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COMMUNICATION

# Dissolution Profiles of Flurbiprofen in Phospholipid Solid Dispersions

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## ABSTRACT

*This study is concerned with the development of a solid dispersion formulation of flurbiprofen (FLP) and phospholipid (PL) with improved dissolution characteristics. The FLP powders were blended with PL to produce FLP-PL physical mixtures or made into solid dispersions with PL by the solvent method. The FLP exhibited significantly improved dissolution rates in PL coprecipitate (coppt) compared to the physical mixtures or FLP alone. The dissolution studies suggested that less than a 20:1 ratio of FLP to PL was required to disperse FLP completely in the carrier. The coppt yielded a ninefold greater initial dissolution rate. Also, the total amount dissolved after 60 min was twofold greater at a 10:1 ratio of FLP to L-(-dimyristoyl phosphatidylglycerol (DMPG). Similar results were observed with a ratio as low as 20:1 (FLP:DMPG). Increasing the DMPG content did not increase the rate to any significant extent. Thus, a small PL:FLP ratio improved the dissolution to a significant level. Thus, an FLP:PL dispersion may have the clinical advantages of quick release and excellent bioavailability.*

## INTRODUCTION

Flurbiprofen (FLP), a potent nonsteroidal anti-inflammatory drug, is a nonselective inhibitor of prostaglandin biosynthesis in humans and is indicated for the acute or long-term treatment of the signs and symptoms of rheumatoid arthritis and osteoarthritis. Unfortunately, it has a short elimination half-life of 3.9 hr and is slightly soluble in water (1). Since the rate of FLP absorption is controlled by the release of drug from its dosage form into the gastrointestinal tract, modifications in the dissolution profile of FLP have obvious clinical significance.

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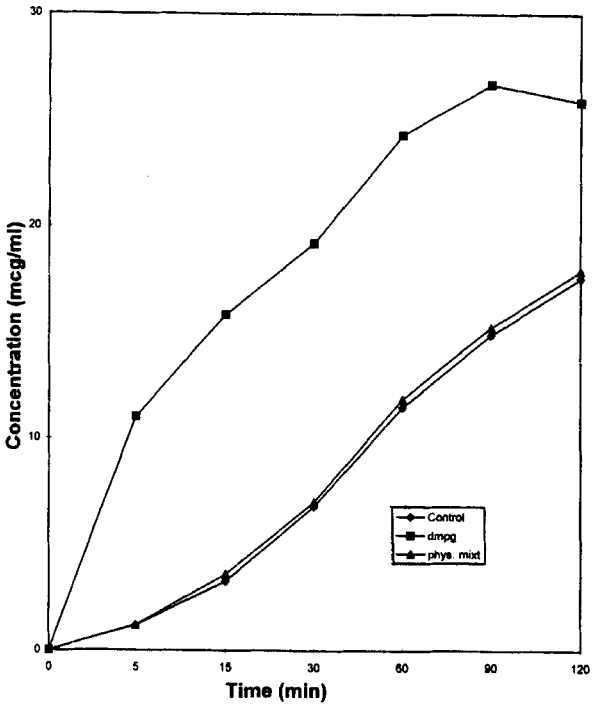


**Figure 1.** Dissolution behavior of FLP:DMPG solid dispersion system at 25°C and in distilled water.

Solid dispersions of drugs have generally been developed to improve the dissolution of poorly water-soluble drugs (2). Various water-soluble materials, such as polyvinylpyrrolidone (3), polyethylene glycols (4) and bile acids (5), have been used in the past to improve the dissolution rate and bioavailability of drugs. In these cases, the dosage form contains large proportions of carriers to be effective. It would certainly be advantageous to incorporate a minimal amount of the carrier to produce rapid dissolution of a drug from a solid dosage form. Recently, phospholipids (PLs) have been introduced to improve the dissolution profiles of drugs. Substantial increases in dissolution characteristics were observed with PL-drug compositions that have high proportions of the drug (e.g., 95% w/w) (6). The choice of PL as a codispersing agent is based on its potential advantage of spontaneous formation of liposome structures in aqueous media, which entrap various solutes either in the aqueous compartments or in the bilayers.

The purpose of the present investigation is to evaluate the effect of PL composition, concentration, and solvent characteristics on the dissolution behavior of FLP prepared as a coprecipitate (coppt) with PL.

