug and the polymer.

Many reports have shown that coprecipitation with PVP can enhance the dissolution rate of poorly water soluble nonsteroidal anti-inflammatory drugs such as indomethacin (1–5), ibuprofen (6–8), naproxen (9), diflunisal (10), and tenoxicam (11). Several studies have also reported an interaction of PVP with nonsteroidal anti-inflammatory drugs (7,9,12) in solution.

The aim of the present work was to examine the possibility of improving the dissolution rate of sulindac, a poorly water-soluble nonsteroidal anti-inflammatory drug, via solid dispersion techniques using PVP K30 as a carrier, and to evaluate the role of solubilization in the enhancement of sulindac dissolution rate.

MATERIALS AND METHODS

Materials

Sulindac was kindly supplied by Merck Sharp and Dohme of Spain S.A., Madrid, Spain. The coprecipitation solvent was ethanol (Merck, Darmstadt, Germany) and the aqueous buffers of pH 2 and 6 were respectively prepared with KCl and HCl or with KH_2PO_4 and Na_2HPO_4 (Merck) of analytical reagent grade. PVP marketed as PVP K30 (Plasdone K 29-32 GAF, ISP, Barcelona, Spain) with an average molecular weight of 40000 was used without further treatment.

Preparation of Sulindac–PVP Coprecipitates

Dispersions were prepared by the solvent method. Sulindac and PVP at suitable weight ratios (90:10, 70:30, and 50:50) were dissolved separately in ethanol at about 40°C. The solutions were mixed and then the solvent was removed under vacuum in a rotary evaporator at 70°C. The residue was dried under vacuum at 25°C for 24 hr, well-ground in a mortar, and stored in a desiccator containing P_2O_5 at room temperature. Likewise, the stability studies were performed with the samples stored in these conditions for 1 year.

Characterization of Solid Dispersions

Powder x-ray diffraction patterns were recorded using a Siemens Kristalloflex 810 diffractometer system (Karlsruhe, Germany) with CuK_α radiation over the interval 2–30°/2θ. The measurement conditions were as follows: target Cu, filter Ni, voltage 40 kV, current 20 mA, time constant 4 sec, and scanning speed 1°/min. The samples were lightly ground and packed into the aluminum sample container.

The DSC curves were recorded on a Perkin-Elmer DSC 7 differential scanning calorimeter (Norwalk, CT) calibrated with 8 mg of indium and zinc using a heating rate of 10°C/min. The thermal behavior was studied by heating 5 mg of sample in a covered sample pan under nitrogen gas flow and the investigation was carried out over the temperature range 60–200°C. Measurements were made in triplicate.

Dissolution from Coprecipitate Systems

Dissolution rates of sulindac from these systems were compared with that of the pure drug in an aqueous phosphate buffer at pH 6. When diffusion is the rate-determining step in a dissolution process, it can be represented by the general Noyes-Whitney (13) equation:

$$\frac{dC}{dt} = k' S(C_s - C)$$

where C is the concentration at time t, C_s is the concentration at saturation, k′ is the dissolution rate constant, and S is the solid surface area.

In order to obtain a zero-order kinetic and determinate the intrinsic dissolution rate, disks of constant area and sink conditions ($C << C_s$) have been used. For this purpose, dispersion samples containing 35 mg of sulindac were compressed by a hydraulic press for KBr tablets for infrared spectroscopy. Disks of 13 mm diameter and 0.074–0.149 mm particle size were prepared. The compression force was 44 kN/cm^2.

The dissolution tests were performed according to the USPXXIII-NFXVIII (1995) paddle method with a Dissolutest 07170025 (Prolabo, France) dissolution apparatus using a rotational speed of 100 rpm at 37 ± 0.1°C and with 900 ml of aqueous phosphate buffer solution at pH 6. Samples of 5 ml were taken with a glass syringe at suitable time intervals and filtered through a 0.8-μm membrane filter (Millipore, Barcelona, Spain). The filtrate was suitably diluted and sulindac concentration was spectrophotometrically determined at 285 nm, using a Perkin-Elmer Lambda 2 spectrophotometer. No significant absorbance was found when a complete dissolution of PVP in these conditions was achieved. The amount of sulindac dissolved was determined as a function of time and the intrinsic dissolution rate (k) was calculated from the slope of these initial straight lines. Dissolution runs for all samples were performed six times.

