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ENHANCEMENT OF DISSOLUTION RATE OF PROBENECID IN PHOSPHOLIPID COPRECIPITATES

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ABSTRACT

The coprecipitates of probenecid (PBC) with various phospholipids (PL) were prepared and their dissolution characteristics were determined by use of a Vanderkamp dissolution test apparatus. Probenecid exhibited significantly improved dissolution rates in all the PL preparations compared to either the physical mixtures or the pure PBC. Among them, the combination of PBC:Egg phosphatidylcholine (EPC) (10:1) as a carrier for the coprecipitate resulted in the fastest dissolution of PBC. A 13.7 fold greater initial dissolution rate and 7.5 fold greater limiting concentration was achieved. Dissolution studies of probenecid suggested that less than 1 to 10 ratio of PBC to PL was required to disperse amorphous PBC completely in the carrier. Increasing the lecithin content further did not improve the release of the drug to any significant extent. Phospholipids with

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phase transition temperature higher than the experimental temperature exhibited significantly less increase in dissolution compared to other phospholipids. Various coprecipitating solvents used in the study were found equally good in improving the dissolution of the drug. The PBC-PL solid dispersion, therefore, appears to have the clinical advantages of quick release and excellent bioavailability.

INTRODUCTION

The rate at which a drug dissolves from its intact or disintegrated and deaggregated form in the GI tract is often responsible for the rate at which the drug appears in the blood, i.e., the absorption rate of the drug. When this is the case, dissolution is said to be the rate-limiting process. Probenecid, a potent uricosuric agent, is used as a single identity in the treatment of gout arthritis and in conjunction with various antibiotic therapy in order to prolong their half-life by competitive inhibition (1). The drug is poorly soluble in water and therefore, its bioavailability is expected to be dissolution rate limited.

In 1961, Sekiguchi and Obi (2) first proposed the utilization of solid dispersions to increase the dissolution and oral absorption of poorly water-soluble drugs. Since then, various water-soluble materials such as polyvinyl pyrrolidone (3), polyethylene glycols (4), bile acids (5) etc. have been used to improve the dissolution rate of a drug. Many of these dosage forms contain a large proportions of carriers to be effective. On the other hand, phospholipids have been used recently with very low carrier:drug ratios to improve the dissolution profiles of drugs (6).

In the present study, the coprecipitation technique was applied to enhance the dissolution rate of probenecid. Various phospholipids were utilized and their effects on dissolution rates were compared.

MATERIALS

Probenecid was obtained in a powder state (7). Pure synthetic phospholipids with label claim of 98 percent purity included : L-α- dimyristoyl phosphatidylcholine (DMPC) (7), L-α- dipalmitoyl phosphatidylcholine (DPPC) (7), L- α - distearoylphosphatidylcholine (DSPC) (7) and egg phosphatidyl choline (EPC) (7). Chloroform, methanol, ethanol and other solvents were reagent grade solvents. Demineralized distilled water was used throughout.

METHODS

Preparation of PBC coprecipitates and Physical Mixtures:

Quantities of probenecid and phospholipids to make the coprecipitates were weighed accurately and dissolved in a sufficient volume of chloroform. The temperature was raised to 37°C and the solvent was allowed to evaporate under the hood in a jacketed beaker, stirring continuously. The evaporation of the solvent was assisted by a gentle stream of nitrogen. When evaporation was almost complete, the remaining coprecipitate was removed from the container using a spatula and placed in vacuum over anhydrous calcium sulfate for 24 hours. The coprecipitates were seived through a 100 mesh screen for size uniformity and kept in a desiccator for analysis and dissolution studies. The physical mixtures of PBC and PLs were prepared by triturating appropriate quantities of drug and PL using a small morter and pestle and transferring to a vacuum desiccator until ready for use.

