DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(10), 1221-1229 (1993)

IMPROVED DISSOLUTION OF INDOMETHACIN IN COPRECIPITATES WITH PHOSPHOLIPIDS-II

Gopal K. Potti, Joseph F. Gallelli, Clement O. Akogyeram*, Bijan Ahmadi and Muhammad J. Habib*,+

Pharmacy Department, Warren G. Magnuson Clinical Center
National Institute of Health, Bethesda, MD

*College of Pharmacy and Pharmacal Sciences
Howard University, Washington, D.C.

ABSTRACT

In our previous report[1] we showed that coprecipitates of Indomethacin (IND)-Phospholipids (PL) improved the dissolution profiles of the drug significantly. This study was undertaken to evaluate the mechanism of such improved dissolution and their commercial aspects upon long term storage conditions and by comparing the results with existing brands of indomethacin capsules. Aging studies of IND-PL were conducted after about one year of the preparation of the coprecipitates and no significant changes in the dissolution rates were observed from the fresh formulations. Powder x-ray diffraction data showed no crystal formation of the coprecipitates. Rather indomethacin was uniformly dispersed in an amorphous state in a solid matrix of phospholipids. The coprecipitates were also formulated into capsules and compared with Indocin^{R}, a commercial brand of Indomethacin. Our capsule formulation yielded about 2 fold greater initial dissolution rate as well as total amount dissolved. Phospholipid formulations thus have good industrial potential to increase the dissolution of poorly water soluble drugs.

INTRODUCTION

Solid dispersion of drugs have generally been developed to improve the dissolution of poorly water-soluble drugs[2]. Many of these have high carrier:drug ratios and some have been

+To whom inquiries should be directed.

reported to have aging problems[3]. Recently, coprecipitates of solvated drugs and phospholipids (as low as 5% phospholipid) have yielded enhanced dissolution properties [4,5] but were found to age and lose their coprecipitate advantage[5]. In our previous report[1,6] it was shown that coprecipitates of indomethacin (IND)-phospholipids (PL) improved the dissolution profile of IND significantly. One of the important criteria for commercialization of any product from laboratory research to the market is the stability and aging of the formulation in course of time. The present study is therefore an extension of the previous report to investigate the mechanism of such improved dissolution of IND and determine the prospects of commercialization of such formulations by studying the aging of the formulations.

MATERIALS

Indomethacin was obtained in a powder state[7]. Pure synthetic phospholipids with label claim of 98 percent purity included : L-α- dimyristoylphosphatidyl glycerol[7] (DMPG), L-α-distearoylphosphatidylcholine[7] (DSPC) and cholesterol (CHOL). Chloroform, methanol, ethanol and other solvents were reagent grade solvents. Demineralized distilled water was used throughout.

METHODS

Preparation of Coprecipitates and Physical Mixtures : Coprecipitates of IND-PL were prepared by the solvent method[8] using chloroform or other solvents in a jacketed beaker by constant stirring, which were subsequently dried and examined within 24 hours. Aging studies at room temperature were conducted after about 12 months of preparation of the coprecipitates. Physical mixtures were prepared by triturating appropriate quantities of drug and phospholipids using a small mortar and pestle then transferring to a vacuum desiccator until ready for use.

Preparation of Capsules : The following formula was used to prepare the capsules :

IND-PL coprecipitate (50 mg active ingredient) = 55.0 mg; Lactose, anhydrous NF 74.0 mg; Pregelatinized Starch NF = 60.0 mg; Sodium Starch Glycolate NF = 9.5 mg; Colloidal Silicon Dioxide = 1.0 mg; Magnesium Stearate NF = 0.5 mg; total blend weight = 200.0 mg. The coprecipitates, pregelatinized starch and magnesium stearates were passed through a #60 screen separately. The coprecipitate and pregelatinized starch were mixed for 5 minutes in a glass mortar by means of a stainless steel spatula. Lactose, anhydrous was added and mixed for 10 minutes, sodium starch glycolate was added and mixed for 5 minutes, colloidal silicon dioxide was added and mixed for 5 minutes, magnesium stearate was added and mixed for another 8 minutes. Finally, the blend was collected in a polyethylene bag and weighed and handfilled into

a #2 pink opaque capsule at an average weight of 262 mg/capsule. Control capsules were prepared exactly the same way as above except that pure IND (50 mg/capsule) was used instead of coprecipitates and the net weight was adjusted by using lactose.