UV Spectroscopy

Taking into account the pK_a 4.7 of sulindac, the change in absorbance with the addition of various concentrations of PVP was measured at pH 2 and pH 6 in the range 250–320 nm. The UV spectra of sulindac either alone (2.5×10^{-5} M) or in presence of different molar concentrations of PVP (1.32×10^{-4}–13.2×10^{-4} M) were recorded using a Perkin-Elmer Lambda 2 spectrophotometer equipped with a thermostated (±0.1°C) cell block. All spectra were run in triplicate. It should also be noted that a blank of PVP was used during the UV runs.

Solubility Determinations

Solubility of sulindac in presence of increasing PVP concentrations from 25 to 37°C was determined at pH 6 and 2 as follows: an excess of sulindac (50 mg) was added to 20 ml of buffer containing different concentrations of PVP (from 0.66×10^{-4} to 26.3×10^{-4} M) and stirred at constant temperature until equilibrium was achieved (48 hr). An aliquot was filtered through a 0.45-μm membrane filter, appropriately diluted and analyzed for sulindac content by a simple, rapid, and accurately direct method using second-derivative absorption spectrophotometry (Perkin-Elmer Lambda 2 spectrophotometer) at 305 nm, which allowed the interference due to PVP to be removed.

The second derivative values were measured against the appropriate blank containing the corresponding PVP solutions and then they were converted to the corresponding concentration by reference to a suitable calibration curve. Three temperatures (25, 30, and 37°C) were tested and each experiment was performed three times.

The apparent 1:1 stability constant, $K_{1:1}$, of a possible complex formed between the drug and PVP was calculated from the initial straight line portion of the phase solubility diagram, according to the equation proposed by Higuchi and Connors (14):

$$K_{1:1} = \frac{\text{slope}}{\text{intercept } (1 - \text{slope})}$$

The enthalpy change, $\Delta H°$, was calculated from the temperature dependence of $K_{1:1}$ values within the range 25–37°C from the Van't Hoff plot of ln $K_{1:1}$ against $1/T$.

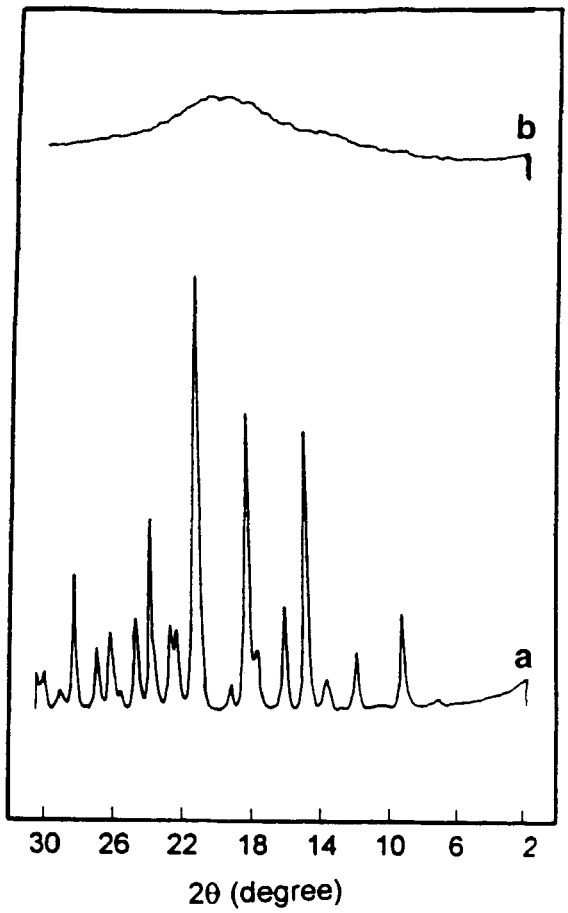

Figure 1. X-ray diffraction patterns of sulindac (a) and sulindac–PVPK30 (90:10) coprecipitate (b).

RESULTS AND DISCUSSION

Characterization of Solid Dispersions

Figure 1 shows the powder x-ray diffraction patterns of sulindac and its coprecipitate with 10% PVP weight fraction. No sharp peaks attributable to sulindac were observed in the coprecipitate, indicating that sulindac crystals were transformed to a noncrystalline form during the cosolvent process. Moreover, the coprecipitates with 30 and 50% PVP showed similar diffraction patterns.

