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Dissolution rates of partially water-soluble drugs from solid dispersion systems. I. Prednisolone

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Summary

A solid dispersion technique with PEG, PVP, urea, sorbitol, mannitol, and cremophor has been used for improving prednisolone dissolution. The optimum dissolution rate composition was for dispersions containing 10% w/w prednisolone. A marked increase in the dissolution rate of prednisolone in solid dispersion was observed compared with that of drug alone or with that of a physical mixture with a carrier.

Introduction

The pharmaceutical application of solid dispersion systems was first demonstrated by Sekiguchi and Obi (1961). They proposed the formation of a eutectic mixture of a very slightly soluble drug with a freely water-soluble and physiologically inert carrier, as a novel method for reducing particle sizes. The methods of preparation of solid dispersion modified by other authors (Goldberg et al., 1966; Chiou and Riegelman, 1969; Geneidi et al., 1978) gave good results to very slightly water-soluble drugs and their dissolution rate increased significantly. For example, the use of PVP as a carrier enhanced the dissolution rate of phenylbutazone 15-fold (Mortada 1980): that of papaverine was increased by 26 (El-Gindy et al., 1976), and cinnarizine was increased 40-fold (Bogdanova et al., 1981). Excellent work on solid dispersion systems was carried out by Chiou and co-workers (1970, 1971, 1977) and solid dispersion techniques have been utilized to reduce the particle size of drugs and to increase their dissolution and absorption rates (Allen et al., 1978).

In this present work, prednisolone, which is poorly soluble in water, was chosen to prepare solid dispersion systems with water-soluble carriers. The aim of this work was to determine whether PEG, PVP, urea, sorbitol, mannitol, or cremophor were suitable as carriers of solid dispersion systems and to determine whether the quantities of these carriers and their chemical structure influenced the dissolution rate of prednisolone from such systems.

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Experimental

Materials

Materials used: Prednisolone (Pharmaceutical

Works "Polfa"), urea (Chemical Works of nitric compounds Kedzierzijn), polyethylene glycol (PEG 6000) (Laborchemikalien Carl Roth OHG), polyvinylpyrrolidone (PVP 25,000, PVP 40,000, PVP 160,000) (Fluka AG), sorbitol (Reachim USSR), mannitol (Ciech-Poch-Gliwice) and cremophor (Badische Auilin und Sodafabrik).

Procedure

The samples studied included the solid dispersions or physical mixtures of 10% prednisolone and 90% carrier. For studies on the influence of the quantity of the carriers on the dissolution rate of drug from solid dispersions and physical mixtures, samples were prepared containing 2.5–50% prednisolone.

Preparation of the solid dispersions

(a) Melting method. The solid dispersions with PEG, urea, mannitol, sorbitol, and cremophor were prepared by the melting method as follows: a suitable amount of prednisolone–carrier mixtures was weighed, mixed and heated directly on a sand bath until fusion, then allowed to cool with continuous stirring. After 24 h storage in a dessicator, the solidified mass was crushed, pulverized and sieved through screens (0.49).

(b) Solvent method. This method was used for a PVP solid dispersion. The samples were prepared by dissolving the mixture of prednisolone and PVP in ethanol 95%. The solvent was then evaporated completely using a vacuum evaporator. The mass was crushed, pulverized and sieved (0.49).

Preparation of the physical mixture

Prednisolone and carrier were weighed accurately in various proportions, mixed thoroughly by trituration in a mortar and then powdered.

Dissolution studies

The dissolution rate of prednisolone from the powdered samples was determined using the flow-through method to water. The apparatus consisted of a dissolution chamber with a water-jacket maintained at a temperature of 37°C, a peristaltic pump and a round-bottom flask (500 ml capacity). The flow rate of the solution was 40 ml/min. The dissolution chamber (18 × 55 mm) had two glass sinters which prevented the insoluble particles of drug from passing into the flask. The dissolution studies were carried out on powdered samples, equivalent to 100 mg prednisolone in 350 ml distilled water; 5 ml samples of the dissolution fluid were taken at different time intervals; they were suitably diluted and assayed spectrophotometrically. The concentration of prednisolone in samples was calculated as percent dissolved vs time t (Figs. 1–3) and vs percentage of drug in the test systems (Fig. 4).

