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Effect of polyvinylpyrrolidone on the crystallinity and dissolution rate of solid dispersions of the antiinflammatory CI-987

Albert S. Kearney *, Dawn L. Gabriel, Surendra C. Mehta, Galen W. Radebaugh

Department of Pharmaceutics and Drug Delivery, Parke-Davis Pharmaceutical Research, Division of Warner-Lambert Company, 170 Tabor Road, Morris Plains, NJ 07950, USA

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Abstract

Solid dispersions of CI-987 (5-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene}-2,4-thiazolidinedione) having varying concentrations of polyvinylpyrrolidone (PVP K 28–32), were prepared in an attempt to improve the dissolution rate of CI-987. The physical characteristics of these solid dispersions were investigated by X-ray diffraction and dissolution rate studies. The dissolution rate of CI-987 can be significantly increased by increasing the weight fraction of PVP in the solid dispersions. The maximum dissolution rate occurred with the solid dispersion having a PVP weight fraction of 0.81 where the CI-987 dissolution rate is 15-times greater than that for CI-987 in the absence of PVP and where X-ray diffraction suggests that CI-987 exists in a totally amorphous state. As the PVP weight fractions decreased from 0.81, the dispersions displayed increasing degrees of crystallinity. The dissolution rate vs PVP weight fraction plot displayed three distinct regions: at low PVP (high drug) weight fractions, a drug-controlled region; at intermediate PVP weight fractions, a region where changes in the degree of crystallinity of CI-987 play a major role; and at high PVP (low drug) weight fractions, a PVP-controlled region.

Key words: Solid dispersion; CI-987; Polyvinylpyrrolidone; Dissolution; Crystallinity

1. Introduction

Poorly water-soluble drugs frequently have dissolution-rate-limited absorptions which lead to poor oral bioavailabilities. One possible way of overcoming this problem is to alter the physical properties of such drugs. A technique to do this involves forming a solid dispersion, where the drug is dispersed (by co-melting, co-precipitating, and/or co-evaporating) within an inert carrier in the solid state (Chiou and Riegelman, 1971a; Ford, 1986). A carrier which has been widely used is the water-soluble polymer, polyvinylpyrrolidone (PVP). Using data generated with sulfathiazole-PVP dispersions, several mechanisms by which solid dispersions can enhance the dissolution rate of the incorporated drug have been elucidated (Simonelli et al., 1969).

The formation of solid dispersions has been shown to increase the in vitro dissolution rates of many drugs such as diazepam, diflunisal, and famotidine (Najib and Suleiman, 1989; Mummaneni and Vasavada, 1990; Rabasco et al., 1991)

* Corresponding author.

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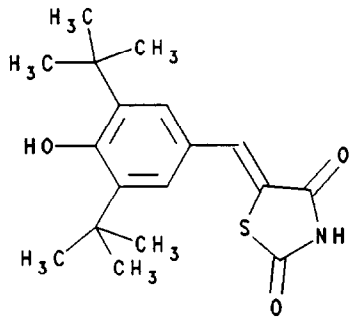


Fig. 1. The structure of CI-987, 5-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]methylene}-2,4-thiazolidinedione.

and to increase the oral bioavailability of griseofulvin (Chiou and Riegelman, 1971b; Barrett and Bianchine, 1975), hydrochlorothiazide (Corrigan et al., 1976), nabilone (Lemberger et al., 1982), and α-pentyl-3-(2-quinolinylmethoxy)benzenemethanol (Sheen et al., 1991) in humans.

CI-987 (5-{[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]-methylene}-2,4-thiazolidinedione; Fig. 1) is an anti-inflammatory compound which is not detected in the blood following its oral administration, as a 0.5% methylcellulose suspension, to rats. This is most likely related to its extremely low water solubility (< 20 ng/ml at 25°C) resulting in a dissolution-rate limited bioavailability. The purpose of this study was to determine if solid dispersions of CI-987 and PVP would significantly improve the dissolution rate of CI-987, to evaluate the CI-987 to PVP ratio needed to achieve the optimal dissolution rate, and to investigate the role that the crystallinity of CI-987 in the dispersions plays in dissolution rate improvements.

2. Materials and methods

2.1. Materials

CI-987 was synthesized by the Chemistry Department of Parke-Davis Pharmaceutical Research (Ann Arbor, MI). The PVP (K 28–32) had an average molecular weight of 40000. All other chemicals were of reagent grade or better, and the water was distilled and deionized prior to use.

