

THE INFLUENCE OF BILE FLOW AND MIXED BILE SALT MICELLE COMPOSITION ON THE ORAL ABSORPTION OF A MODEL COMPOUND (DDT)

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In man, lipid digestion stimulates bile flow which may enhance drug dissolution and solubilisation (Bates & Sequeira 1975). In addition, incorporation of unsaturated long chain fatty acids (ULCFA) into the bile salt micelle increases solubilisation of lipophilic molecules (Hofman & Small 1967) and potentiates drug absorption (Muranushi et al 1980). Palin et al (1980) have shown that the oral absorption of DDT in the rat was greater from arachis oil, a triglyceride containing ULCFA, than from Miglyol 812, a triglyceride containing saturated medium chain fatty acids (SMCFA). The relative effects of the oils on bile flow and composition, and on the solubilisation and absorption of DDT from mixed bile salt micelles, have been investigated.

Bile was collected from anaesthetised rats pre-dosed with 1 ml volumes of each oil, and the bile flow and total bile salt output from each animal determined. No differences in the effect of the oils on either parameter were noted over a 3 hour period. The solubility of DDT in mixed micellar solutions containing sodium glycocholate (40 mM) and an ULCFA or SMCFA (26 mM), at 37° and pH 6.4, was shown to be greater in the presence of the ULCFA (see Table 1). However, using an in situ rat gut loop technique, the rate of uptake of DDT from micellar solutions of the same composition in which a constant concentration of DDT (0.42 mM) was solubilised by sonication, was found to be independent of the hydrocarbon chain length of the fatty acid (see Table 1). The results suggest that although the intra-luminal bile salt concentration is constant, arachis oil digestion enhances DDT solubilisation within the bile salt micelles compared with Miglyol 812 digestion, by releasing ULCFA. Following solubilisation DDT uptake from the mixed micelles was independent of the hydrocarbon chain length of the constituent fatty acids. The oral absorption of lipophilic drugs dependent on solubilisation by mixed bile salt micelles may be enhanced by co-administration of lipid containing ULCFA to increase drug solubility within the micelle.

Table 1. The effect of different fatty acids (26 mM) on the solubility of DDT in micellar solutions of sodium glycocholate (40 mM) in phosphate buffer (pH 6.4, 0.05M) and on the percentage of the original concentration of DDT remaining in the rat gut loop after 30 minutes (mean \pm SD).

Fatty acid	Chain length: double bonds	% remaining t=30 min	Solubility (μ g/ml)
Octanoic	8:0	45.47 \pm 8.53	26.11 \pm 3.07
Lauric	12:0	35.69 \pm 8.77	23.29 \pm 3.73
Linoleic	18:2	56.83 \pm 9.18	138.88 \pm 6.59
Oleic	18:1	37.24 \pm 10.83	127.74 \pm 23.59

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