Assay procedure

Prednisolone was assayed spectrophotometrically at $\nu = 246$ nm using a UNICAM SP500 spectrophotometer.

X-Ray diffraction studies

X-Ray diffraction spectra were obtained using difractometer Dron-2 and Cu-Kα radiation. The rate of counting was 4000 pulses/s. Diffraction spectra were run 2°/min in term of 2θ angle (Fig. 5).

Results and Discussion

The results of the studies showed that the dissolution rate of prednisolone from all solid dispersions increased markedly from those of the physical mixture and the drug alone (Table 1, Fig. 1).

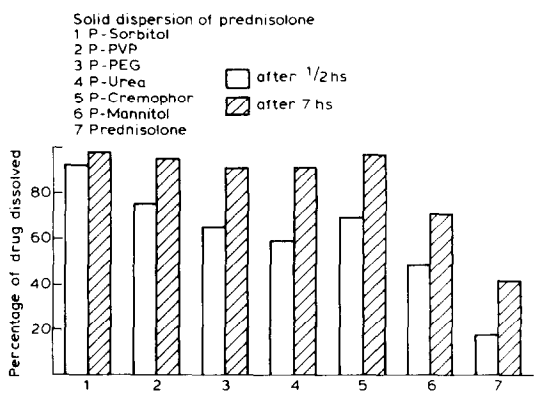

Fig. 1. Amount of prednisolone dissolved from solid dispersions after 0.5 h and 7 h.

TABLE I

Amount of prednisolone (%) dissolved after 7 h

Carrier:	Prednisolone	Physical mixture 1:10	Solid dispersion 1:10
	In the solution of the carrier *	In water	In water
Sorbitol	54.20	80.90	100.00
Cremophor	90.00	93.05	97.15
PVP 40,000	64.00	82.42	96.45
PEG 6000	65.10	67.20	96.00
Urea	56.00	59.90	92.20
Mannitol	46.90	64.40	71.74

* Concentration of the carrier in solution equals the amount of the carrier contained in the sample of physical mixture and solid dispersion (900 mg/350 ml).

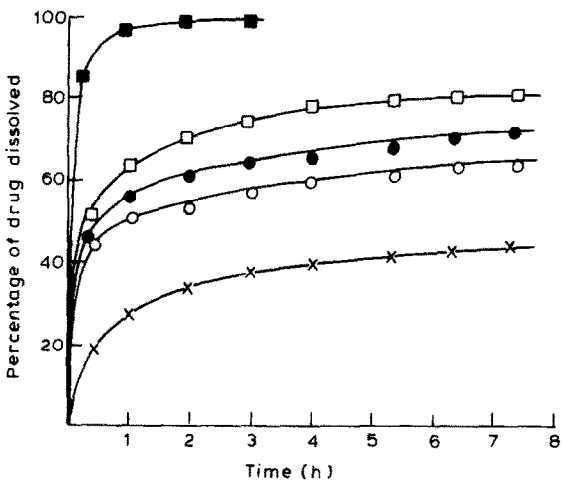

Fig. 2. Dissolution rates of prednisolone from physical mixtures (Ph.M.) and solid dispersions (S.D.). O——O, prednisolone–mannitol (Ph.M.); ●——●, prednisolone–mannitol (S.D.); □——□, prednisolone–sorbitol (Ph.M.); ■——■, prednisolone–sorbitol (S.D.); ×——×, pure prednisolone.

Nevertheless, there was no observed relationship between the higher dissolution rate and chemical structure of the carriers. Nor was it possible to predict quantitatively to what extent any carrier would improve the dissolution rate of the drug in solid dispersion. For example sorbitol and mannitol, which are chemically similar, produced different effects on dissolution rate. Results indicated that sorbitol was one of the better carriers and the maximum drug dissolved (100%) was achieved after 3 h. Yet at the same time, only 63.17% prednisolone was dissolved from the mannitol solid dispersion (Fig. 2). When PEG, PVP and urea were used as carriers they gave similar results (Fig. 1).