The DSC scans of pure drug and solid dispersion systems are presented in Fig. 2. The sulindac–PVP curves showed only one broad peak in the range 160–190°C, which decreased when the polymer content increased. An interaction between the carboxyl group of the drug and the amide group of the pyrrolidone nucleus

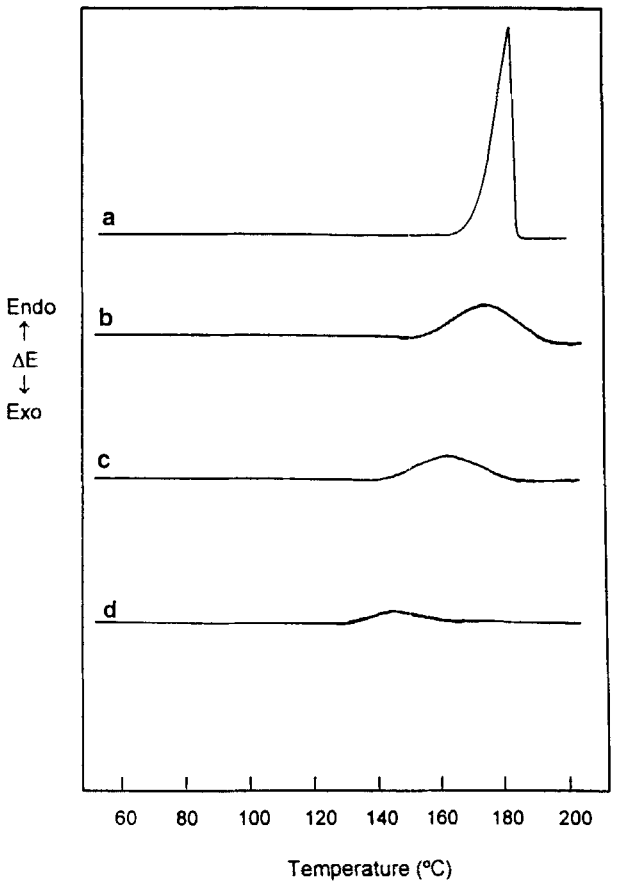

Figure 2. Thermal behavior of sulindac (a) and solid dispersions sulindac-PVPK30: 90:10 (b), 70:30 (c), and 50:50 (d).

is possible and the decrease of the enthalpy of fusion can be due to this interaction. The widening of the endothermic melting peak can be explained by the highly dispersed form of the drug.

Dissolution of Coprecipitate Systems

All solid dispersion systems exhibit a faster drug dissolution than sulindac alone. At 30 min the amount of sulindac dissolved was 4, 9, 12, and 16 mg for the drug alone and solid dispersions containing 10, 30, and 50% of PVP, respectively. The increase in dissolution rate is directly related to the PVP:sulindac ratio in the solid.

Table 1 reports the intrinsic dissolution rate values (k) for sulindac and the sulindac-PVP systems. The dispersion containing 50% by weight of PVP resulted in a three-times increase in the intrinsic dissolution rate of the drug. Linearity was observed between the intrinsic dissolution rate and %PVP ($r > 0.999$).

The higher dissolution rate of the drug in the coprecipitates compared with the drug alone can be ascribed to a complex formed, while the increase in these intrinsic solution rates values, resultant from an increase in the polymer content, is probably due to a more dispersed state of the drug resulting in its higher wettability.

Table 1

Intrinsic Dissolution Rates of Sulindac-PVP K30 Solid Dispersions

Sulindac-PVP(%)	k (mg min^{-1} cm^{-2})[a]
100:0	0.036 ± 0.002
90:10	0.063 ± 0.001
70:30	0.081 ± 0.002
50:50	0.097 ± 0.001

[a]Values are the mean ± SD of six measurements at 37°C.

Interaction in Solution

UV Spectral Studies

The UV spectra of sulindac solutions with increasing concentrations of PVP at 25°C and pH 6 showed a modification in the absorbance of the drug when the concentration of PVP was increased. There was also a weak bathochromic shift in the λ_{max} peak and a well-defined isosbestic point at 300 nm. Similar spectral changes were observed in the UV spectra of sulindac in the presence of PVP K30 at pH 2 and 25°C. An inter-

