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IMPROVED DISSOLUTION OF INDOMETHACIN IN COPRECIPITATES WITH PHOSPHOLIPIDS-I

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ABSTRACT

Indomethacin powders were blended with phospholipids to prepare physical mixtures or made into solid dispersions by the solvent method and their comparative dissolution profiles were studied. Indomethacin exhibited significantly improved dissolution rates in phospholipid coprecipitates compared to either the physical mixtures or the pure indomethacin. The coprecipitates of lecithin-indomethacin 1:16 weight ratio had a 6.5 fold greater initial dissolution rate, and the total amount dissolved after 60 minutes was 140% greater compared to indomethacin alone. Increasing the lecithin content to 1:4 resulted in only a modest additional increase in the initial dissolution rate (40%) and the limiting concentration (14%).

INTRODUCTION

In the past water-soluble materials were used in high proportions to prepare coprecipitates in order to increase the rate of dissolution of a drug[1-4]. Recent evidence[5] has indicated that pronounced increases in the dissolution rate and substantially larger amounts of drug in solution are obtainable from coprecipitates with phospholipids (PL) of compositions which have a high proportion of drug e.g., 95% w/v. The choice of PL as co-dispersing agents is based on their potential advantages related to their liposome-type behavior which they form

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spontaneously in aqueous media and entrap various solutes either in the aqueous compartments or in the bilayers[6].

Indomethacin (IND) is practically insoluble in water and its absorption varies significantly between different dosage forms. This study was therefore undertaken to investigate the possible improvement in the dissolution characteristics of IND-PL coprecipitates.

MATERIALS

Indomethacin was obtained in a powder state[7]. Pure synthetic phospholipids with label claim of 98 percent purity included : L-α- dimyristoylphosphatidylcholine[7] (DMPC), L-α-dipalmitoylphosphatidylcholine[7] (DPPC), L-α- dimyristoylphosphatidylglycerol[7] (DMPG) and egg phosphatidylcholine[7] (EPC). Chloroform, methanol, ethanol and other solvents were reagent grade solvents. Demineralized distilled water was used throughout.

METHODS

Preparation of Physical Mixtures : Indomethacin powders were passed through 80 mesh sieve and the seived IND were blended with appropriate quantities of phospholipids uniformly in a morter and pestle to make physical mixtures.

Preparation of Coprecipitates : Solid dispersions of phospholipids and indomethacin were prepared by the solvent method[8] from an organic solvent yielding coprecipitates. The evaporation of the solvent was assisted by a gentle stream of nitrogen. Further drying was carried out under vacuum over anhydrous calcium sulfate. All samples were examined within 24 hours after preparation following sieving at 80 mesh for size uniformity.

Dissolution Study : The dissolution rate measurements were carried out using a Vanderkamp 600 dissolution test apparatus. The dissolution flasks were immersed in a water bath maintained at 37°C. The rotation speed was normally 100 rpm in a 750 ml dissolution medium. At different time intervals samples were withdrawn employing a 1μm porosity filter screen. Measurement of concentrations of indomethacin was carried out using a Milton Roy 1201 UV/visible scanning spectrophotometer at 318 nm. A 50 mg indomethacin equivalent sample was dispersed in the medium in each instance. Experiments were run in duplicate and the results averaged.

RESULTS

The dissolution of indomethacin from a phospholipid coprecipitate was found to be considerably greater than from either the physical mixtures or the pure indomethacin. Typical dissolution profiles are given in Figure 1 where it is apparent that the dissolution rates as well as the amount dissolved from the coprecipitates exceeded those of pure indomethacin or the