Dissolution Rate Study :

The dissolution rate studies of PBC and its coprecipitates were done in a Vanderkamp 600 dissolutioon test apparatus at 37°C. Nine-hundred milliliters of deionized water was placed in the vessels, the paddle stirring speed was set at 100 rpm and 50 mg equivalent of the drug was added to the medium after the temperature was reached. The paddle was placed 2.5 cm from the bottom of the vessel. At different time intervals samples were withdrawn employing a 1μm porosity filter screen. The volume in the vessel was replaced with deionized water after each sample was taken. Measurement of concentrations of PBC was carried out using a Milton Roy 1201 uv/visible scanning spectrophotometeer at 254 nm using deionized water as the blank. None of the PLs interfered with the measurement of the absorbances at this wavelength. Experiments were run in duplicate and the results averaged.

RESULTS AND DISCUSSIONS

Figure 1 shows the dissolution of probenecid from PL solid dispersion prepared at various ratios of DMPC to probenecid. The dissolution of pure PBC and its physical mixture with DMPC are also shown in Figure 1 for comparison. It clearly indicates a greater dissolution of probenecid from coprecipitate than the physical mixture or the pure compound. The coprecipitate at an PBC-DMPC weight ratio of 10:1 yielded a 13.7 fold greater initial dissolution rate and 7.5 fold greater limiting concentration which is essentially the total amount dissolved after 60 minutes. Table 1 shows that by increasing the DMPC concentration from 10:1 to 5:1 does not increase the disssolution to any significant level. On the other hand if we look at various ratios we find

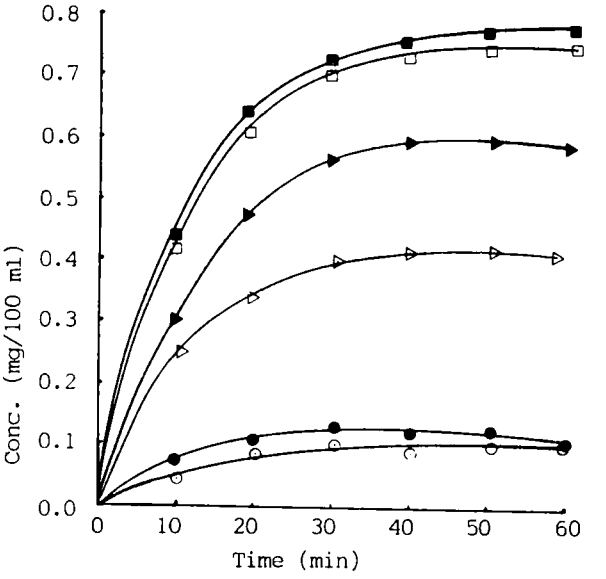

Figure 1 : Dissolution behavior of PBC in distilled water and at 37°C. Key : pure PBC (○); physical mixture with DMPC (10:1) (●); coprecipitates with DMPC : (5:1) (■); (10:1) (⊡); (20:1) (▲); (30:1) (△).

TABLE I

Comparison of Amount Dissolved from PBC-DMPC Coprecipitates and Pure PBC in Distilled Water and 37°C.

Composition (PBC:DMPC)	Amount dissolved in 10 min	20 min	40 min	60 min
1:0	0.03	0.06	0.08	0.10
5:1	0.43	0.62	0.78	0.78
10:1	0.41	0.60	0.71	0.75
20:1	0.29	0.46	0.58	0.58
30:1	0.25	0.31	0.35	0.36

that, at higher ratios of PBC to DMPC than 1 to 10, the bulk concentration rapidly rises to 0.29 mg/100 ml in 10 minutes with subsequent small increases but at lower ratios than 1 to 10, the bulk concentration reached a plateau of 0.43 mg/100 ml in less than 10 minutes and a gradual increase occurred to 0.78 mg/100 ml. These results suggest that a ratio of equal to or less than 1 to 10 is required to disperse the amorphous PBC completely in PLs. Values of limiting concentration obtained from the coprecipitates also shows that a substantial increase in the apparent solubility of PBC in the dissolution medium.

