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Notes

Effect of cholic and deoxycholic acid conjugates on solubility and dissolution of indomethacin and phenylbutazone

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Summary

The bile acids, cholic acid and deoxycholic acid, were conjugated with the tripeptides, glycylglycylglycine and alanylglycylglycine, to prepare the sodium salts *N*-[3α,7α,12α-trihydroxy-24-oxocholan-24-yl]glycylglycylglycine, *N*-[3α,7α, 12α-trihydroxy-24-oxocholan-24-yl]alanylglycylglycine, *N*-[3α,12α-dihydroxy-24-oxocholan-24-yl]glycylglycylglycine and *N*-[3α,12α-dihydroxy-24-oxocholan-24-yl]alanylglycylglycine. The effect of these compounds on the solubility and dissolution behaviour of the poorly water-soluble drugs indomethacin and phenylbutazone was investigated. All the biosurfactants enhanced the dissolution and solubility of both the drugs in phosphate buffer pH 7.2 at 25°C.

The role of bile components such as bile salts and lecithin in the intestinal absorption of fats and fat-soluble vitamins is well known. The ability of bile salts to solubilize steroid hormones (Thakkar, 1970), antibiotics (Bates et al., 1966; Goyal et al., 1982), dyes (McBain et al., 1941), non-steroidal anti-inflammatory drugs (Miyazaki et al., 1979, 1980), etc., has been studied. The bile salts used in all these studies, are found in human bile, i.e. sodium cholate, sodium glycocholate, sodium taurocholate and sodium deoxycholate. No attempt has been made to change the structure of the side chain of bile acids. In the present investigation the carboxyl group present in cholic acid and deoxycholic acid was conjugated with tripeptides (glycylglycylglycine and alanylglycylglycine). The effect of this change in the structure of side chain was studied on the solubility and dissolution of the non-steroidal anti-inflammatory drugs, indomethacin and phenylbutazone.

The synthesis of tripeptide conjugates of cholic acid and deoxycholic acid was carried out by a modified procedure reported earlier (Gauthier and Nguyen, 1987).

The solubilities of drugs were determined in M/15 phosphate buffer pH 7.2 containing various concentrations of surfactants at 25°C. Excess amounts of drugs were suspended in biosurfactant solutions. The suspensions were shaken for 24 h. Aliquots were filtered and assayed spectrophotometrically using a Shimadzu UV-190 double-beam spectrophotometer. The results are shown in Fig. 1.

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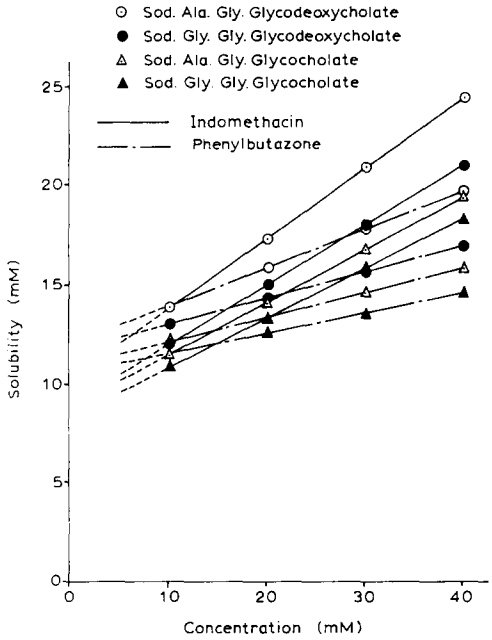

Fig. 1. Solubilization curves of indomethacin and phenylbutazone in phosphate buffer pH 7.2 at 25 °C.

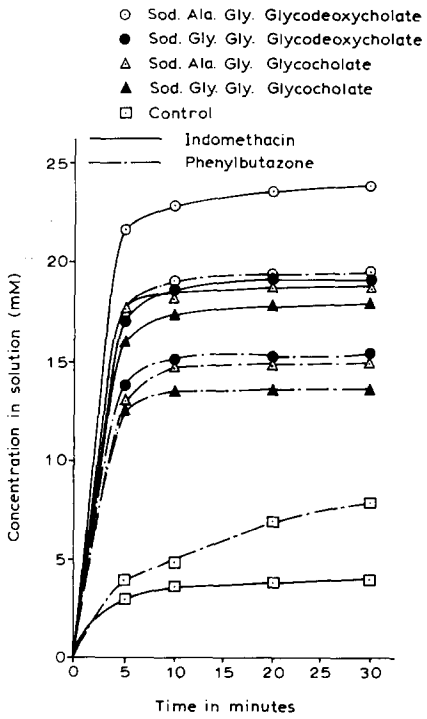

Fig. 2. Dissolution curves of indomethacin and phenylbutazone in phosphate buffer pH 7.2 at 25 °C.

