DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 18(1), 135-141 (1992)

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION OF INDOMETHACIN AND PHENYLBUTAZONE BY CHOLIC AND DEOXYCHOLIC ACID CONJUGATES

Meena Tripathi, D.V. Kohli and R.K. Uppadhyay
Department of Pharmaceutical Sciences,
Dr. H.S. Gour Vishwavidyalaya, SAGAR - 470 003 (M.P.) INDIA

SUMMARY

Amino acids, cysteine and phenylalanine were conjugated with bile acids, cholic and deoxycholic acid to prepare cysteinocholic acid [N - (3α, 7α, 12α - trihydroxy - 24 - oxocholan - 24 - yl) cysteine], phenylalanocholic acid [N - (3α, 7α, 12α - trihydroxy-24-oxocholan-24-yl) phenylalanine], cysteinodeoxycholic acid [N - (3α, 12α-dihydroxy-24-oxocholan-24-yl) cystiene] and phenylalanodeoxycholic acid [N - (3α, 12α-dihydroxy-24-oxocholan-24-yl) phenylalanine]. Subsequently, they were converted into their sodium salt. These compounds were evaluated for their surfactant properties mainly solubilization and dissolution enhancing properties. The drugs selected for this study were poorly water soluble non-steroidal anti-inflammatory drugs, indomethacin and phenylbutazone. All the biosurfactants enhanced the solubility and dissolution of both the drugs.

INTRODUCTION

In human bile, bile acids are conjugated with amino acids, glycine and taurine. These conjugates occur in bile as their sodium salt. The role of bile salts in the absorption of fat and fat soluble vitamins is well known. The effect of these conjugated bile salts on the solubility of poorly water soluble drugs like steroid hormones [1], antibiotics [2], dyes [3], non-steroidal anti-inflammatory drugs [4] has been studied. In these studies bile salts and conjugated bile salts found in human bile were used. No attempt has been made to conjugate other amino acids and study their effect on solubility and dissolution of

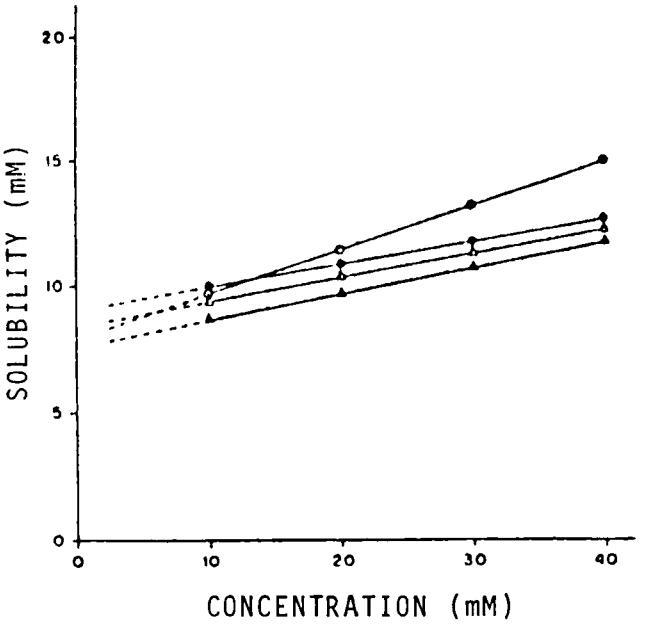

Fig. 1

Solubility curves of indomethacin in phosphate buffer pH 7.2 at 25°C. (○) -Sod. CySHdeoxycholate; (●) -Sod. CySHcholate; (△) -Sod. Phedeoxycholate and (▲) -Sod. Phecholate.

poorly water soluble drugs. Therefore, cholic and deoxycholic acid conjugates of cysteine and phenylalanine were synthesized and studied.

MATERIALS AND METHOD

Materials:

Deoxycholic acid (Fluka, Buchs Switzerland), cholic acid, cysteine and phenylalanine (BDH Pharmaceuticals, London) were used as received. All solvents were analytical grade reagents.