## EXPERIMENTAL

### Materials

FLP was obtained in a powder state from Sigma Chemical Company. Pure synthetic PLs with a label claim of 98% purity (Sigma Chemical Company) were used and included L-α-dimyristoylphosphatidylcholine (DMPC), L-α-dimyristoyl phosphatidylglycerol (DMPG), L-α-distearoylphosphatidylcholine (DSPC), and egg phosphatidylcholine (EPC). Chloroform, methanol, ethanol, and other solvents were reagent grade. Demineralized water was used as the aqueous vehicle. All materials and reagents were used as received from the vendors.

### Methods

#### Preparation of Coprecipitates and Physical Mixtures

Coppts of FLP-PL were prepared by the solvent method (7) using chloroform or other solvents in a jack-

*Table 1*

*Dissolution of Flurbiprofen-Phospholipid Composition in Distilled Water at 25°C*

| Composition (FLP:PL) | Type of PL | IDR[a] (μg/ml/min) | Limiting Concentration after 60 min (μg/ml) |
|---|---|---|---|
| 1:0 | No PL | 0.24 | 11.49 |
| 20:1 | DMPG | 1.81 | 22.24 |
| 10:1 | DMPG | 2.20 | 24.30 |
| 20:1 | DPPC | 1.24 | 19.02 |
| 20:1 | DMPC | 1.90 | 22.64 |
| 10:1 | DSPC | 1.14 | 18.49 |

[a] IDR = initial dissolution rate.

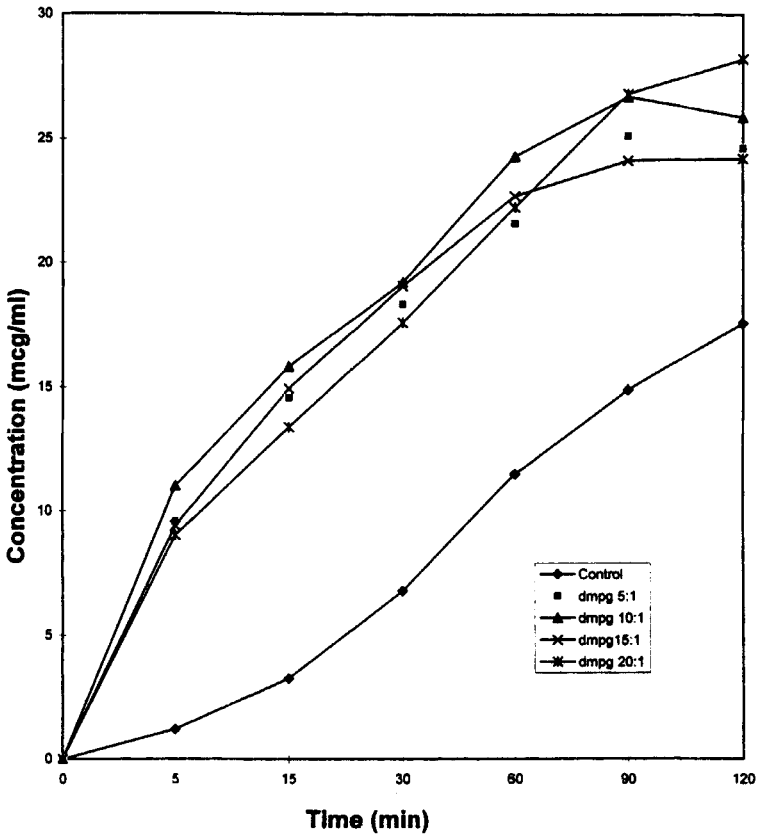


**Figure 2.** Effect of the concentration of DMPG on the dissolution of FLP coprecipitates at 25°C and in distilled water.



eted beaker with constant stirring. They were subsequently dried and examined within 24 hr. Physical mixtures were prepared by lightly triturating appropriate quantities of drug and PLs, using a small mortar and pestle, then transferring to a vacuum desiccator until ready for use.

### Dissolution Studies

The dissolution rate measurements were carried out using a Vanderkamp 7000 dissolution test apparatus (paddle method). The dissolution flasks were immersed in a water bath at 37°C. The dissolution medium (900 ml) was continuously stirred by a USP standard paddle at 100 rounds per minute. Samples were added on the surface of the stirred dissolution medium at the beginning of the study. At different time intervals, 3-ml samples were withdrawn automatically by a Vanderkamp 8000 dissolution fraction collector using a 10-μm porosity filter screen. Measurement of concentrations of FLP was carried out employing a Shimadzu ultraviolet (UV)/visible scanning spectrophotometer at a wavelength of 247 nm. Interference by the excipients was not observed during analysis. Experiments were run in duplicate, and the results were averaged. The difference between highest and the lowest readings was always less than 6%.

