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DISSOLUTION OF SULPHAMETHOXAZOLE FROM POLYETHYLENE GLYCOLS AND POLYVINYLPYRROLIDONE SOLID DISPERSIONS

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ABSTRACT

Solid dispersions of sulphamethoxazole have been prepared by fusion and solvent methods using polyethylene glycols 6000 and 9000, and polyvinylpyrrolidone (mol.wt. 40,000) as water-soluble carriers. Coprecipitates with the latter were superior to other carriers in releasing the drug into solution. Melts with the former produced faster rates of dissolution of sulphamethoxazole than the coprecipitate from the solvent method. Solubility of the drug increased also with corresponding increase in the concentration of these carriers.

INTRODUCTION

The mechanism of increasing solubility of insoluble or slightly soluble drug via solid dispersion technique is extensively reviewed by Chiou and Riegelman (1). To optimize the bioavailability and absorption rates of poorly soluble drugs, both the carrier and the method of preparation of the solid dispersion should be carefully selected. Recently, a marked increase in the dissolution rate of sulphamethoxazole in the solid glass dispersions was reported (2). This paper communicates the effect of polyethylene glycols 6000 and 9000, and PVP (mol.wt. 40,000) in different levels, incorporated by various techniques in dispersions, on the dissolution characteristics of sulphamethoxazole.

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MATERIALS AND METHODS

The materials used include sulphamethoxazole (Ranbaxy Laboratories Ltd., New Delhi, India); polyethylene glycol 6000 (Sisco Research Labs., Bombay); polyethylene glycol 9000 (S.D. Fine Chem. Pvt. Ltd., Boisar); polyvinylpyrrolidone, mol. wt. 40,000 (Sigma Chemicals Co., St. Louis, U.S.A.). All other chemicals were analar or reagent grade and were used as received.

Preparation of the Solid Dispersions -

(i) Fusion Method : Solid dispersions with polyethylene glycols (PEG) were prepared by the fusion method as previously described (3). Physical mixtures representing drug to PEG 6,000 or 9,000 ratios of 1:1, 1:1.5 and 1:2 (w/w) were heated over a thermostatic plate with constant stirring until a clear homogenous melt was obtained. Melts were quickly poured in a thin layer on a glass slab. and were cooled and solidified gradually at room temperature. After 1 hr, solidified dispersions were dried in a vacuum desiccator for 2 days and the mass was pulverized and sieved over 120 mesh size.

(ii) Solvent Method: Co-precipitates of sulphamethoxazole and PEG 6,000 or 9,000 in 1:1, 1:1.5 and 1:2, and polyvinylpyrrolidone (PVP) in 1:0.25, 1:0.5, 1:1 and 1:2 (w/w) ratios were prepared by dispersing accurately weighed quantities of the drug in methanol-acetone (1:1) mixture; this was then mixed with a solution of the polymer in the same solvent system, and the organic solvent was subsequently evaporated in vacuo. The residue was then dried and sieved as under 'fusion method'.

(iii) Precipitate Coacervate Method: The method employed for coacervate formation was the same as described by Badawi and El-Sayed (4). Both the drug and PVP in 1:0.25, 1:0.5, 1:1 and 1:2 (w/w) ratios were dissolved by heating in sufficient amount of alcohol. Water was then added dropwise till the formation of precipitate was complete, then the precipitate was filtered, dried and sieved similarly.

Dissolution Rate Studies -

Sulphamethoxazole (400 mg) or the equivalent of the test preparation was introduced into 900 ml 0.1N HCl at 37°±0.1°C and agitated at 100 rpm. At frequent time intervals after the test preparation was added to the dissolution medium, a five ml sample was withdrawn, filtered, and replaced with 5.0 ml of fresh dissolution medium. The amount of the drug in solution at each time interval, appropriately corrected for this dilution effect, was determined by colourimetric method as previously described (5) at 520 nm after diluting with 0.1N HCl.

IR Spectral Analysis -

Infrared spectra of the drug alone or of the solid dispersions were determined using KBr pellets.

Thin Layer Chromatography -

Ethanolic solutions of sulphamethoxazole and solid dispersions were each spotted on silica gel G(E. Merck, Darmstadt) plates. The plates were developed with chloroform-methanol (4:1), and ethyl acetate-methanol (9:1), air dried and visualized under u.v. light. The spots were also located by spraying with a one percent solution of p-dimethyl-aminobenzaldehyde in a mixture of 90 volumes of ethanol (95% v/v) and 10 volumes of hydrochloric acid.

Solubility Determination -

An excess of sulphamethoxazole was added either to 50 ml water or of solutions of varying levels of carriers, in 25 ml glass-stoppered bottles which were rotated on a water-bath at 37°±1°C until equilibrium. Samples were filtered and assayed as described.