Preparation of Cholic acid and Deoxycholic acid conjugates :

Sodium salt of cysteinocholic acid, phenylalanocholic acid, cysteinodeoxycholic acid and phenylalanodeoxycholic acid were

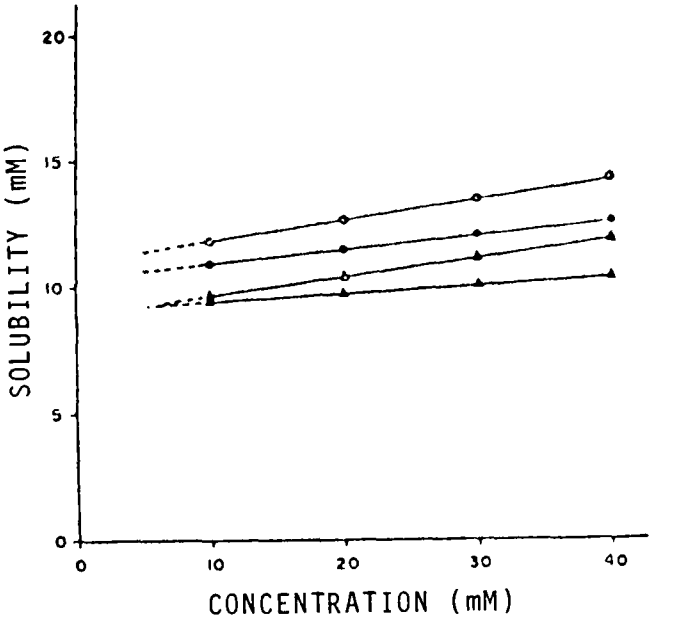

Fig. 2

Solubility curves of phenylbutazone in phosphate buffer pH 7.2 at 25°C. (○) -Sod. CySHdeoxycholate; (●) -Sod. CySHcholate; (△) -Sod. Phedeoxycholate and (▲) -Sod. Phecholate.

synthesized by the method reported earlier [5]. The synthesized compounds were characterised by IR, MS, and elemental analysis. The purity of the synthesized compounds was checked by TLC.

Solubility studies :

The solubilities of drugs were determined in 1/15 M phosphate buffer pH 7.2 containing various concentrations of bio-surfactants at 25° [6].

Dissolution studies :

The dissolution studies were carried out in 1/15 M phosphate buffer pH 7.2 at 25° [7].

TABLE - 1

Saturation Ratio for Indomethacin and Phenylbutazone

S. No.	Name of Compound	Saturation ratio*	Mol. of micellar drug	
			Mol.of micellar indomethacin	Biosurfactant Phenylbutazone
1.	SCD		0.180	0.083
2.	SCC		0.120	0.060
3.	SPD		0.113	0.050
4.	SPC		0.087	0.040

* Slope of the linear portion of the solubilization curve determined by least squares method.

SCD- Sodium cysteino deoxycholate; SCC- Sodium cysteinocholate; SPD- Sodium phenylalano deoxycholate; SPC- Sodium phenylalanocholate

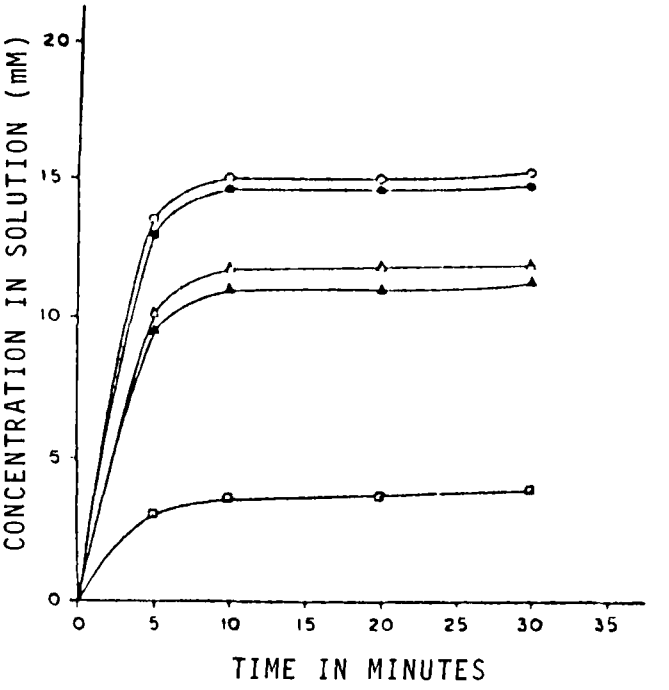

Fig. 3

Dissolution curves of indomethacin in phosphate buffer pH 7.2 of 25°C. (○) - Sod. CySHdeoxycholate; (●) - Sod. CySHcholate; (△) - Sod. Phedeoxycholate; (▲) - Sod. Phecholate and (□) - Control.

