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Study of the influence of sodium taurocholate (STC) and sodium glycocholate (SGC) on the mass transfer of certain drugs. Digoxin

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Summary

Digoxin has an aqueous solubility of 1.811 mg/100 ml and a dissolution efficiency of 13.7%. The presence of bile salts raised the solubility to 3.621 and 4.039 mg/100 ml and the dissolution efficiency to 25.7 and 19.3% for STC and SGC, respectively. The relatively low solubility of digoxin compared to other polar drugs points to its non-polar behaviour.

The addition of lecithin or cholesterol to bile salt solutions, slightly decreases the solubility and dissolution rate of digoxin, probably due to competition between lecithin and cholesterol and digoxin for the same binding site of bile salt micelles. However, the simultaneous presence of lecithin and cholesterol together with bile salts increases, slightly, the solubility and dissolution rate of digoxin, most probably due to increased volume and hydrophobicity of the core of mixed micelles.

Addition of fatty acids to SGC solution does affect but very slightly the solubility and dissolution rate of the drug. The fatty acid lowers, to some extent the solubility of the drug in STC solutions, while the dissolution rate is only slightly affected. Addition of monolaurin to bile salt solutions decreases the solubility of the drug to some extent. However, GM myristate and GM stearate slightly enhance both the solubility and dissolution rate of the drug. The presence of GM laurate slightly lowers the dissolution rate of the drug in STC solutions but not in SGC ones. The influence of GM laurate on the solubility of digoxin seems to be quite comparable to that of lecithin.

The simultaneous presence of the investigated additives in STC or SGC systems increases slightly the solubility and dissolution rate of the drug. This has been explained on the basis of increased hydrophobicity and volume of the core of mixed micelles.

Introduction

Many publications have reported the occurrence of brand-to-brand and even batch-to-batch variability as far as the biological availability of digoxin from its solid dosage forms is concerned. Such a variability was also reflected on the in vitro dissolution parameters of such preparations (Bertler et al., 1972; Huffman et al., 1975; Ghirardi et al., 1977; Martindale, 1977).

Differences in the bioavailability of digoxin preparations were attributed to physicochemical factors (Shah et al., 1974;, Florence et al., 1974;, Khalil, 1974; Omar, 1976; Reddy et al., 1976; Bochner et al., 1977), preparation procedure (Hasegawa et al., 1978) and biological factors (Bertler et al., 1972; Lindenbaum, 1973).

Attempts were made to solubilize digoxin, which is reported to be excreted in bile (Smith, 1973), in bile salts. Thus, Reddy and his coworkers (Reddy et al., 1976) used deoxycholic acid as a solid carrier to disperse the drug. On the other hand, El-Gholmy and Bakry (1975) prepared digoxin injections using sodium cholate or sodium deoxycholate as solubilizers. The solubility of other steroidal compounds in bile salt solutions was also considered (Cantarow et al., 1944; Ekwall and Sjöblom, 1949, 1950; Ekwall et al., 1951b; Thakkar, 1970).

It was thus deemed interesting to analyze the factors contributing to the dissolution of this drug by bile salts in the human intestine.

As already undertaken with the poorly soluble drugs griseofulvin (non-polar) (Mattha et al., 1980) and sulfisoxazole (polar) (Kassem et al., 1980), the solubility and dissolution rate of digoxin in aqueous solutions of the individual bile salts STC or SGC were studied in presence of some other important bile constituents (lecithin, cholesterol) and some products related to fat digestion (fatty acids: lauric, myristic, palmitic; and monoglycerides; glyceryl monolaurate (GML), glyceryl monomyristate (GMM) and glyceryl monostearate (GMS). Temperature (37°C), pH (6.4), bile salt (0.04 M) and electrolyte (sodium ion concentration = 0.15 mol/l) concentrations were adjusted so as to simulate physiological conditions (Sjövall, 1959; Bates et al., 1966b).

Materials and methods

Materials

Sodium taurocholate: BDH Chemicals, Poole, U.K. Sodium glycocholate: I.C.N. (Pharmaceuticals, Life Sciences Group, Plainview NY, U.S.A.), both used as received. Pure egg lecithin: E. Merck, Darmstadt. Cholesterol: U.S.P. XIX, E. Merck, Darmstadt.

