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The effect of α-tocopherol on the in vitro solubilisation of lipophilic drugs

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Abstract

α-Tocopherol is an excellent solvent for many poorly soluble drugs. The aim of this work was to study whether or not the presence of α-tocopherol has an influence on the solubilisation of poorly soluble drugs in simulated intestinal fluids (SIF). The solubilising capacity of mixed micelles containing α-tocopherol towards three lipophilic drugs was investigated. The solubilisation of α-tocopherol in an aqueous micellar phase was increased by the addition of monoglycerides (MG) and free fatty acids (FFA), preferably of medium chain length, as compared to a simple bile salt solution. The addition of α-tocopherol to mixed micellar solutions seems to have an effect on the solubilising capacity, which can be correlated to the partition coefficient of the drug to be solubilised. A positive effect on the solubilisation of griseofulvin and felodipine was found. For a highly lipophilic drug (Lu28-179), a positive effect on solubilisation was observed only in media containing MG and FFA of medium chain length. Generally, α-tocopherol cannot be considered an important factor for the solubilisation of highly lipophilic drugs in SIF. The presence of lipolytic digestion products (LDP) of the proper chain length in relation to the drug to be solubilised is much more important.

Keywords: α-Tocopherol; Solubility; Lipolytic degradation products; Fatty acid chain length; Bile extract; Partition coefficient

1. Introduction

Poorly soluble drugs are often highly lipophilic and may have poor oral bioavailability, because uptake is limited by the dissolution rate. It is well known that administration of such drugs in lipid-based formulations or by co-administration with food increases the uptake, owing to delayed gastric emptying and/or the formation of solubilised phases. The solubilised phases consist of bile acids and phospholipids from the bile, which form mixed micelles with lipolytic digestion products (LDP) (i.e. monoglycerides (MG) and free fatty acids (FFA)). These may facilitate diffusion of the drug through the unstirred water layer at the intestinal brush border (Cohn et al., 1992; Humberstone and Charman, 1997).

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α-Tocopherol is a very lipophilic compound and an excellent solvent for many poorly soluble drugs (Sonne, 1995). It may therefore provide sufficient solvent capacity to administer such drugs in a dissolved form in a suitable volume, and thereby overcome the problem of limited uptake. In order to bypass the unstirred water layer, poorly soluble drugs are solubilised into micelles or mixed micelles. The intestinal absorption of α-tocopherol is dependent on the presence of bile (Gallo-Torres, 1970) and is further increased by co-administration of triglycerides (TG), preferably those of medium chain length (MCTG). This is probably due to solubilisation in mixed micelles (Gallo-Torres et al., 1978). It is therefore assumed that α-tocopherol would be able not only to dissolve poorly soluble drugs before delivery to the gastrointestinal tract, but also to form micelles with bile salt and/or LDP, in which the drug can be transported through the unstirred water layer, thus increasing its absorption.

The aim of this work was to study whether or not the presence of α-tocopherol has an influence on the solubilisation of poorly soluble drugs in simulated intestinal fluids (SIF) in both the fed and the fasted state. In this respect the solubilisation of α-tocopherol itself in different SIF containing LDP of either medium or long chain lengths was studied. In addition, we investigated the sizes of micelles formed with and without co-solubilised α-tocopherol and lastly, the solubilising capacity of mixed bile salt micelles with or without co-solubilised α-tocopherol towards three poorly soluble drugs.

2. Materials and methods

2.1. Materials

Griseofulvin ($\log P = 2.2$, solubility in tocopherol ($S_{\text{tocopherol}}$) = 5 mg/g) (Leo Pharmaceuticals, Denmark); felodipine ($\log P = 4.8$, $S_{\text{tocopherol}} = 5$ mg/g) (AstraZeneca, Sweden); Lu28-179 ($\log P \approx 8$, $S_{\text{tocopherol}} = 36$ mg/g) (H. Lundbeck, Denmark); α-tocopherol (BASF, Norway); bile extract (Sigma B8631); mono-olein (Danisco, Denmark, Rylo MG 15); oleic acid (Sigma O1630); mono-caprine (Danisco, Denmark, Emulsifier TS-PH 003); and capric acid (Sigma C1875). All chemicals were of reagent grade. Details on certain characteristics and analytical methods for Lu28-179 are confidential.