RESULTS AND DISCUSSION

Solid Dispersions of Polyethylene glycols (6000 and 9000) -

Figure 1 shows that there was almost more than fourfold and sevenfold increase in the dissolution rate of sulphamethoxazole when present in 1:2 solid dispersion systems with PEG 6000 and

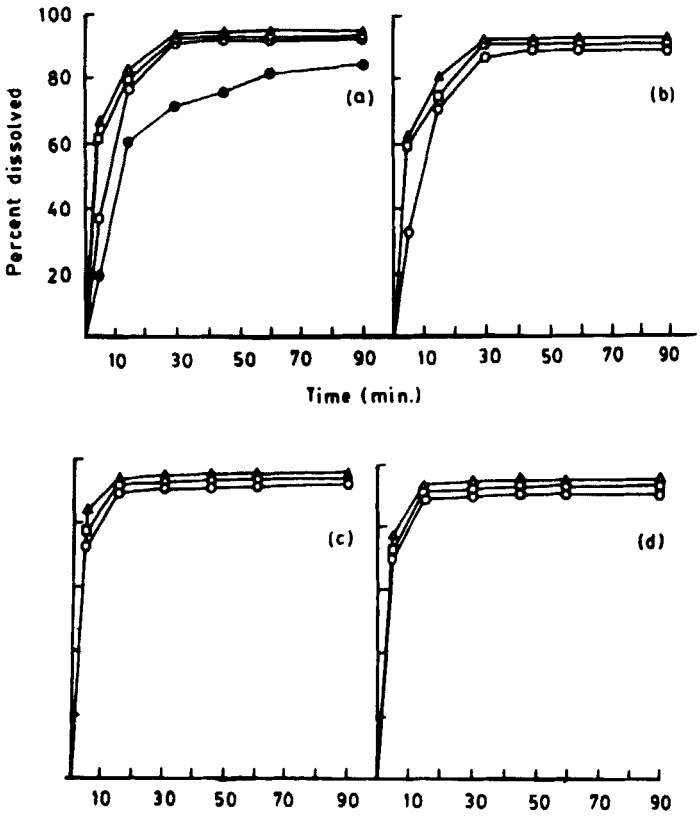

FIGURE 1

Dissolution rate of dispersions of Sulphamethoxazole prepared in PEG 6000 by the (a) melt, (b) solvent, and in PEG 9000 by the (c) melt (d) solvent methods. Key: O 1:1, □ 1:1.5, and Δ 1:2 (Drug-Carrier ratio).

9000, respectively. While comparing the effect of molecular weight of PEG on dissolution rate it was observed that the molecular weight indeed significantly changed the dissolution rate of sulphamethoxazole, the 9000 molecular weight being the most rapid of the two systems.

A comparison of the release of sulphamethoxazole from melt and coprecipitate dispersions in Fig. 1 shows that, at the three concentration levels studied, the dissolution rate of the drug from both the dispersions was seemed to be very close. However,

from the melts it was slightly faster than the coprecipitates and this is consistent with the observations for griseofulvin-PEG 6000 dispersion system reported by Chiou and Riegelman (6). While, McGinity et al. (7) showed the fastest drug release from the sulphabenzamide-PEG 6000 dispersions prepared by the solvent method. The choice of equilibrating solvent with respect to the solubility of the drug and carrier appears to have a marked influence on the final physical characteristics of the coprecipitate. From the figures, it can be seen that the dissolution curves show two phases, an initial rapid phase and a slow and more prolonged phase. The first could be due to rapid solubility of the fraction of sulphamethoxazole present in a state of molecular dispersion in the molten mass and the slow phase to the release of the drug present as dispersed particles.

Solid Dispersions of Polyvinyl-pyrrolidone -

From the figure 2, it can be observed that there was increase in the sulphamethoxazole dissolution rate from these dispersions with corresponding increase in the weight fraction of PVP. This profile resembled that of Badawi and El-Sayed (4) who described a model to enhance the dissolution rate of the different coacervate systems prepared. The dissolution rate from the 1:2 (w/w) coprecipitate and coacervate dispersion systems was more than twentyfold faster than that of the drug alone (Fig.1,a). However, coprecipitate induced a slightly better solubilization of the drug than coacervate. The enhanced dissolution rate of the drug results either from the complex, or coacervate formation, or the drug being molecularly dispersed, or the formation of high energy amorphous drug phase.