Lauric, myristic and palmitic acids: biochemical grade, Akzo Chemie, Italy. Glyceryl monolaurate and glyceryl monomyristate: pure, Akzo Chemie, Italy. Glyceryl monostearate: pure, Emery Industries, U.S.A. Sodium chloride (A.R.), picric acid (A.R.).

Digoxin: B.P., Burroughs Wellcome, U.K.

Apparatus

Cecil spectrophotometer model CE595; synchronous motor (Hanson Research); pH meter, type PHM 22r (Radiometer-Copenhagen); membrane filters (Sartorius-Membranfilter GMBH-34, Göttingen, F.R.G., pore size 0.6 μm, 25 mm diameter; Warburg shaker; planimeter (type GK 800, Metrimpex, Budapest, Hungary).

Methods

The same as described in a previous publication (Mattha et al., 1980). Phosphate buffer was not used in the preparation of dissolution media since it interfered with the assay of digoxin. However, the buffering action of bile salts (Ekwall et al., 1951a) kept the solution around a pH of 6.4

For the determination of digoxin, the method of Shah and his coworkers (Shah et al., 1974) based on following its absorption in the UV range of the spectrum could not be used due to interference of the bile salts.

The B.P. colorimetric method (B.P., 1973) for the determination of digitoxin in tablet dosage forms was adopted, after a slight modification according to El-Gholmy and Bakry (1975) so as to suit digoxin. Thus, 3 ml of recently prepared alkaline picrate reagent (consisting of 20 ml of 1% w/v aqueous solution of picric acid, 0.1 ml of 5% w/v sodium hydroxide and sufficient water to produce 100 ml) was added to 5 ml of the clear filtrate from solubility or dissolution rate experiments. The solution was allowed to stand for 16 min and the absorbance at 495 nm was measured. A blank consisting of 5 ml water and 3 ml of the alkaline picrate reagent was used.

In the case of systems containing STC or SGC, control experiments were carried out. A solution identical to the blank, but containing 0.1 mg of the drug was prepared as standard for each set of determinations. The amount of solubilized drug was determined from a previously constructed calibration curve as shown in Fig. 1.

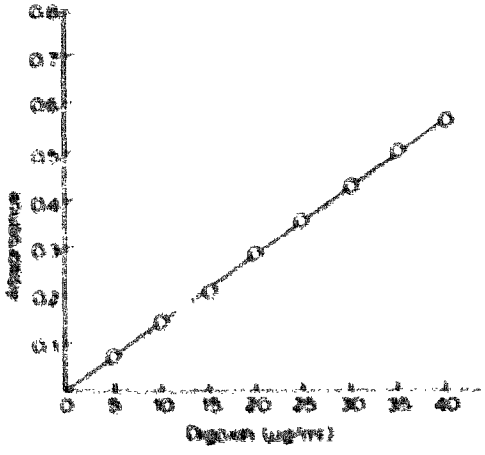

Fig. 1. Standard curve of digoxin.

Results and discussion

Table 1 and Figs. 2, 3 and 4 illustrate the influence of lipid additives on the mass transfer of digoxin.

Influence of STC or SGC

Table 1 shows that, in absence of bile salt, digoxin had a solubility of 1.811 mg/100 ml and a dissolution efficiency of 13.7%. The presence of the bile salts raised the solubility to 3.621 and 4.039 mg/100 ml and the dissolution efficiency to 25.7 and 19.3% for STC and SGC systems, respectively.

The consideration of data reported in Table 1 reveals that, like in the case of griseofulvin (Mattha et al., 1980) the bile salt seems to play the major role in the solubilization of the drug. Again, the solubility of the drug in SGC solutions is somewhat higher than in STC ones. By its solubilization in bile salt solutions, digoxin behaves as some steroidal hormones (Cantarow et al., 1944; Ekwall, 1953; Ekwall et al., 1957; Thakkar, 1970), class I polar lipids in general and cholesterol (Carey and Small, 1970, 1972). Given that the saturation ratios of the drug in STC and SGC solutions are about 0.000046 and 0.000051, respectively (calculated on the basis of data given in Table 1 and taking the solubility of the drug in water into account) one finds that about 0.0006 molecule of the drug is solubilized by one molecule of STC or SGC. And, since the aggregation number of the bile salts is 2–9 under experimental conditions adopted in the present work (Fontell, 1971; Carey and Small, 1972), the principle of one or more molecules of solubilizate per micelle

TABLE I

INFLUENCE OF LIPID ADDITIVES ON THE SOLUBILITY AND DISSOLUTION RATE (EXPRESSED IN TERMS OF DISSOLUTION EFFICIENCY, D.E.%) OF DIGOXIN (37°C) IN AQUEOUS SYSTEMS CONTAINING 0.04 M STC OR SGC (SODIUM ION CONCENTRATION = 0.15 M).