2.2. Preparation of SIF

Table 1 lists the composition of the 11 SIF used.

The fluids were prepared by dissolving the bile extract in water at low agitation and under gentle heating. MG and/or FFA were then added. When

Table 1
Compositions of simulated intestinal fluids

No.	BS (mM)	MCMG (mM)	MCFFA (mM)	LCMG (mM)	LCFFA (mM)
1	4				
2	**16**				
3	30				
4	16			30	
5	16				60
6	**16**			**15**	**30**
7	**16**			**30**	**60**
8	16	30			
9	16		60		
10	**16**	**15**	**30**		
11	**16**	**30**	**60**		

BS, bile salts from bile extract; MCMG, medium chain monoglycerides (mono-caprine); MCFFA, medium chain free fatty acid (capric acid); LCMG, long chain monoglyceride (mono-olein); LCFFA, long chain free fatty acid (oleic acid).

all was solubilised, the pH was adjusted to 6.5 with 45 mM KH_2PO_4 and 2 N NaOH. The fluids were homogenised for 10 min at 8000 rpm by an Ultra Turrax T25.

The bile salt concentrations were based on the amount found in humans (3–45 mM) (Kararli, 1995) and represented both the fed and the fasted states. The total bile salt concentration in the porcine bile extract was 49% (estimated by means of Enzabile) and the average molecular weight of the bile salts was estimated to be 500 g/mol. The concentrations of MG and FFA were based on the content of the aqueous phase of human postprandial duodenal content as measured by Hernell et al. (1990) and on the theoretical ratio between MG and FFA, 1:2, in the degradation of TG. Hernell et al. (1990) determined the MG concentration in the interface of ultracentrifuged distal duodenal content to 19.6 ± 11.3 mM after ingestion of a test meal containing 118 mM of TG. In the present study two concentrations (15 and 30 mM) of MG are studied as to measure the possible concentration effect on solubilisation.

To estimate the solubility of α-tocopherol in the SIF, 5 g of α-tocopherol was added to 50 ml of each of the SIF (Table 1) before homogenisation. The mixture was centrifuged at 5°C and 40 000 rpm for 30 min on a Beckman Ultra Centrifuge L5-50. The lower aqueous phase was analysed by HPLC for α-tocopherol.

To estimate drug solubility in the SIF with or without co-solubilised α-tocopherol, 20–500 mg of drug (griseofulvin, felodipine, or Lu28-179) was weighed out into glass containers. Four to 10 ml of homogenised SIF (Table 1, media in bold) was added and the container was rotated in an incubator at 37°C for 24 h. After sedimentation, samples of the aqueous phase were collected and filtered (0.2 μm), and the filtrate was analysed by HPLC for griseofulvin, felodipine, or Lu28-179. α-Tocopherol was added to the SIF before homogenisation and in amounts equal to the saturation concentration estimated above.

2.3. Analyses

The HPLC method for the analysis of α-tocopherol was modified from Müllertz (1991). The HPLC system consisted of a Waters 510 pump, a Waters Scanning Fluorescence Detector 470, a Waters WISP injector 712, and an HP 3390 A integrator. The column was a 250×4.6 mm Spherisorb S5 ODS1, kept at 30°C by a column oven. The wavelengths of excitation and emission were 290 and 330 nm, respectively. The mobile phase consisted of methanol/hexane/water (90:5:5 v/v). The flow was 1.0 ml/min and the injection volume 20 μl. The peak height was used as a measure of the concentration of α-tocopherol.