The amount of prednisolone dissolved from the solid dispersions with above carriers was twice as great as that from the drug alone. The degree of enhancement achieved by PVP showed some decrease as the molecular mass increased. While the amount of dissolved prednisolone from solid dispersions with PVP 25,000 and PVP 40,000 were 92,5%, 96,45% respectively, it was approximately 86% dissolved using PVP 160,000.

Similar investigations with physical mixtures showed that smaller amounts of drug were dissolved than solid dispersions. Cremophor was the only carrier to give the same results for both forms studied. Comparison of these results with those of the dissolution rate of prednisolone in carrier solutions showed that a solubilizing effect had taken place and this had evoked a better dissolution rate.

As shown in Fig. 3 the solubilizing effect of the carrier systems were differentiated according to their chemical structure. There was no distinct differences between the values of drug dissolved in the solution of PEG, cremophor, or urea and from physical mixtures with them. But sorbitol and mannitol had a less effective solubilizing effect. The amounts of prednisolone dissolved in PVP 40,000 solutions were mid-way between the amount of prednisolone dissolved in water and that in the physical mixture.

Correlation of the amount of drug in solid dispersion and physical mixture in the range of concentration studied (2.5%–50%) to its dissolution rate showed that 10% is the optimum value for both PEG and urea (Fig. 4). It was evident that in the concentration range 10–50%, the amount of dissolved drug decreased as the percentage of the carriers increased. This amount of dissolved drug decreased when the drug concentration was below 10% in the investigated for-

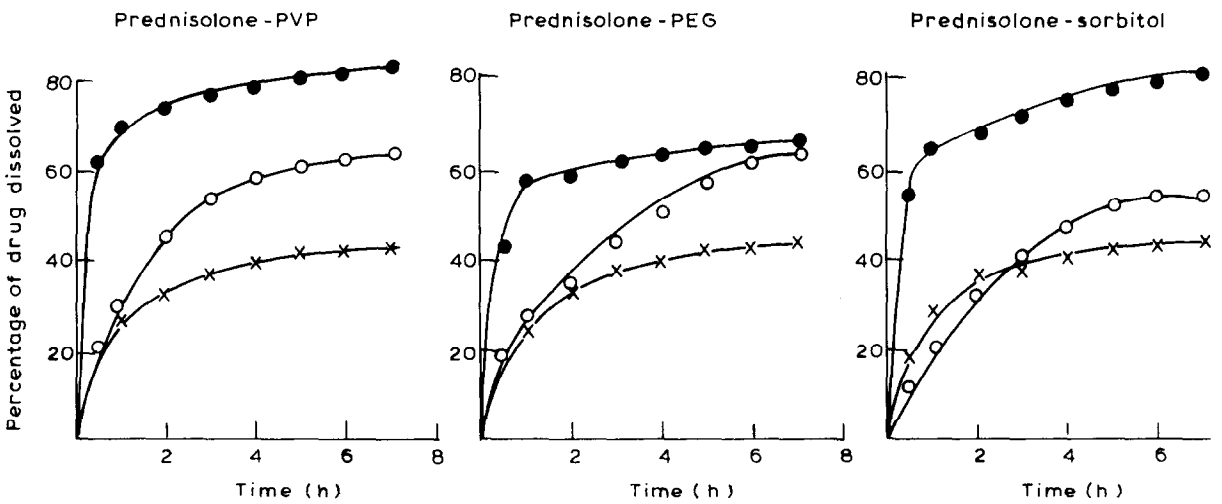

Fig. 3. Dissolution rates of prednisolone. ●——●, physical mixtures; ○——○, in solution of the carrier; ×——×, pure prednisolone.

mulations. For example, the same values of dissolved drug was achieved for 2.5% and 30% solid dispersions. The optimal results for 10% solid dispersions can be probably explained by the formation of a soluble complex between prednisolone and its carrier.

The corresponding investigations with physical mixtures showed that decreasing the concentration of prednisolone in the test systems below 10% did not significantly influence their dissolution profile.