Chromatographic Behaviour -

TLC examination revealed the presence of only one spot with R_f value = 0.51, system I and 0.68, system II, which were identical to the pure sample of the drug. Sulphamethoxazole-PVP coprecipitates was not resolved into two separate spots. Therefore, TLC indicated the existence of complexation between sulphamethoxa-

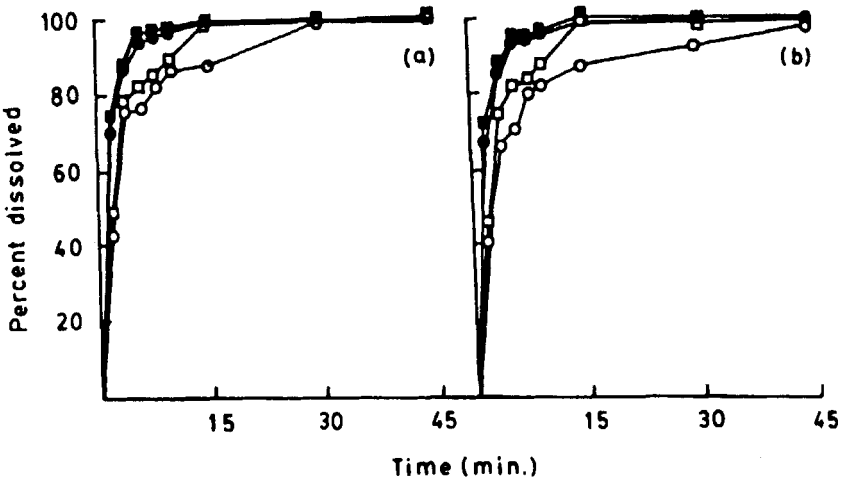

FIGURE 2

Dissolution rate of dispersions of sulphamethoxazole in PVP prepared by the (a) solvent method, (b) precipitate- coacervate method.

Key: ○ 1:0.25, □ 1:0.5, ● 1:1 and ■ 1:2 (Drug-carrier ratio).

zole and PVP. While in the case of sulphamethoxazole-PEG dispersions prepared by the fusion method, TLC indicated no decomposition of the drug took place during preparation.

Infra-Red Spectra -

The IR spectrum of sulphamethoxazole exhibited a sharp band at 3500 cm^{-1} (NH of amino group), while the IR spectrum of the sulphamethoxazole-PVP system shows a broad band in this region. This broad band present in all PVP dispersion systems is attributed to the presence of hydrogen bonding between the N-H group of sulphamethoxazole and the carbonyl group of the PVP. This is an indication of complex formation in all the cases. On the other hand, the band characteristics for the drug were unaffected in the drug-PEG dispersion systems indicating no evidence of complexation between sulphamethoxazole and PEG.

Solubility -

Figure 3 shows the solubility of the drug increased with increase in concentrations of the water-soluble carrier and that too in

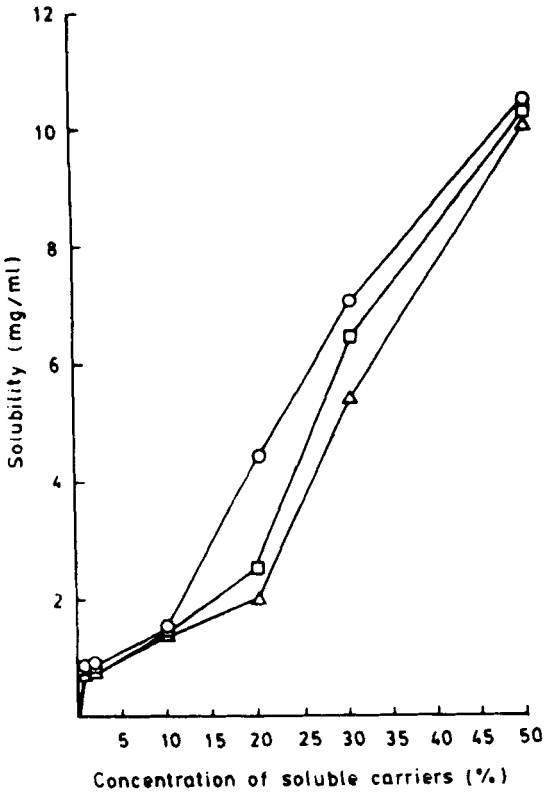

FIGURE 3

Solubility profile of sulphamethoxazole vs concentration soluble carriers.

Key: ○ PVP solution, □ PEG 9000 solution and △ PEG solution.

the order of PVP>PEG 9000 PEG>6000. No change in λ_{max} of the drug was observed in any of the resulting solutions.

From these findings, it can be concluded that the drug-PVP coprecipitate (1:2, w/w) shows the best results. However, the demonstrated fairly fast in vitro release of the drug from dispersion systems suggests their high potential application for the formulation of most water-insoluble drugs, the bioavailability of such dosage forms as compared to the conventional forms, however, will be the subject of further study.

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