The HPLC method for the analysis of griseofulvin was modified from Tur et al. (1997), and AstraZeneca developed the HPLC method for the analysis of felodipine. The HPLC systems for these analyses consisted of a Waters 590 pump, a PYE Unicam UV detector set at a wavelength of 295 nm (griseofulvin) or 254 nm (felodipine), a Waters WISP injector, and an HP 3396 series II integrator. The column was a 4.6×250 mm Supelcosil LC-18-DB (5 μm), kept at 30°C by a column oven. The flow was 1.5 ml/min and the injection volume 25 μl. The mobile phase for the analysis of griseofulvin consisted of 45% v/v acetonitril in 45 mM potassium dihydrogen phosphate, pH 3.0. The mobile phase for the analysis of felodipine consisted of acetonitril/methanol/0.01 M sodium dihydrogen phosphate buffer (40:25:35) at pH 3.0. The peak heights were used as a measure of the concentration of the drugs.

The concentration of Lu28-179 was determined by an HPLC method with UV detection. Samples were diluted with mobile phase before injection. All analyses were done at H. Lundbeck, Denmark.

2.4. Determination of the size of micelles

The size of colloidal particles in five of the simulated media (Table 1, media in bold) with and without co-solubilised α-tocopherol was measured by Dynamic Light Scattering (DLS) on a DynaPro-801, Molecular Sizing Instrument (Protein Solutions). The media were centrifuged (room temperature, at 9000 rpm, for 10 min) and filtered (100 nm) before the measurements were made. These measurements yielded translational diffusion coefficients from an autocorrelation of

Table 2
Concentration of solubilised tocopherol in simulated intestinal fluids ($n = 3$)

No.	Content of the media	Concentration of tocopherol (mg/ml)
1	4 mM BS	0.24 ± 0.06
2	16 mM BS	0.68 ± 0.42
3	30 mM BS	0.91 ± 0.10
4	16 mM BS+30 mM LCMG	1.67 ± 0.11
5	16 mM BS+60 mM LCFFA	0.35 ± 0.08
6	16 mM BS+15 mM LCMG+30 mM LCFFA	1.63 ± 0.04
7	16 mM BS+30 mM LCMG+60 mM LCFFA	1.73 ± 0.10
8	16 mM BS+30 mM MCMG	1.30 ± 0.04
9	16 mM BS+60 mM MCFFA	0.73 ± 0.53
10	16 mM BS+15 mM MCMG+30 mM MCFFA	1.15 ± 0.27
11	16 mM BS+30 mM MCMG+60 mM MCFFA	2.67 ± 0.45

See also Table 1.

the variations in the intensities of the collected photons. The hydrodynamic radius (R_h) was then calculated by the Stoke-Einstein equation. All laser light fluctuation was correlated by Dynamics 3.3 software to originate from one component (monomodal evaluation).

2.5. Statistical analysis

The data were analysed statistically by Student's t-test.

3. Results and discussion

3.1. Solubilised α-tocopherol

Table 2 shows the amount of solubilised α-tocopherol in the SIF.

α-Tocopherol is practically insoluble in water (< 0.1 mg/ml) (Ph. Eur., 2001). The solubility of α-tocopherol was increased in simple bile salt solutions, and it seemed to depend on the concentration of bile salt, although no statistical significance was detected between 4 an 30 mM of bile salt.

The combination of long chain MG and bile salt increased the solubilisation of α-tocopherol, as compared to 16 mM bile salt alone ($P < 0.05$). Long chain FFA neither had any significant effect on the solubilisation of α-tocopherol alone or in combination with long chain MG. The combination of medium chain MG and bile salt did not increase the solubilisation of α-tocopherol significantly, as compared to 16 mM bile salt alone. Medium chain FFA did not have any significant effect on the solubilisation of α-tocopherol alone, but the combination with medium chain MG increased the solubilisation significantly ($P < 0.01$). Medium chain MG seemed to be able to provide a greater solubilising capacity than did long chain MG ($P < 0.05$) at high concentrations.