## RESULTS AND DISCUSSION

### Dissolution Studies

Figure 1 shows the dissolution profile of FLP from PL solid dispersions prepared at a ratio of 10:1 (FLP:DMPG). The dissolution profiles of the pure FLP and the physical mixture 10:1 (FLP:DMPG) are also shown for comparison. The figure clearly indicates a greater rate and extent of dissolution of FLP from the coppt than the corresponding physical mixture or the pure compound. Table 1 shows that the coppt at a ratio of 10:1 (FLP:DMPG) yielded a 9.3-fold greater initial dissolution rate (computed over the first 5 min of dissolution) than the pure FLP. It also produced a 2.1-fold greater limiting concentration than the pure FLP, which is essentially the

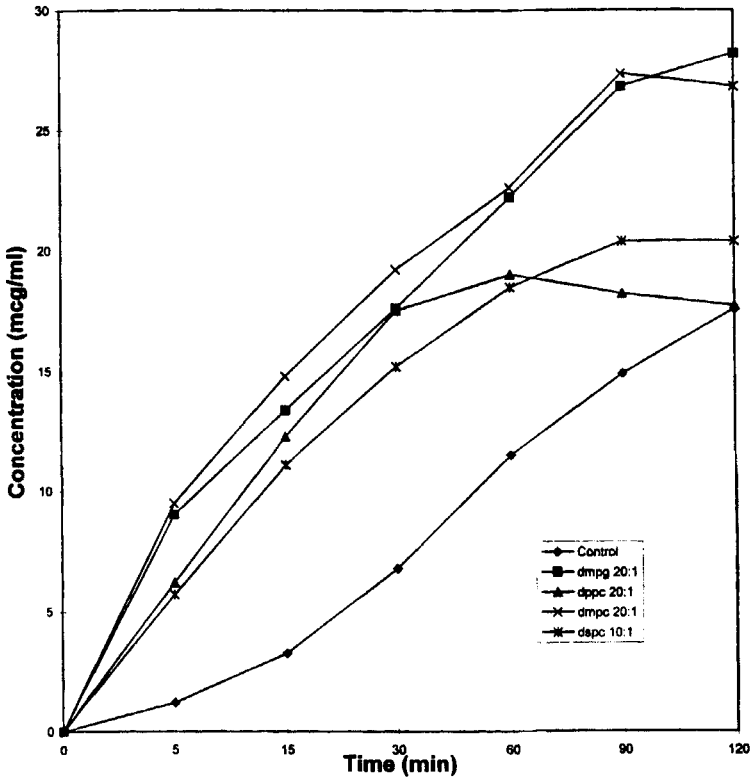


**Figure 3.** Effect of phospholipid composition on the dissolution of FLP:PL coprecipitates at 25°C and in distilled water.



total amount dissolved after 60 min. Figure 1 also shows that the initial rate of release of FLP from coppts is greatly improved during the first 10 min of dissolution; after that, the rates of drug release from both coppt and pure FLP are very similar. This result is consistent with similar studies with carbamazepine (8).

Figure 2 shows the dissolution profiles of FLP solid dispersions prepared at various ratios of FLP:DMPG. It shows that increasing the DMPG concentration from 10:1 to 5:1 does not increase the dissolution to any significant level. On the other hand, at a FLP:DMPG ratio of 20 to 1, the dissolution profile looks very similar to the higher FLP:DMPG ratios. These results suggest that a ratio of 20 to 1 is sufficient to disperse crystalline FLP completely in DMPG to produce a coppt.