Effect of Phospholipid Composition

The rate of dissolution of PBC from 10:1 (drug:PL) coprecipitates with EPC, DMPC, DPPC or DSPC is shown in Figure 2. It is apparent that the initial dissolution rate and the limiting concentration after 60 minutes are greater for all coprecipitates than that obtained by the dissolution of pure PBC. Furthermore, the release of drug decreases with an increase in the fatty ester chain length of the PL. For example, DSPC has a higher chain length than DPPC which is again higher than DMPC or EPC. Thus, DPPC and DSPC showed less improvement in the release of the drug than DMPC or EPC as can be seen in Figure 2. PL improves the dissolution of a drug by their ability to form liposome when in contact with water (6). The increase in the release of the drug may be due to an intrinsic solubility of the drug in the medium of the stationary layer or due to a partitioning process. In any case, if it is assumed that DPPC or DSPC behave like DMPC or EPC in the formation of the crystalline lattice of the coprecipitate, the decreased release of PBC when combined with a longer chain compound is probably related to their phase transition temperature (Tc) and their corresponding

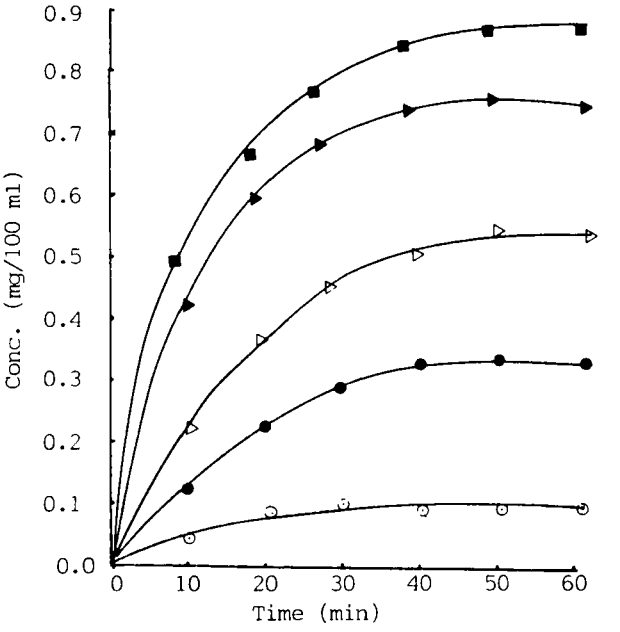

Figure 2 : Effect of various phospholipids on the dissolution behavior of PBC in distilled water at 37°C and at a 10:1 (PBC:PL). Key : pure PBC (⊙); DSPC (●); DPPC (△); DMPC (▲); EPC (◆).

physical state at 37°C. The Tc of EPC, DMPC, DPPC and DSPC is 1°, 23°, 41° and 58°C (8) respectively. Since the Tc of DSPC is too far above 37°C, it would remain in solid state at the experimental temperature and would not disperse spontaneously and decreased dissolution was observed.

Influence of the Coprecipitating Solvent :

It is known that coprecipitate forming solvent sometimes play a role in improving the dissolution of drugs in aqueous medium (6). This study is therefore conducted to establish any role played by the solvent on the release of PBC. The results are given in Table II. It is obviuos from the table that all of the solvents

TABLE II

Comparison of Various Coprecipitating Solvents on the Dissolution of PBC:DMPC (10:1) in Distilled Water and at 37°C.

Solvent	Amount dissolved in		
	10 min	20 min	60 min
Chloroform	0.41	0.60	0.75
Methanol	0.35	0.55	0.72
Ethanol	0.39	0.58	0.72

produced the similar rate and amount of drug release. Thus it is proved that solvents do not not play any role in the formation of coprecipitates. Simply, PBC combines with phospholipid in a manner that provides an appropriate orientation of the phospholipid molecules to enable rapid dispersion into bilayers when contact is made with water.

CONCLUSIONS

The coprecipitates of probenecid with various phospholipids in different proportions showed a faster dissolution in-vitro than plain probenecid or probenecid-phospholipid physical mixtures. A phospholipid with a phase transition below the room temperature should be chosen for the best possible result in improving the dissolution charactersitics of the drug. Thus, the EPC and DMPC at a ratio of 10:1 (drug:PL) provided the best combination for improved dissolution of probenecid. A choice of coprecipitating solvent can be made if that is necessary considering the industrial aspect of the

formulation because solvent does not play a specific role in the coprecipitate dissolution processs. More studies are needed to determine the ageing effect on dissolution and its impact on the commercialization of the product.

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