2.2. Preparation of solid dispersions

The solid dispersions were prepared using a solvent evaporation method (Chiou and Riegelman, 1971a). The required amounts of CI-987 and PVP were co-dissolved in a minimal amount of 95% ethanol. The solvent was then removed in vacuo at room temperature (23 ± 2°C) with a rotary evaporator. The resulting residue was dried overnight in a vacuum oven operating at room temperature for 24 h. The actual drug content of the solid dispersions was determined by HPLC.

2.3. Powder X-ray diffraction studies

The powder X-ray diffraction analyses were performed with a Rigaku Geiger-Flex diffractometer (Tokyo, Japan) using Ni-filtered, Cu-Kα radiation, a voltage of 40 kV, and a current of 40 mA. The scanning rate was 5°/min over a 2θ range of 3–50° and with a sampling interval of 0.02°. The samples were prepared in one of two ways: the pure CI-987 was packed as powder into the sample holder, whereas the solid dispersions and physical mixture were sprinkled onto a thin layer of Apiezon® grease on a glass slide because of the limited quantities of material available.

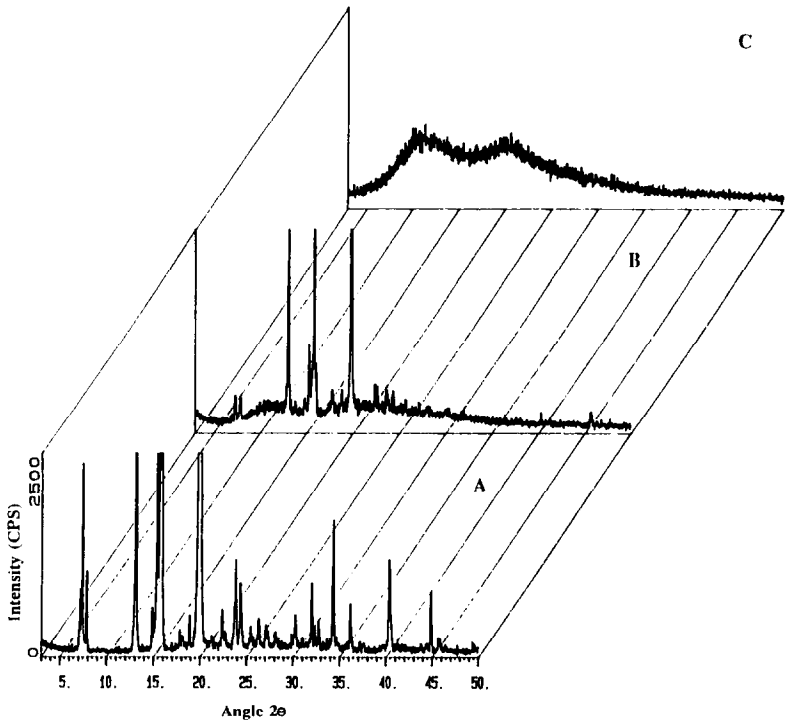
2.4. Analytical methods

The HPLC analyses were performed on an HP 1090 Liquid Chromatograph operating at a wavelength of 355 nm. The column was a Supelco LC-18 (4.6 × 150 mm) having a particle size of 5 μm. The mobile phase was composed of 56 : 14 : 30 acetonitrile : methanol : 50 mM acetate buffer (pH 4) in water, and the flow rate was 1.5 ml/min.

2.5. Dissolution studies

The dissolution of fixed surface area discs (0.98 cm^2) prepared from pure CI-987 and the solid

Fig. 2. The X-ray diffractograms for pure CI-987 (A); the 0.81 PVP weight fraction physical mixture (B); and the 0.81 (C), 0.43 (D), 0.51 (E), and 0.62 (F) PVP weight fraction dispersions. The *y*-axis has been fixed at 2500 counts per s for comparison purposes (even though diffractograms A and B are off-scale).