It is difficult to explain the mechanism of the enhanced dissolution properties of prednisolone in

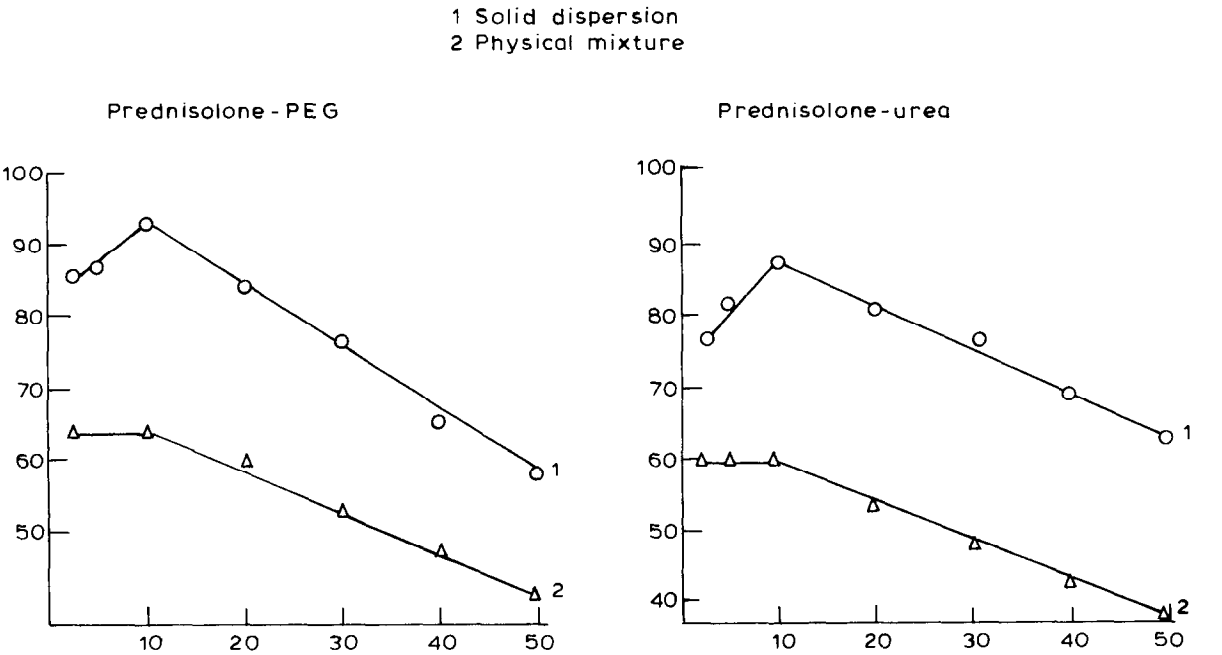

Fig. 4. Amount of prednisolone dissolved after 7 h vs percentage of drug in test systems.

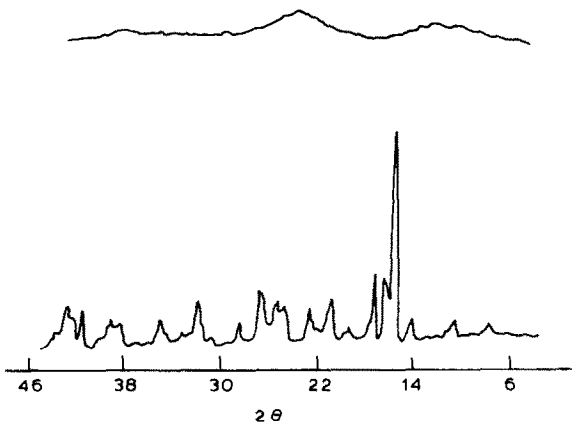

Fig. 5. X-Ray diffraction spectra of pure prednisolone (bottom) and solid dispersion prednisolone–PVP 40,000 (top).

solid dispersions with different carriers. The present results showed that improved wettability of drug molecules and their solubilization by the carriers were not basic processes. Molecular dispersion of drug through the matrix of the carriers was of greater importance. Although changes in crystalographical structure of the drug during preparation of solid dispersion was evident, X-ray diffraction studies indicated an amorphous form of prednisolone in solid dispersion with PVP (Fig. 5). In contrast the presence of identical prednisolone diffraction peaks in the spectrum of pure drug and solid dispersion systems with PEG, urea, mannitol, and sorbitol showed that these solid dispersions contained prednisolone in crystalline form.

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