ADDITIVE	STC		SGC	
	S[a]	DE%	S[a]	DE%
Water	1.811	13.70	1.811	13.70
Bile salt	3.621	25.70	4.039	19.73
Lecithin (0.2%)	3.203	23.33	3.760	17.00
Cholesterol (0.025%)	3.064	21.33	3.621	15.50
Lecithin + cholesterol	3.760	28.33	4.735	23.00
Lauric acid (0.4%)	3.343	23.33	3.900	17.70
Myristic acid (0.2%)	3.482	25.00	3.955	20.50
Palmitic acid (0.05%)	3.340	23.17	3.900	18.70
GML (0.4%)	3.148	22.33	3.343	19.00
GMM (0.2%)	3.867	27.17	4.178	22.33
GMS (0.025%)	3.859	27.50	4.318	24.00
All additives	3.710	27.00	4.457	25.70

[a] Solubility in mg/100 ml.

(Carey and Small, 1970, 1972) is not obeyed and the phenomenon considered is very probably not true micellar solubilization. The relatively low solubility of digoxin in bile salt solutions compared to other polar molecules points to the non-polar behaviour of the drug molecule in the systems investigated. This characteristic was noted for some polar sterol esters and ethers (Small, 1970a and b) and cholesterol (Carey and Small, 1970).

Like griseofulvin (Mattha et al., 1980) and very probably cholesterol, digoxin might be bound to bile salt micelles through hydrophobic bonding. Again, the slightly higher solubility of the drug in solutions of SGC compared to STC solutions is probably due to the higher polarity of the taurocholate micelles (Norman, 1960a and b; Kratohvill and Dellicolli, 1968; Bates et al., 1966).

Influence of lecithin and/or cholesterol

The addition of lecithin to the bile salt system decreases the solubility and dissolution rate of the drug to some extent (Fig. 2 and Table 1); the difference in solubility is not great. As shown in the case of griseofulvin (Mattha et al., 1980) a competition between the amphiphilic lecithin molecules and the drug for bile salt micelles is probably behind such a behaviour. As in the case of griseofulvin, solubilization seems to take place mainly through interaction with bile salt micelles.

Again, the addition of cholesterol to the bile salt solution slightly decreases the