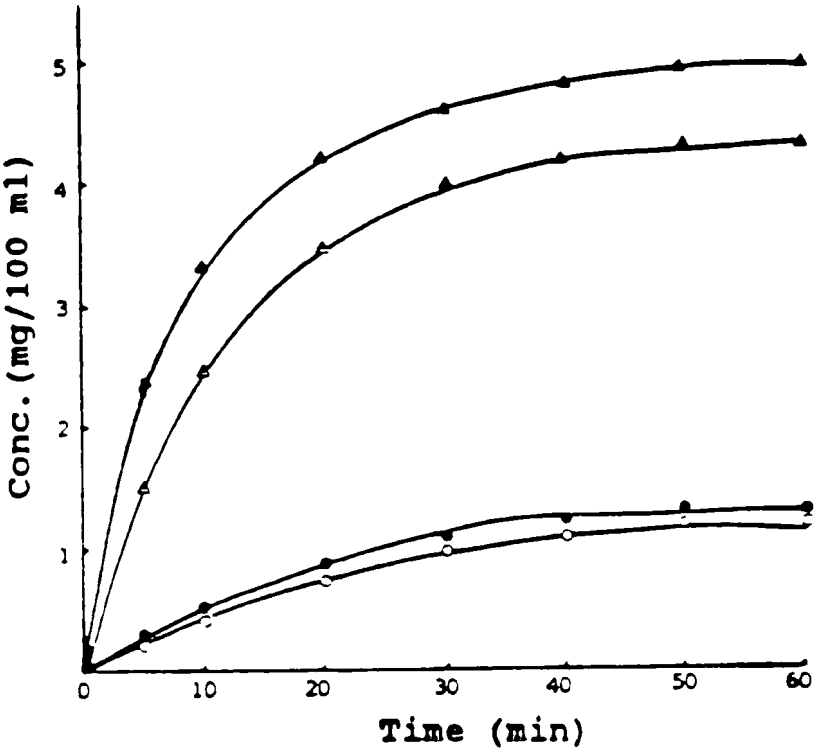

Figure 1 : Dissolution behavior of IND in dist. water at 37°C. Key : (⊙) pure IND; (●) physical mixture (16:1); (△) coprecipitate with DMPC (16:1); (▲) coprecipitate with DMPC (4:1).

TABLE I

Comparison of % Dissolved from various IND-DMPC Coprecipitates in Dist. Water at 37°C.

Composition (IND:DMPC)	Percent dissolved in 10 min	20 min	40 min	60 min
1:0	2.1	8.5	25.1	29.7
16:1	23.2	50.0	65.7	72.5
4:1	32.5	65.2	73.6	82.6

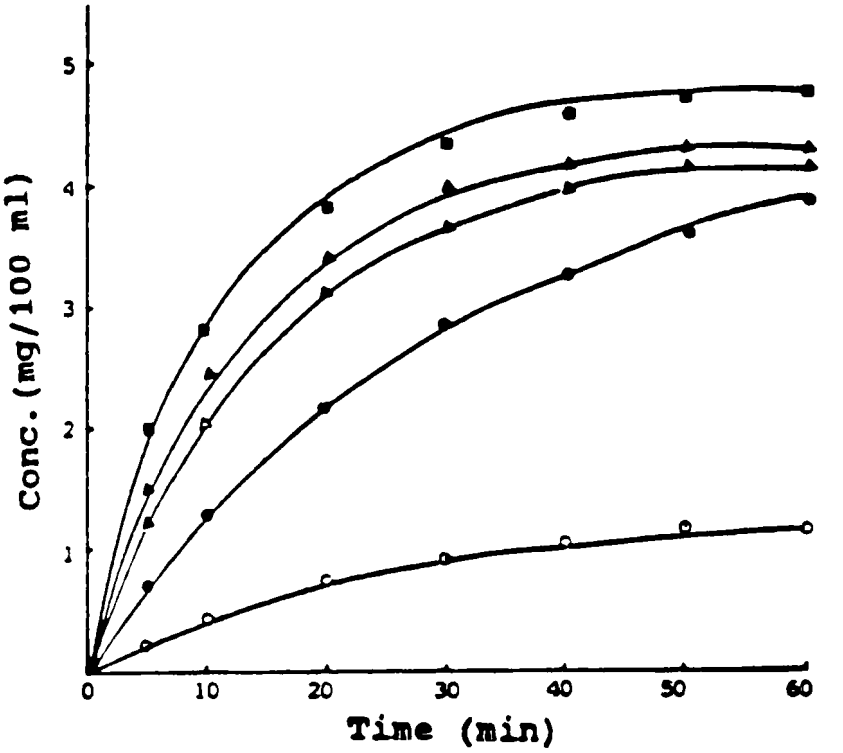

Figure 2 : Effect of various phospholipids on the dissolution behavior of IND in dist. water at 37°C and at 16:1 (IND:PL). Key : (○) pure IND; (●) DPPC; (△) EPC; (▲) DMPC; (■) DMPG.