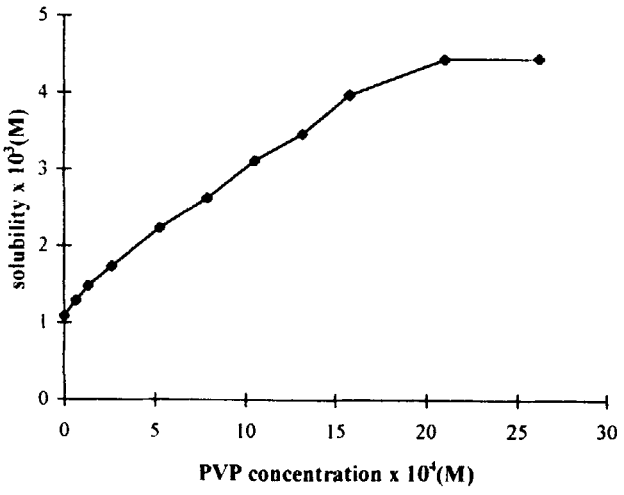

Figure 3. Phase solubility diagram of sulindac as a function of PVP concentration at pH 6 and 25°C.

action between sulindac and the polymer can be established from the UV spectral studies.

Solubility Studies

Figure 3 shows the equilibrium phase-solubility diagram observed for sulindac with increasing concentrations of PVP at pH 6 and 25°C. The solubility increased linearly up to a PVP content of 15.8×10^{-4} M and a typical supersaturation phenomenon was observed (B_s-type phase diagram). The slope of the initial straight line was 1.7 ($r > 0.998$), which indicated that at least one complex S_mL_n with $m \neq 1$ was present in solution.

The apparent solubility of the drug in increasing concentrations of povidone was determined as a function of the temperature at pH 2. Figure 4 shows the results observed at 25, 30, and 37°C. An A_p-type phase diagram was observed. Hilton (1) found similar results with indomethacin. The enhancement of the solubility at this pH is larger than at pH 6 due to a major interaction of the non-ionized molecules of drug with the polymer based on the fact that the drug is capable of interacting through hydrogen bonding with the pyrrolidone moiety of the polymer. At the highest carrier concentration used (26.3×10^{-4} M) the solubility of sulindac increases up to more than 22 times at 25°C and 17 times at 30 and 37°C. The values of the apparent 1:1 stability constants

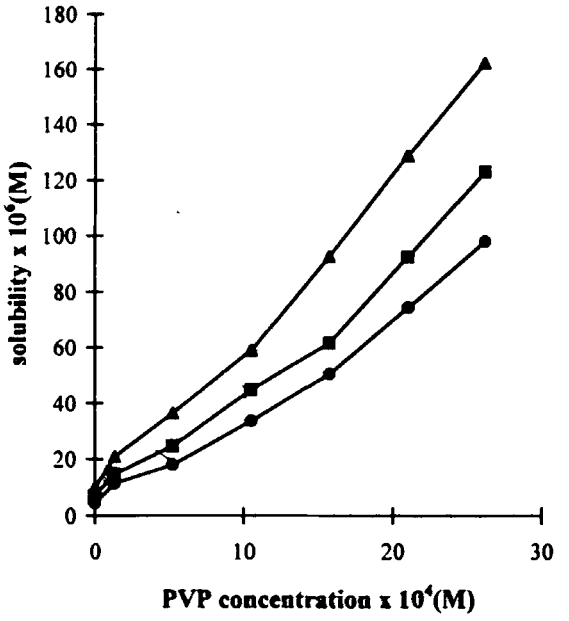

Figure 4. Phase solubility diagrams of sulindac as a function of PVP concentration at pH 2 and 25 (●), 30 (■), and 37°C (▲).

Table 2

Apparent Stability Constants for the Interaction Sulindac–PVP K30 at pH 2

Temperature (°C)	$K_{1:1}$ (M^{-1})[a]
25	4600
30	4200
37	3700

[a]Values are the mean of three measurements.

($K_{1:1}$) of the soluble complex at each temperature have been calculated from the slope of the initial straight line portion. These results are shown in Table 2. The enthalpy value, $\Delta H°$, was −14 kJ/mol, indicating that the binding process is exothermic.

CONCLUSIONS

The results of this study indicated an interaction between sulindac and PVP, which increased the drug solubility. Moreover, the dissolution rate of sulindac can be greatly increased by the use of coprecipitation techniques with this polymer.

The dispersion with only 10% of polymer showed no x-ray diffraction peaks, which indicated that sulindac was in a noncrystalline form and confirmed the existence of an interaction in solid state.

In addition, changes in the UV spectra and the enhancement in the solubility of sulindac when the PVP concentration increased allowed us to establish that sulindac forms a soluble complex with PVP and the binding process is exothermic.

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