In a study by Gallo-Torres et al. (1978) the absorption of α-tocopherol in rats was enhanced by emulsification in medium chain length TG, as compared to long chain length TG. The effect was attributed to a greater dispersion of the medium chain LDP, which resulted in a faster uptake. This result is supported by the present study. Borgström (1967) investigated the partitioning of cholesterol (which resembles α-tocopherol in being an insoluble, non-swelling amphiphile) between an oil phase and a micellar phase. Cholesterol was found to be more soluble in micellar phases containing medium chain length LDP than that with long chain length LDP. This result is consistent with the present results. In a study by Takahashi and Underwood (1974) the solubility of α-tocopherol was found to be 3–7 times greater in mixtures containing long chain LDP than in mixtures containing the corresponding LDP of medium chain length. However, all the media tested by Takahashi and Underwood contained non-hydrolysed TG, which was not the case in the present work. Moreover, the present study shows that the solubility of α-tocopherol in an aqueous phase might depend on the concentration of the LDP and bile salts, which was not investigated by Takahashi and Underwood.

The present results show that the solubilisation of α-tocopherol increases with the addition of

LDP to the bile salt solution. At high levels, medium chain length MG and FFA seem to be more efficient in forming mixed micelles and solubilising α-tocopherol.

3.2. Solubilisation of drugs

Figs. 1–3 illustrate the solubilisation capacities towards griseofulvin, felodipine and Lu28-179, respectively, of five of the SIF with or without co-solubilised α-tocopherol. The concentration of co-solubilised α-tocopherol in the media is equal to the concentrations shown in Table 2.

The aqueous solubility of griseofulvin is 15–30 μg/ml (Bates and Sequeira, 1975; Mithani et al., 1996). The solubility in a simple bile salt solution was increased approximately 3-fold. The presence of α-tocopherol had no effect on this solubility.

The addition of LDP to the simple bile salt solution increased the solubility of griseofulvin significantly. The effect was greater with medium chain LDP than with long chain LDP ($P < 0.001$). The solubilising capacity of the media depended on the concentration of LDP ($P < 0.01$–0.001). α-Tocopherol had a positive effect on the solubilisation of griseofulvin in these media.

The solubility of felodipine in a simple bile salt solution was significantly ($P < 0.01$) decreased by the presence of α-tocopherol. The addition of MG and FFA had a major impact on the solubilising capacity towards felodipine, as compared to the simple bile salt solution. Long chain MG and FFA in low concentrations had a greater solubilising capacity than had medium chain MG and FFA ($P < 0.01$). This difference was not significant at high concentrations. α-Tocopherol increased the solubility of felodipine, as compared with SIF alone, but this effect was not significant.

The solubility of Lu28-179 in a simple bile salt solution was very low, and the presence of α-tocopherol did not influence the solubility. The addition of long chain MG and FFA had a major impact on the solubility of Lu28-179. The solubility depended on the concentration of the long chain LDP ($P < 0.05$). The addition of medium chain LDP had a minor, but significant, impact on the solubility ($P < 0.001$–0.05).

α-Tocopherol seemed to have a significant, negative effect on the solubility of Lu28-179 in media with high concentrations of long chain MG and FFA ($P < 0.01$). Significant, positive effects of α-tocopherol were seen in media with medium chain MG and FFA ($P < 0.01$). It was noted that the solubilities of Lu28-179 in media containing co-solubilised α-tocopherol were equal ($P > 0.05$), in spite of differences in the chain length and concentrations of LDP in the media.