corresponding physical mixtures. The coprecipitates yielded a 6.5 fold greater initial dissolution rate. Also, the total amount dissolved after 60 minutes was 140% greater at an IND-DMPC weight ratio of 16:1. Table I shows that by increasing the DMPC concentration from 16:1 to 4:1 does not increase the dissolution to any significant extent. Only a 40% increase in the initial dissolution rate and a further 14% increase in the limiting concentration was obtained. Thus a small amount of the carrier was sufficient for a dramatic increase in the dissolution.

Effect of Phospholipid Composition : The release of indomethacin from coprecipitates with DMPC, DPPC, DMPG or EPC is shown in Figure 2. The dissolution of pure indomethacin is also shown for comparison. It is apparent that the release rate and the amount released after 60 minutes are greater for all coprecipitates of phospholipids than that obtained by

TABLE II

Comparison of Various Coprecipitating Solvents on the Dissolution of IND:DMPC (16:1) in Distilled Water and at 37°C.

Solvent	Percent dissolved in		
	10 min	20 min	60 min
Chloroform	23.2	50.0	72.5
Methanol	21.5	46.2	69.8
Ethanol	20.9	42.5	66.9

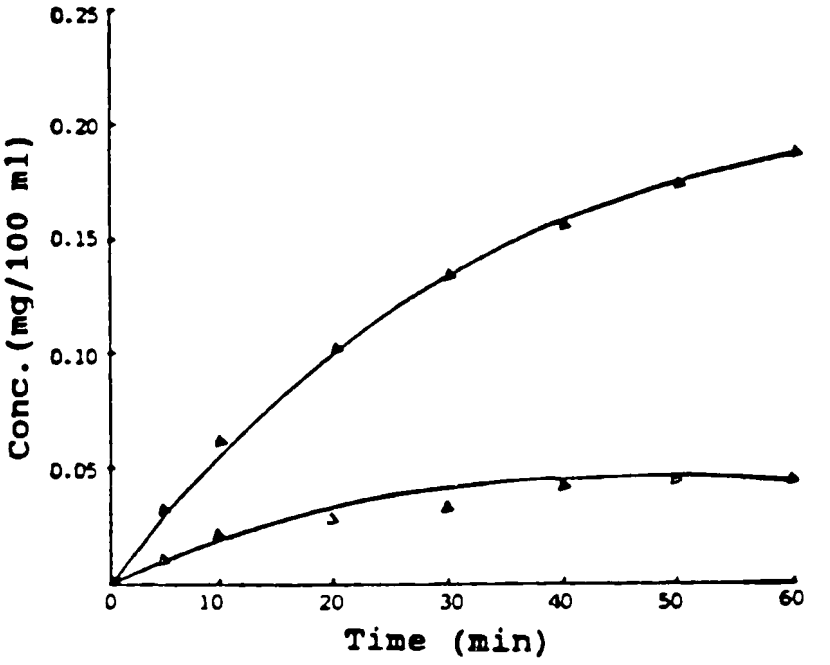

Figure 3 : Dissolution behavior of IND in HCl-KCl buffer of pH 2.0 at 37°C. Key : (△) pure IND; (▲) coprecipitate with DMPC at 16:1 ratio.