### Effect of Phospholipid Composition

The rates of dissolution of FLP from coppts at FLP:PL ratios of 10:1 for DMPG, EPC, DMPC, DPPC, or DSPC are compared in Fig. 3. It is apparent that the initial dissolution rate and the limiting concentration after 60 min are greater for all coppts than that obtained from the dissolution of pure FLP. Furthermore, the release of drug decreases with an increase in the chain lengths of fatty ester of the PL. For example, DPPC and DSPC have higher chain lengths than DMPC or EPC. Thus, DPPC and DSPC both show less improvement in the release of the drug than DMPC or EPC, as can be seen in Fig. 3. A PL improves the dissolution of a drug by its ability to form liposomes when in contact with water (6). The increase in the release of 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 behaves like DMPC or EPC in the formation of the crystalline lattice of the coppt, then the decreased release of FLP when combined with a longer chain compound may be related to the phase transition temperature $T_c$ and the corresponding physical state at 25°C. The $T_c$'s of EPC, DMPC, DPPC, and DSPC are 1°C, 23°C, 43°C, and 58°C (9), respectively. Since the $T_c$'s of DPPC and DSPC are above 25°C,

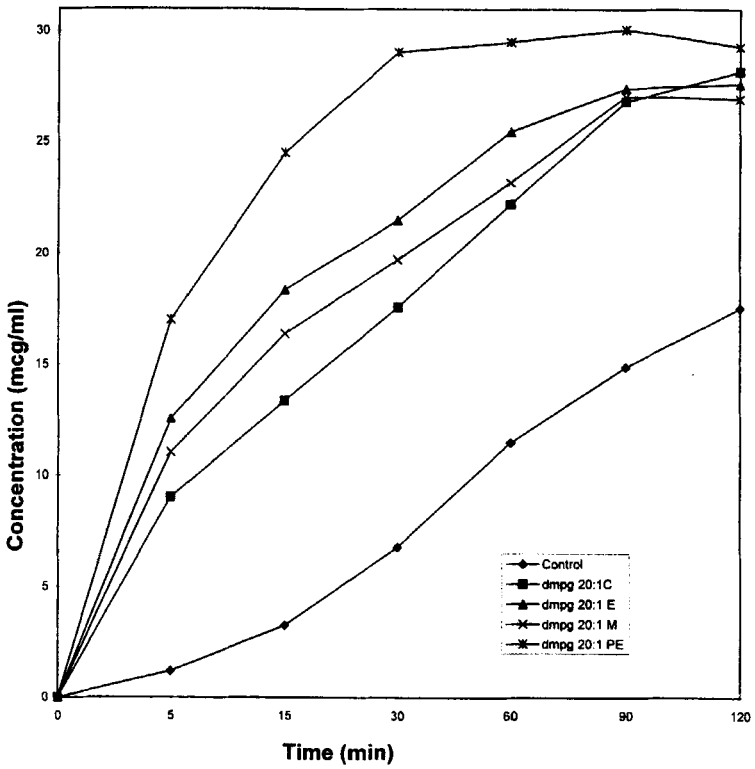


**Figure 4.** Effect of the coprecipitating solvent on the dissolution of FLP:DMPG (20:1) coprecipitates at 25°C and in distilled water.



it would remain in solid state at the experimental temperature and would not disperse spontaneously, thereby decreasing the dissolution, as was observed. On the other hand, DMPG improved the rate of dissolution of FLP the most. DMPG has a net negative charge on its polar head group, which could form an electrostatic complex with the amino group of FLP. This favorable orientation could have increased FLP concentration in the vicinity of DMPG liposomes and hence could have increased the initial rate of dissolution, as was observed.

### Influence of the Coprecipitating Solvent

It is reported (6) that the solvent for a coppt sometimes plays a role in improving the dissolution characteristics of drugs in aqueous medium. Therefore, this study was conducted to ascertain the role of the solvent on the release of FLP. The results are given in Fig. 4. It is obvious from the table that all of the solvents produced a similar rate and amount of drug release. Thus, it can be concluded that solvents do not play a role in the dissolution pattern of the FLP coppt. Although a small amount of the residual solvent may be present even after a long period of drying, it does not seem to have any effect on the rate of dissolution of the FLP coppt. Simply, FLP combines with PL in a manner that provides an appropriate orientation of the PL molecules to enable rapid dispersion into bilayers when contact is made with water.

## CONCLUSION

The coppts of FLP with various PLs in different proportions showed faster dissolution characteristics in vitro than the plain FLP or FLP-PL physical mixtures. A PL with a phase transition below the body temperature yields the best possible result in improving the dissolution characteristics of the drug. DMPG at a ratio of 20:1 (drug:PL) provided the optimum combination for improved dissolution of FLP. This ratio provided a ninefold greater initial dissolution rate, and the extent of dissolution was improved twofold after 60 min. The coprecipitating solvent does not influence the dissolution characteristics of the FLP from the coppts. Therefore, FLP-PL coppts may have the clinical advantages of quick in vivo release and better bioavailability compared to the FLP alone.

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