Dissolution Study : The dissolution rate measurements were run using a Vanderkamp 600 dissolution test apparatus (Paddle method). 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 1 μm porosity filter screen. Measurement of concentrations of IND was carried out employing a HP 8450A Diode Array UV/visible scanning spectrophotometer at 318 nm. A 50 mg IND equivalent sample was dispersed in the medium in each instance. Experiments were run in duplicate and the results averaged. The difference between the two readings were always within 5%. Distilled water was used as the dissolution medium.

X-ray Diffraction Study : Samples for low-angle powder x-ray diffraction studies were uniformly dispersed on a glass slide. Diffraction spectra were then obtained by using Scintag, USA Corp. diffractometer with a monochromated Cu-K_α radiation.

RESULTS AND DISCUSSIONS

The dissolution of a drug from a solid dispersion system consists of three processes : 1) the coprecipitate interacts with water in its vicinity[9], 2) finely dispersed drug in the matrix is released, and 3) solubilized drug is supersaturated in the diffusion layer[8]. The release of IND from a lipid-containing coprecipitate is postulated to involve the release of amorphous IND in step 2) similar to the release of dispersed drug from a bioerodable matrix polymer drug delivery system. In addition, the liposome forming ability of phospholipids also may play a role in the process.

Dissolution Studies : The dissolution of IND from a coprecipitate was found to be considerably greater than from physical mixtures or pure IND even after one year of aging. Typical dissolution profiles using various phospholipids at a 16:1 weight ratio are given in Figure 1. It is apparent that the initial dissolution rate (IDR) (computed over the first 5 minutes of dissolution) and the total amount dissolved after 60 minutes from the coprecipitates exceeded those of pure IND or the corresponding physical mixture. But different phospholipids or phospholipid combinations showed different degrees of improvement in the dissolution profiles. Thus, DSPC and DMPG:CHOL (1:1) showed less improvement in the release of the drug than

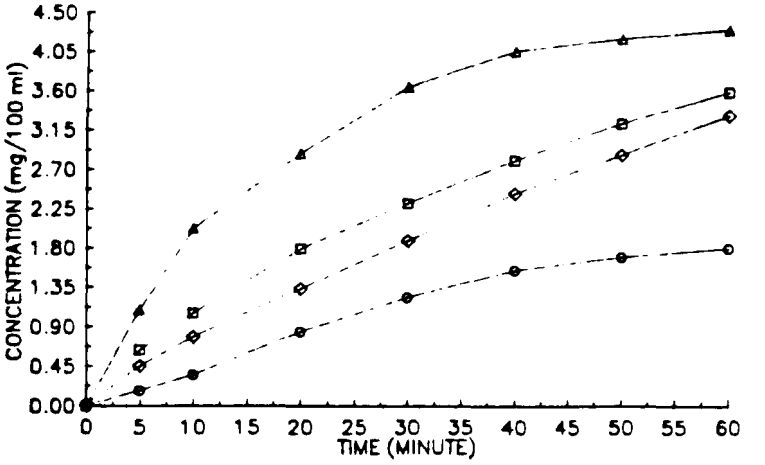

Figure 1 : Dissolution behavior of IND:PL solid dispersion system at 37°C and in distilled water. Key : (○) pure IND; Coprecipitates at a 16:1 ratio of IND:PL - (◇) DSPC; (□) DMPG:CHOL (1:1); (△) DMPG.