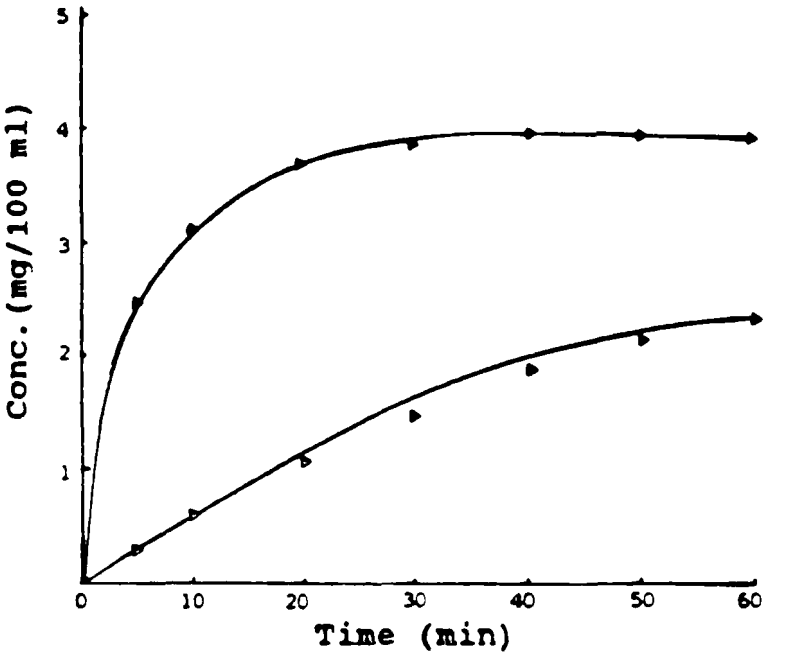

Figure 4 : Dissolution behavior of IND in phosphate buffer of pH 7.4 at 37°C. Key : (△) pure IND; (▲) coprecipitate with DMPC at 16:1 ratio.

indomethacin alone. It was also observed that the release of indomethacin was decreased with an increase in PL chain length (e.g. DPPC). This is probably due to a higher phase transition temperature (Tc) of DPPC (43°C) than the experimental temperature (37°C) which will remain in solid state at the experimental temperature. Thus, DPPC would not disperse spontaneously and decreased dissolution was observed. DMPG on the other hand improved the dissolution of indomethacin the most. Although DMPG has similar Tc as DMPC, it probably formed a complex between the negatively charged head group of DMPG and positively charged indomethacin. A dual effect, one due to a liposome forming ability and the other due to a complex formation, increased the dissolution of indomethacin the greatest.

Influence of the Coprecipitating Solvent : Previous report on griseofulvin[5] showed that only chloroform, when used as the coprecipitating solvent, could improve the dissolution of the drug. Other coprecipitating solvents had little effect on altering the rate of release of griseofulvin from coprecipitates. This report therefore studied the various solvent effect on indomethacin

dissolution. The results are shown in Table II. It can be seen that, unlike griseofulvin, other solvents improved the dissolution of indomethacin to a similar extent. It appears therefore that solvated drug is not always essential to improve the release of a drug from the coprecipitates and IND-PL could rapidly disperse into bilayers when contact is made with water and increase the saturation concentration of the drug on the surface of the particle.

Effect of pH of the Dissolution Medium : Dissolution studies were also conducted by varying the pH of the medium and the results are shown in Figure 3 and 4. Comparative studies show that the release of indomethacin at both pH 2.0 and 7.4 is higher in coprecipitate than in pure indomethacin although at pH 2.0 the rate of dissolution is much slower in both the control and coprecipitates compared to that at pH 7.4.

CONCLUSIONS

The results obtained using IND-PL coprecipitates indicate that substantially higher release rates of drug can be achieved with as little as 6% w/w phospholipids and much higher drug concentrations in the aqueous medium can be obtained within one hour compared with that obtained by the dissolution of plain indomethacin. Unlike griseofulvin[5], chloroform can be substituted by other organic solvents in making the coprecipitates to achieve the improved release of the drug. A composition of 16:1 (IND:DMPC) was found optimum for increasing the dissolution of the drug. Improved dissolution was obtained in both acidic or alkaline media. More studies are needed to determine the aging effect on dissolution and its impact on the commercialization of the product. These studies are underway and will be communicated in the next report.

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