C
B
A
Intensity (CPS)
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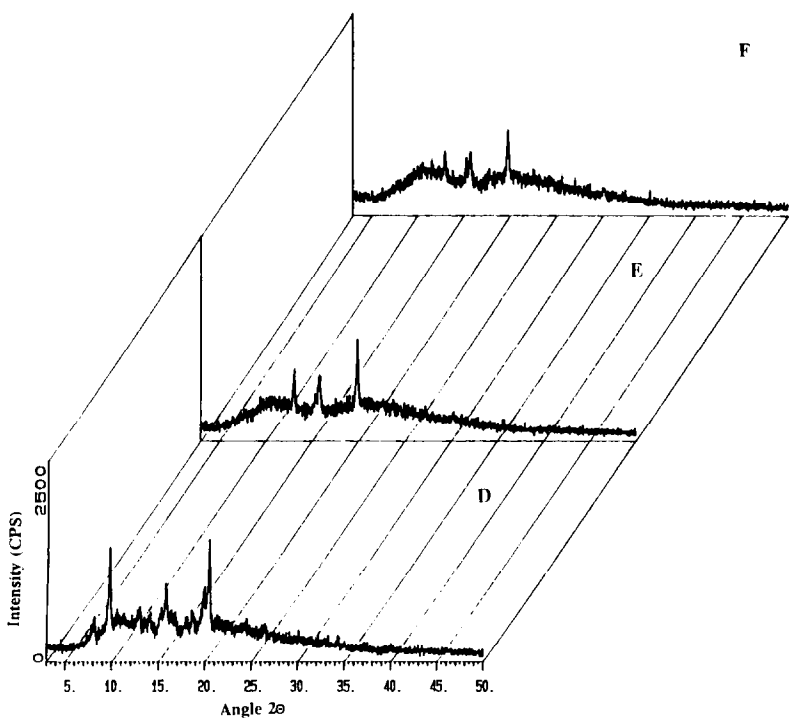
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Angle 2θ

dispersions was carried out in triplicate in amber USP dissolution vessels containing 900 ml of 10% (w/v) polysorbate 80 NF in water at 37°C. The amber vessels were used because the stability of CI-987 was light sensitive, and the dissolution media contained 10% Polysorbate 80 because of the poor solubility of CI-987 in more conventional media. Dissolution studies were conducted with a slightly modified version of the dissolution apparatus used by Simonelli and co-workers (1969) at an agitation speed of 50 rpm. This apparatus left a single surface of the disc exposed to the dissolution medium.

Between 130 and 150 mg of sample was compressed into stainless steel dies. A compaction pressure of 1350 lb/inch^2 (psi) was used for the solid dispersions since this was the minimum pressure needed to yield an intact disc, whereas a pressure of 3000 psi was needed for the bulk drug. These dies were subsequently fastened into plexiglas holders. The studies were initiated by suspending these disc holders into the dissolution media which exposed one flush surface of the drug-containing discs to the media and maintained these discs at a fixed distance from the paddles. At predetermined intervals, 3 ml of the medium was removed and pushed through a 0.45 μm, teflon syringe filter assembly. After discarding the first 1–2 ml of filtrate, a 1 ml aliquot was diluted to 10 ml with methanol and assayed for CI-987 by HPLC.

3. Results and discussion

3.1. Powder X-ray diffraction studies

The physical state of CI-987 in the various preparations was evaluated by powder X-ray diffraction. Fig. 2 shows the diffraction patterns of the solid dispersions of CI-987 having PVP weight fractions between 0.43 and 0.81, a physical mixture of PVP and CI-987 having a PVP weight fraction of 0.81, and pure CI-987. PVP (not shown in Fig. 2) is amorphous, whereas pure CI-987 is crystalline as demonstrated by sharp and intense diffraction peaks. The physical mixture having a PVP weight fraction of 0.81 and the solid dispersions having PVP weight fractions less than 0.81 (Fig. 2) showed diffraction peaks consistent with the presence of crystalline CI-987. In contrast, the solid dispersion having a PVP weight fraction of 0.81 showed no CI-987 diffraction peaks indicating that the CI-987 present existed in an amorphous state; the presence of diffraction peaks in the physical mixture, having the same PVP weight fraction, shows that the loss of drug peaks with the dispersion is not the result of a dilution effect.

These results strongly suggest that CI-987 in the dispersions becomes increasingly less crystalline up to a PVP weight fraction of about 0.81 where the diffractogram is consistent with CI-987 existing in a totally amorphous state. A more quantitative assessment of this concept can be found in work performed on frusemide-PVP solid dispersions (Doherty et al., 1985). The degree of crystallinity of frusemide decreased, in a non-linear fashion, up to a PVP weight fraction of 0.6 where frusemide existed in a totally amorphous state.