DMPG alone. Phospholipid improves the dissolution of a drug by their ability to form liposomes which increases the intrinsic solubility of the drug in the medium due to a partitioning process. Although DSPC or DMPG:CHOL combination behaves similarly to DMPG in this respect, DSPC has a phase transition temperature (Tc) of 58°C whereas DMPG has a Tc of 23°C (10). Since the Tc of DSPC is too far above 37°C, the experimental temperature, it would remain in solid state and would not disperse spontaneously. CHOL is known to have a stabilizing or rigidifying effect on liposomes (11). Therefore, a combination with CHOL also would remain in solid state and thus decreased dissolution was observed. Figure 2 shows the ageing effect on the rate of dissolution of IND and is compared with a fresh aging and the pure drug. The one year old sample retained the similar improvement in dissolution as the freshly prepared aging of IND. It is therefore apparent that aging of IND:DMPG coprecipitate did not change the dissolution profile to any significant extent. Table I shows the effect more quantitatively. The IDR of the coprecipitate exhibited an increase of 6.0 fold with as little as

6% of DMPG in the total sample (16:1 weight ratio) when examined a fresh sample and an increase of 5.5 fold when examined after one year of preparation. In contrast, the IDR of the physical mixtures did not increase compared to pure IND. Values of concentration of IND

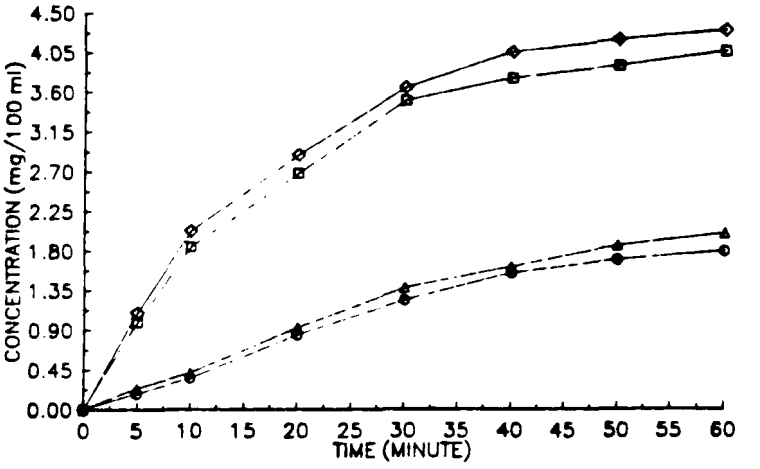

Figure 2 : Aging effect on the dissolution behavior of IND:DMPG (16:1) coppts. at 37°C and in distilled water. Key : (○) pure IND; (△) physical mixture; (□) one year old coppts; (◇) freshly prepared coppts.

TABLE I

Dissolution of IND-DMPG Composition at 37°C and in Distilled water.

Composition (wt. ratio)	Initial Dissolution rate (mg/100 ml/min)	Concn. after 60 min(mg/100 ml)
1:0 (pure IND)	0.036	1.8
16:1 (Physical Mixt)	0.040	2.0
16:1 (fresh coppt)	0.217	4.3
16:1 (1 year old coppt)	0.197	4.0

TABLE II

Comparison of % Dissolved from IND-DMPG (16:1) Coppts, Physical Mixtures and Pure IND.

Composition	Percent Dissolved in			
	10 min	20 min	40 min	60 min
Pure IND	5.4	12.7	23.2	27.0
Physical mixture(10:1)	6.3	13.9	24.3	30.0
Fresh Coppt. (10:1)	30.4	43.3	60.9	64.5
1 yr old Coppt. (10:1)	27.7	40.2	56.4	60.9

obtained after 60 minutes from both freshly prepared and one year old sample indicated clearly a substantial increase in the apparent solubility of IND in the dissolution medium. The superior dissolution of coprecipitates is further exemplified by the data in Table II. Percent dissolved of IND from coprecipitates is more than twice that dissolved from physical mixtures at the corresponding times.