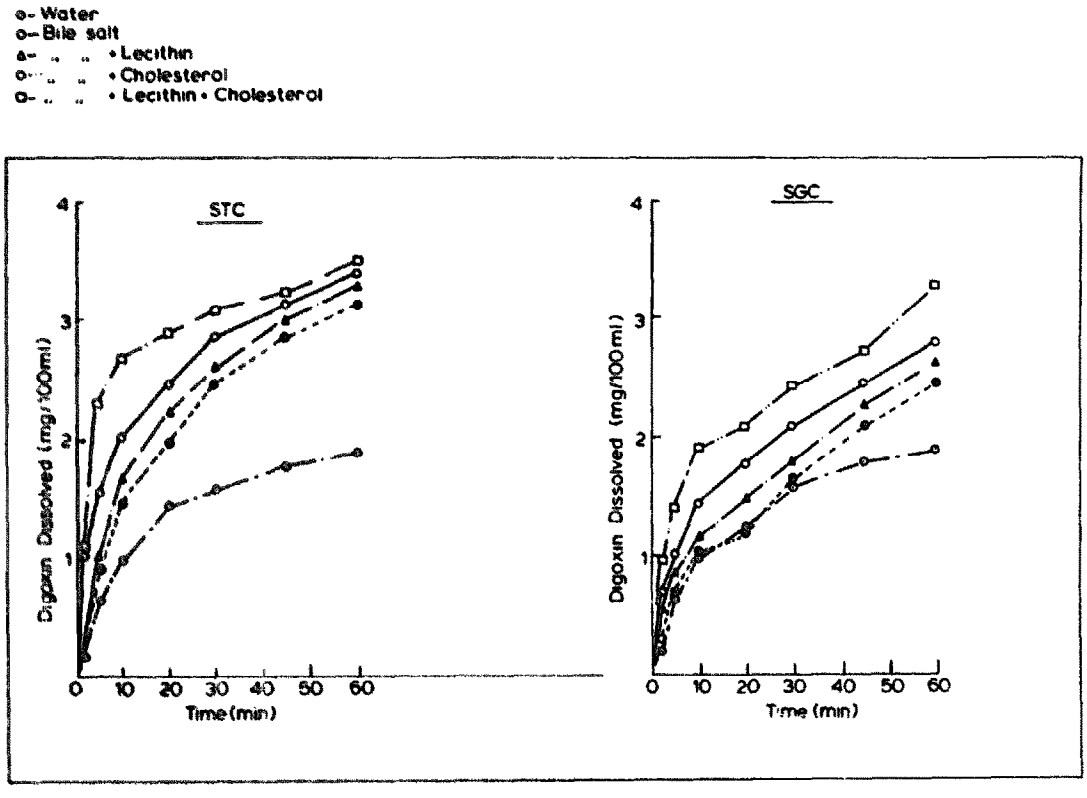

Fig. 2. Influence of lecithin and/or cholesterol on the dissolution rate of digoxin in buffered solutions containing trihydroxy bile salts.

solubility and dissolution rate of the drug; this may be due to competition with cholesterol for the same binding sites, both being steroids (Carey and Small, 1972).

On the other hand, the addition of cholesterol to the bile salt/lecithin system enhanced the solubility and dissolution rate of the drug. As in the case of griseofulvin (Mattha et al., 1980) this might be due to the higher hydrophobicity of the core of bile salt–lecithin–cholesterol mixed micelles and to the increase in the size of the mixed micelle; this latter factor is important in the case of a big molecule such as digoxin.

Influence of fatty acids

Fatty acids are shown (Table 1 and Fig. 3) to affect but very slightly the solubility and dissolution rate of the drug when added to SGC solutions. The same additives (Table 1 and Fig. 3) decrease to some extent the solubility of the drug in STC solutions while the dissolution rate of the drug is only slightly affected.

Influence of monoglycerides

Table 1 and Fig. 4 show that in presence of all additives, the solubility and dissolution rate of the drug in STC solutions is very slightly increased. The solubility and dissolution rate of the drug are increased in a more significant way in the case of SGC solutions; however, the increase is not dramatic. The increased hydrophobicity and size of the cores of mixed micelles might be responsible for such a behaviour.