The dissolution studies were carried out in phosphate buffer pH 7.2 at 25 °C. The concentration of drug dissolved was determined spectrophotometrically using the above Shimadzu spectrophotometer. The synthesized compounds were found not to interfere with the spectrophotometric analysis at the concentration present in the diluted samples. The results are shown in Fig. 2.

A large number of surface-active agents are characterized by a molecular structure which has a clear cut polarity between hydrophilic and hydrophobic parts of the molecule. The common dihydroxy and trihydroxy bile salts, on the other hand, are steroids which possess a rigid cyclopentanophenanthrene nucleus, on one side of which are clustered hydroxyl groups and on the other, the methyl groups. Protruding from one end of the steroid nucleus is a short aliphatic chain terminating in a strongly hydrophilic group. The molecule contains one hydrophobic side, one hydrophilic side and a short hydrophilic tail. Because of their

TABLE 1

Saturation ratio for indomethacin and phenylbutazone

S. No.	Name of compound	Saturation ratio [a] (mol micellar drug/mol micellar surfactant)	
		Indomethacin	Phenylbutazone
1.	Sodium *N*-[3α,7α,12α-trihydroxy-24-oxocholan-24-yl] glycylglycylglycine	0.260	0.106
2.	Sodium *N*-[3α,7α,12α-trihydroxy-24-oxocholan-24-yl] alanylglycylglycine	0.270	0.136
3.	Sodium *N*-[3α,12α-dihydroxy-24-oxocholan-24-yl] glycylglycylglycine	0.300	0.140
4.	Sodium *N*-[3α,12α-dihydroxy-24-oxocholan-24-yl] alanylglycylglycine.	0.366	0.230

[a] Slope of the linear portion of the solubilization curve determined by least-squares method.

molecular structure, bile salts do not behave in a fashion analogous to ordinary aliphatic detergents (Small et al., 1969). Lengthening of this hydrophilic tail by the use of amino acids, dipeptides (unpublished data) and tripeptides leads to better hydrophilic lipophilic balance which is reflected in enhanced solubility and dissolution of the poorly water soluble drugs indomethacin and phenylbutazone.

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 (Hofmann, 1963). As shown in Table 1, the saturation ratios for indomethacin in the biosurfactant solution are many times greater than those of phenyl butazone, indicating that the biosurfactant micelles show a higher affinity for indomethacin molecule. Micellar solubilization has been broadly classified into three types (Klevens, 1950): (a) non-specific solubilization — the solubilisate is incorporated into the hydrocarbon center of the micelle away from the polar head groups; (b) specific solubilization — the solubilisate is incorporated by penetration into the palisade layer with the solubilisate molecule oriented in approximately the same manner as is the surfactant molecule in the micelle; (c) adsorption solubilization — in this type of solubilization, the solubilisate is absorbed onto the polar surfaces of the micelle. Cholate and deoxycholate micelles are formed by hydrophobic association of the hydrocarbon backbones of the rigid steroid nuclei in such a way that the hydrophilic sides, containing the hydroxyl groups and the negatively charged ionic groups, are exposed to water (Small et al., 1969). On comparing the molecular architecture of sodium alanylglycylglycodeoxycholate and indomethacin, it seems that the hydrophobic interaction of the solubilisate and the surfactant molecule occurs at the hydrophobic side of the steroid nucleus and the C-18, C-19 angular methyl groups which incorporate the methoxy group and the benzene nucleus of the hydrocarbon center leaving the acetic acid carboxyl group to interact with the hydrophilic side (3α, 12α-hydroxy group and the hydrophilic tail) leading to the penetration of indomethacin into the palisade layer forming mixed micelles (Thakkar, 1970; Miyazaki et al., 1981). Phenylbutazone forms a mesomeric anion at pH 7.2 (Stella and Pipkin, 1976) which inhibits the incorporation of phenylbutazone in the palisade layer of the micelles. The enhanced solubility of phenylbutazone may be due to a wetting effect. The results of dissolution studies are similar to those of solubility studies. The results of this study show that the peptide conjugated bile salts enhance the solubility and dissolution of poorly water-soluble drugs, indomethacin and phenylbutazone. However, further studies should be carried out with other amino acids and peptides.

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