Other coprecipitating solvents equally improved the rate of dissolution even after 1 year of aging[8]. Commercialization of this formulation is thus possible. Coprecipitates were then formulated into capsules (freshly prepared and one year old) and dissolution studies conducted and the results are compared with the dissolution profile of Indocin[R] capsule taken from a commercial outlet. The results are shown in Figure 3 where it is apparent that our formulation yielded about 2 fold greater initial dissolution rate as well as total amount dissolved. This proves the superiority of a coprecipitate formulation and it is possible to improve the bioavailability of Indomethacin by using this method.

The X-ray Diffraction Patterns : In our previous report[8] we have postulated that the release of IND from the coprecipitate is due to the release of amorphous IND from the IND-PL solid dispersion system. The rate and extent of drug dissolving is influenced by the erosion kinetics of the matrix material in addition to its liposome forming ability of the phospholipids. To gain insight into these mechanisms powder x-ray diffraction spectra were taken. Figure 4 shows the diffraction patterns of pure IND, IND:DMPC physical mixture (16:1) and coprecipitate (16:1)

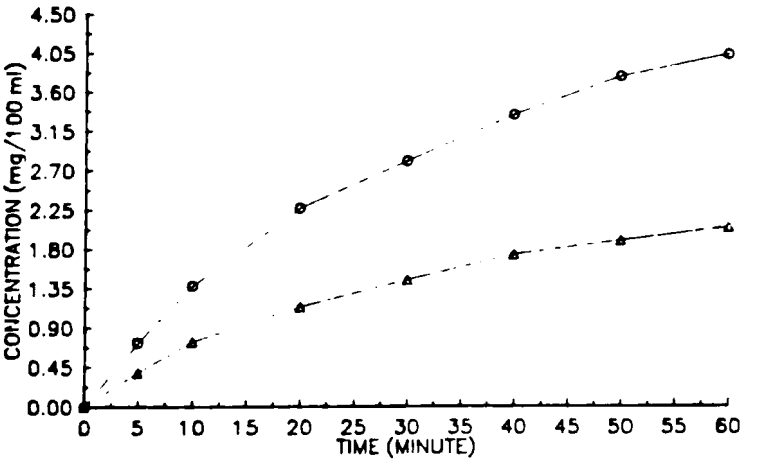

Figure 3 : Dissolution of IND solid dispersion capsules at 37°C and in distilled water. Key : (⊙) IND:DMPG (16:1) capsule;(△)Indocin® capsule.

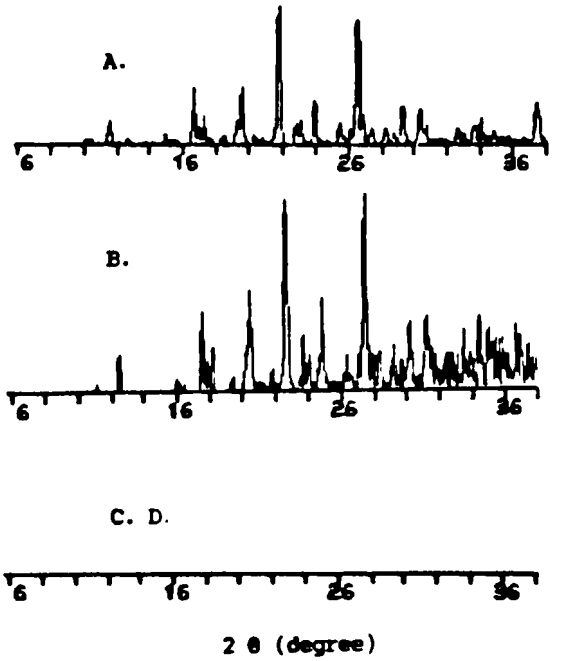

Figure 4 : Low angle powder X-ray diffraction spectra of IND (A), 16:1 IND:DMPG physical mixture (B), 16:1 IND:DMPG coprecipitate fresh sample (C) and 16:1 IND:DMPG coprecipitate one year old sample (D).