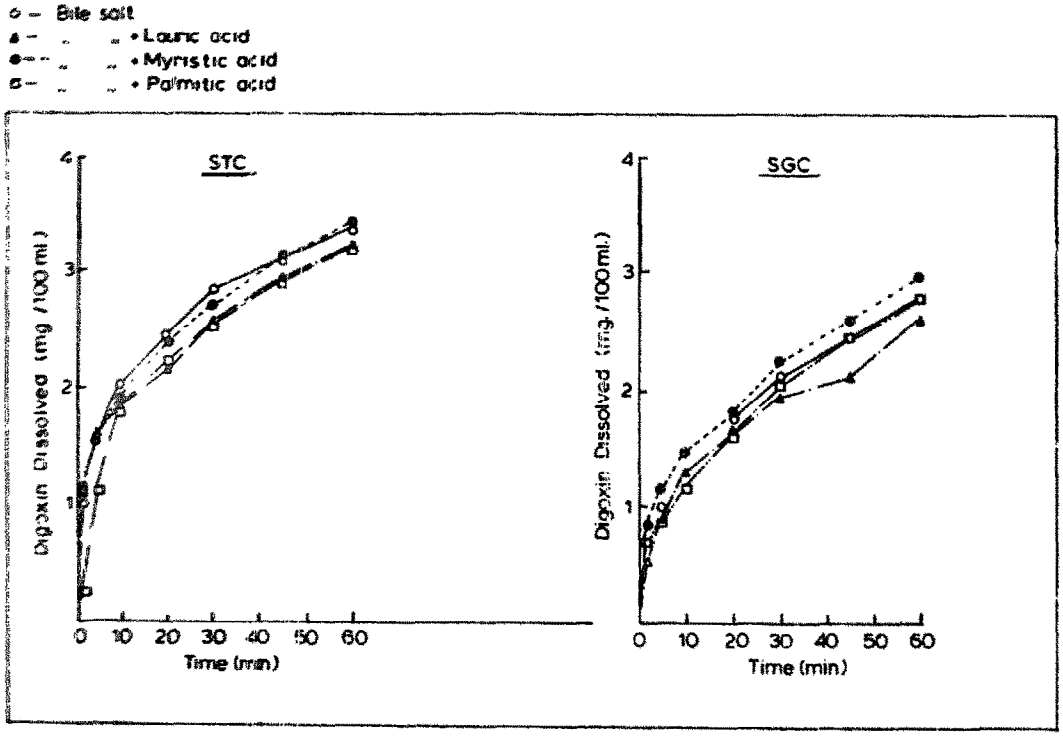

Fig. 3. Influence of fatty acids on the dissolutions rate of digoxin in aqueous solutions containing trihydroxy bile salts.

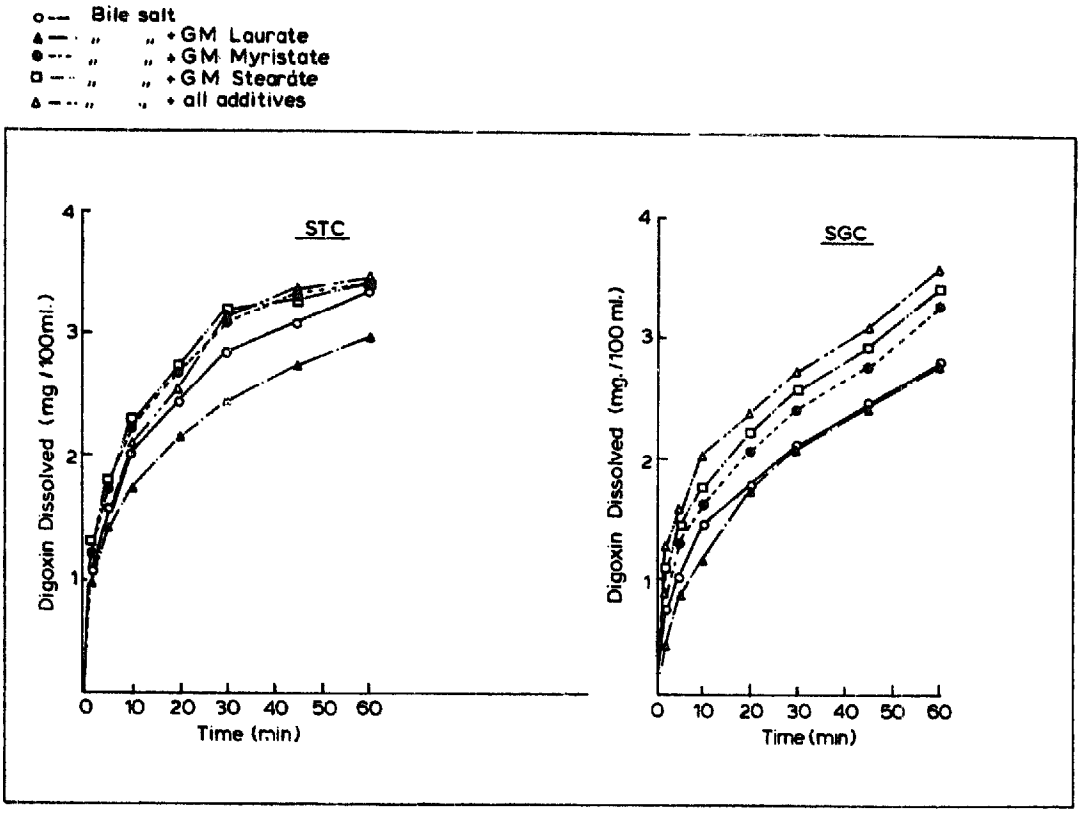

Fig. 4. Influence of monoglycerides and all additives on the dissolution rate of digoxin in aqueous solutions containing trihydroxy bile salts.

Conclusions

(1) The trihydroxy bile salts, STC and SGC, enhance the mass transfer of digoxin.

(2) The bile salt component of the investigated systems seems to be the primary determinant in drug dissolution. Simple bile salt micelles present in the intestine thus seem to play the major role in drug dissolution.

(3) Changes in the composition of the mixed bile salt–lipid micelles present in the dissolution medium seem to affect only slightly the solubilizing potential of these micelles.

(4) The combination of any of the two bile salts with all the investigated lipids of the intestinal mixture improves the dissolution of digoxin in bile salt solutions.

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