THE SOLUBILIZATION AND DISSOLUTION OF PROGESTERONE BY BILE SALT MIXTURES

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Bile salts, in combination with phospholipids, play an important role in the intestinal absorption of endogenous materials, such as cholesterol, and of exogenous materials, such as drugs of low aqueous solubility. Many previous investigations have examined the solubility characteristics of steroids, a major class of lipophilic drugs, in solutions of single bile salts. The solubility in binary mixtures of bile salts and also in mixtures of bile salt and phospholipid has not previously been investigated, and is thus the subject of the present study. Dissolution data are also presented for progesterone in bile salt mixtures, since dissolution is often the rate determining step in the absorption of drugs of low solubility.

After equilibration for 24 hours at 37^{o}C and removal of excess steroid by centrifugation, the maximum additive concentration of progesterone in bile salt solution was determined spectrophotometrically at 244 nm. Due to phospholipid absorbance at 244 nm, the solubility of progesterone in the presence of phospholipid was determined by gas-liquid chromatography after ethereal extraction, using testosterone as the internal standard (Beckett & Pickup, 1975). The solubility in 10 mM mixtures of sodium taurodeoxycholate (STDC) and either sodium taurocholate (STC) or sodium glycodeoxycholate was found to decrease linearly in both cases from 100% STDC to 100% of the other bile component. In contrast, the solubility in 16 mM mixtures of sodium deoxycholate (SDC) and either lysophosphatidylcholine (LPC) or phosphatidylcholine (PC) was non-linear, both curves exhibiting minima at approximately 30% phospholipid, 70% SDC. For both LPC and PC, the same amount of progesterone was solubilized over the range 30-100%. The two curves diverge at a ratio of 30% SDC, 70% phospholipid: 100% PC solubilizing only half the amount of progesterone as 100% LPC. The LPC, SDC mixture is micellar at all compositions whereas the PC, SDC mixture reverts to a liquid crystalline state at a mole ratio of 70:30 (Small & others, 1969), the region where the curves diverge.

Dissolution data at 37^{o}C are obtained using the method of Bates & others (1966) and the composition of the dissolution media plotted against the amount of progesterone in solution after 20 and 30 minutes. For a 10 mM mixture of SDC and sodium cholate (SC), there is a slight but linear increase in the amount of dissolved progesterone as the composition of the media alters from 100% SC to 65:35, SC:SDC. From this ratio to 100% SDC, the curve is also linear, but of increased gradient. The occurrence of a change of state around the inflection in the curve has been confirmed by surface tension measurements. Similar dissolution data are also obtained for a 10 mM mixture of the two conjugated bile salts STC:STDC, the inflection in the curves occurring at a compositon of 25:75, STDC:STC.

It is concluded that solubilization may be a controlling factor in the dissolution of hydrophobic drug molecules in the presence of physiological surfactants, although the contribution of wetting has not been completely evaluated.

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