both freshly prepared and one year old sample. The crystalline properties of IND are characterized by two major and three minor peaks in the spectrum, whereas the DMPC spectrum displays the properties of an amorphous material (4). The identifiable peaks of IND are also visible in the spectrum of the 16:1 physical mixture even though there appears that some broadening and loss of detail of the peaks has occurred. The positions of the diffraction peaks of IND were not altered compared with that of the pure compound. But with the coprecipitates of IND-DMPC we found no identifiable peaks of IND. It shows therefore that IND lost its crystal structure upon coprecipitation. This suggests that DMPC interact with IND during and after the solvent removal process and synergetically inhibit or retard the crystallization of the drug. It can be concluded that IND was uniformly dispersed in an amorphous state in a solid matrix of DMPC. X-ray diffraction spectrum of one year old sample were also shown in Figure 4. It is identical with the freshly prepared sample of coprecipitates. This probably explains why the aging of the coprecipitate could still retain the improved dissolution of the freshly prepared coprecipitate. This is quite contrary to a previous report on griseofulvin-DMPC coprecipitate where the improved dissolution was totally dependent on solvent and time.

CONCLUSIONS

The results of IND-PL coprecipitates indicate that these formulations have good industrial potential to increase the dissolution of poorly water soluble drugs. The mechanism of improved dissolution is believed to involve the conversion of the crystal structure of IND into an amorphous form and continuous erosion of the drug from the matrix of PL. This effectively increases the saturation concentration of the drug. The IND:DMPG combination provided the best result and an optimum ratio of 16:1 was observed. Aging of any of the coprecipitates did not loose or reduce the improved dissolution of the coprecipitates. Chloroform can be substituted by ethanol or methanol if that became necessary for the commercialization of the formulation. Phospholipid solid dispersion of indomethacin therefore may have the clinical advantages of quick release and excellent bioavailability of the drug.

REFERENCES

1. M.J. Habib and B. Ahmadi, Improved dissolution of Indomethacin in coprecipitates with phospholipids., Pharm. Res. (suppl.)7(9), s-146, (1990).
2. W.L. Chiou and S. Riegelman, Increased dissolution of water-insoluble cardiac glycoside and steroid via solid dispersion in polyethylene glycol 6000, J. Pharm. Sci., 60, 1569, (1971).

3. J.L. Ford and M.H. Rubinstein, Aging of Indomethacin-polyethylene glycol 6000 solid dispersion. Pharm. Acta. Helv., 54, 353, (1979).
4. S. Venkataram and J.A. Rogers, J. Pharm. Sci., Characteristics of drug-phospholipid coprecipitates I:physical properties and dissolution behavior of griseofulvin-dimyristoylphosphatidylcholine systems. 73, 757, (1984).
5. G.K. Vudathala and J.A. Rogers, Dissolution and controlled release of Fludrocortisone acetate from coprecipitates with phospholipids. Pharm. Res. (suppl.), 6(9), s-161 (1989).
6. M.J. Habib, B. Ahmadi, G.K. Potti and J. F. Gallelli, Improved dissolution of Indomethacin in coprecipitates with phospholipids-I. Drug Dev. Ind. Pharm. (1991), in press.
7. Sigma chemical company, St. Louis, Missouri.
8. W.L. Chiou and S. Riegelman, Pharmaceutical applications of solid dispersion system. J. Pharm. Sci., 60, 1281, (1971).
9. H. Sekikawa, J. Fujiwara, T. Naganuma, M. Nakano and T. Arita, Dissolution behavior and gastrointestinal absorption of phenytoin in phenytoin-polyvinylpyrrolidone coprecipitate. Chem. Pharm. Bull., 26, 3033 (1978).
10. B.D. Ladbrooke and D. Chapman, Thermal analysis of lipids, proteins and biological membranes. A review and summery of some recent studies. Chem. Phys. Lipids., 3, 304, (1969).
11. M.D. Houslay and K.K. Stanley in "Dynamics of Biological Membranes" John Wiley & Sons publishers, pp. 71-81, (1982).