3.2. Dissolution studies

The dissolution rates were obtained from the initial, linear region of the dissolution-time profiles. The effect of varying the weight fraction of PVP on the dissolution rate of CI-987 from the solid dispersions is shown in Fig. 3. These data are also included in Table 1 along with the factor by which a given solid dispersions increases the CI-987 dissolution rate relative to pure CI-987. The maximum dissolution rate was obtained for the dispersion having a PVP weight fraction of 0.81. This dispersion had a dissolution rate which was 15-fold greater than that of pure CI-987. The shape of the dissolution rate vs PVP weight fraction profile, observed for the CI-987-PVP solid dispersions, is consistent with what has been observed previously for sulfathiazole-PVP (Simonelli et al., 1969, 1976) and hydroflumethiazide-PVP dispersions (Corrigan and Timoney, 1975).

The profile shows three distinct phases: (1) At low PVP weight fractions (< about 0.2), the dissolution rate of CI-987 from the dispersions is nearly independent of the fraction of PVP present. In

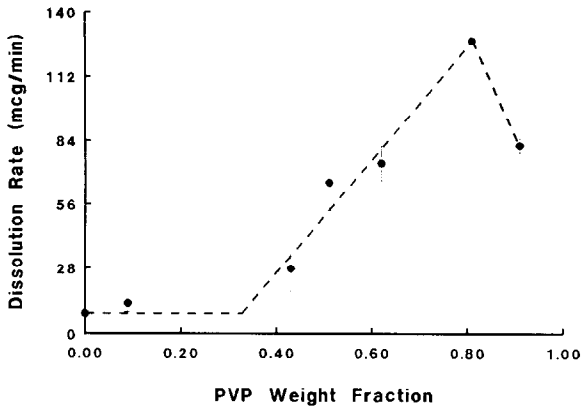

Fig. 3. the effect of varying the weight fraction of PVP on the dissolution rate of CI-987 from solid dispersions at 37°C and in 10% (w/v) polysorbate 80 in water. (The error bars represent standard deviations, and the dashed lines were added to highlight the three distinct regions of the profile.)

this region, the dissolution rate is controlled by and approximates pure crystalline CI-987. This occurs because as PVP is released and its boundary recedes, the surface of the disc becomes drug-enriched (Simonelli et al., 1969). (2) At intermediate PVP weight fractions (0.2–0.81), the dissolution rate of CI-987 increases as the fraction of PVP present is increased. This trend, relative to that observed at low PVP weight fractions, is consistent with a change in the physical state of CI-987. The X-ray diffraction data indicate that a major factor controlling drug release in this region of the profile is the decrease in the degree of crystallinity of CI-987 within the dispersion as the fraction of PVP is increased. This is further supported by the finding that the maximum dissolution rate occurs with the dispersion where CI-987 appears to exist in a totally amorphous state (i.e., a PVP weight fraction of 0.81). At this weight fraction of PVP, where the maximum dissolution of drug occurs, both the drug and PVP boundaries recede at similar rates. (3) At high PVP weight fractions (> 0.81), the dissolution rate decreases as the fraction of PVP present is increased. This trend, relative to that observed at intermediate PVP weight fractions, is consistent with a change in the rate-controlling component. In this region, the PVP boundary recedes slower than the drug boundary and the dissolution rate is controlled by PVP (Simonelli et al., 1969).

Table 1
The dissolution rate of CI-987 from PVP solid dispersions in 10% (w/v) polysorbate 80 in water at 37°C

PVP weight fraction	CI-987 dissolution rate (μg/min) [a]	Relative rate [b]
0.00	8.52 (±1.75)	1.0
0.09	12.8 (±3.5)	1.5
0.43	27.8 (±9.9)	3.3
0.51	65.6 (±12.4)	7.7
0.62	74.1 (±7.7)	8.7
0.81	127.5 (±1.3)	15.0
0.91	81.8 (±3.1)	9.6

[a] The value in parenthesis is the standard deviation of the mean value of the individual dissolution rates ($n = 3$).
[b] The dissolution rate of CI-987 from a given solid dispersion relative to the dissolution rate of pure CI-987.

4. Conclusions

These studies show that significant increases in the dissolution rate of CI-987 can be achieved with solid dispersions containing PVP. As seen with other poorly water-soluble compounds, the dissolution rate vs PVP weight fraction profile for CI-987 solid dispersions is well described by three distinct phases. The maximal dissolution rate and the presence of a totally amorphous dispersion occur at a relatively high PVP weight fraction of 0.81. Determining the drug to PVP ratio where the crystalline form is completely eliminated is important because the presence of any seed crystals can accelerate the crystallization rate of the drug resulting in a loss of the desirable solubility/dissolution-rate characteristics of the amorphous form. As with any delivery system, the in vivo behavior and the effects of aging will need to be studied.

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