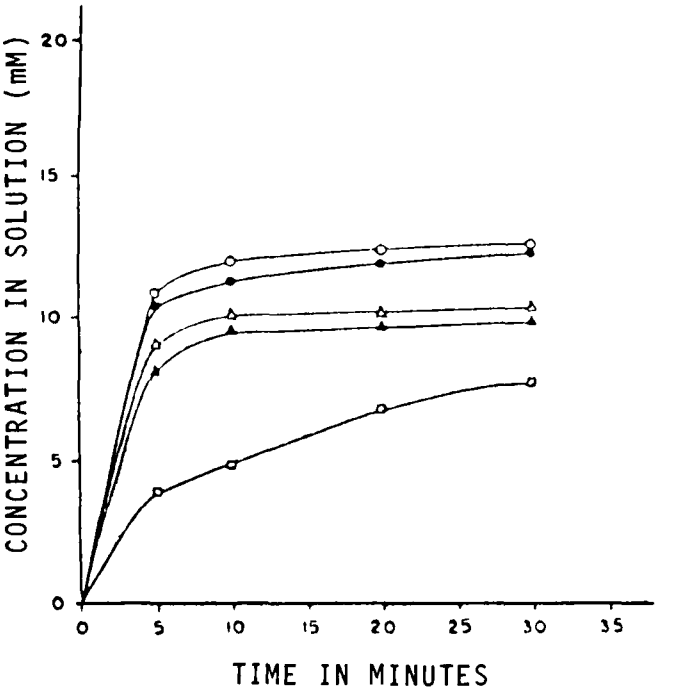

Fig. 4

Dissolution curves of phenylbutazone in phosphate buffer pH 7.2 at 25°C. (○) - Sod. CySHdeoxycholate; (●) - Sod. CySHcholate; (△) -Sod. Phedeoxycholate; (▲) - Sod. Phecholate and (□) - Control.

RESULTS AND DISCUSSION

Figures 1 and 2 show the solubilization curves of indomethacin and phenylbutazone with synthesized compounds. The solubility of both the drugs increases with increase in the concentration of biosurfactant. The solubility of indomethacin is enhanced most by sodium cysteinodeoxycholate. Similar results are obtained for phenylbutazone but solubility is enhanced to a lesser extent.

The slope of the linear portion of the solubilization curve represents the ratio of micellar drug to micellar bile salt and

is termed the saturation ratio [8]. As shown in the table-1 the saturation ratio for indomethacin are higher as compared to that for phenylbutazone, indicating that the bile salt micelles display a significantly higher affinity for indomethacin molecule. The solubilization has been considered to occur at four sites, inclusion in the hydrocarbon interior of the micelle; deep penetration into the palisade layer and adsorption on the surface of the micelles [9]. The cholate and deoxycholate micelles are formed by hydrophobic association of rigid hydrocarbon backs of the steroid nuclei in such a way that hydrophilic sides containing the hydroxyl groups and the negatively charged ionic groups are exposed to water [10]. At pH 7.2 there is an electronic similarity between indomethacin and biosurfactant as both have carboxylate groups, this would predominately be incorporated deep in the palisade layer of the biosurfactant micelles resulting in mixed micelle formation. At pH 7.2 phenylbutazone forms a mesomeric anion [11] so it is not incorporated into the palisade layer. Enhanced solubilization of phenylbutazone may be attributed to wetting.

The results of dissolution studies (Fig. 3 & 4) show that the synthesized compounds enhance the dissolution of these drugs. However, further studies are required to evaluate its in vivo performance.

REFERENCES

1. Thakkar, A.L., **J. Pharm. Sci., 59**, 1499 (1970).

2. Bates, T.R., Gibaldi, M. and Kanig, J.L., **J. Pharm. Sci., 55**, 191 (1966).

3. McBain, J.W., Merrill, R.C. and Vinograd, J.R., **J. Am. Chem. Soc., 63**, 607 (1941).

4. Miyazaki, S., Inoue, H., Yamahira, T. and Nadai, T., **Chem. Pharm. Bull., 27**, 2468 (1979).

5. Gauthier, B. and Nguyen, H.Q., **Ann. Pharm. Franc., 5**, 556 (1947).

6. Miyazaki, S., Yamahira, T., Morimoto, Y. and Nadai, T., **Int. J. Pharm., 9**, 303 (1981).

7. Goyal, V.C., Kohli, D.V. and Uppadhyay, R.K., **Indian Drugs, 19**, 233 (1982).

8. Hofmann, A.F., **Biochem. J., 57**, 57 (1963).

9. Nakagawa, T., Non-ionic surfactants, vol. 2, Marcel Dekker, Inc., N.Y., 1967.

10. Small, D.M., Penkett, S.A. and Chapman, B., **Biochem. Biophys. Acta, 176**, 178 (1969).

11. Stella, V.J. and Pipkin, J.D., **J. Pharm. Sci., 65**, 1161 (1976).