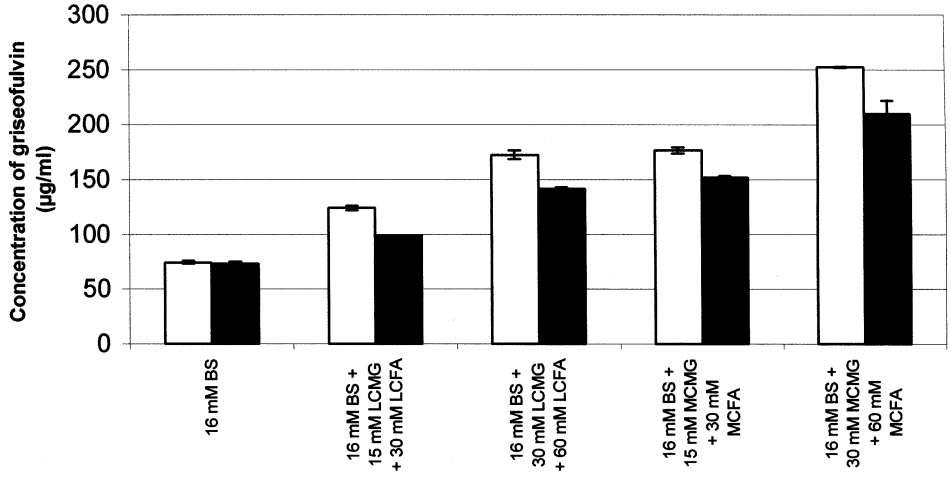

Fig. 1. The solubilisation of griseofulvin in simulated intestinal fluids with (□) and without (■) solubilised α-tocopherol ($n = 3$) (see also Table 1).

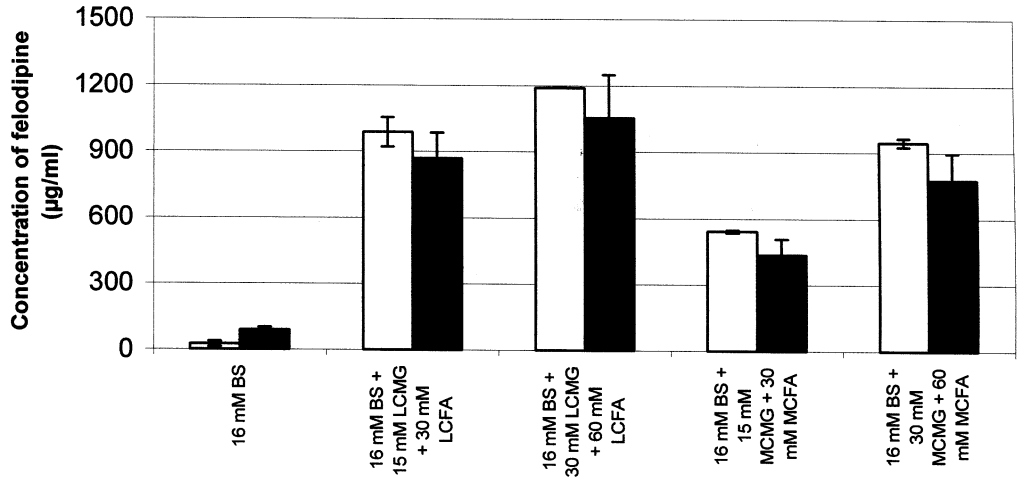

Fig. 2. The solubilisation of felodipine in simulated intestinal fluids with (□) and without (■) solubilised α-tocopherol ($n = 3$) (see also Table 1).

Comparison of Figs. 1–3 shows that the solubility of the three different drugs were in the range of 25–100 μg/ml in the simple bile salt solution. The addition of MG and FFA — i.e. the formation of mixed micelles — increased the solubility of griseofulvin up to three times, of felodipine up to 12 times, and of Lu28-179 up to 117 times. In the case of felodipine and Lu28-179, long chain components were best at increasing the solubility, whereas in the case of griseofulvin medium chain LDP were best. For griseofulvin the solubility depended on the concentration of LDP.

Generally, the solubility and dissolution rate of poorly water-soluble drugs in bile salt systems cannot be predicted, owing to the compound-specific nature of the interaction (Charman et al., 1997). Felodipine and Lu28-179 have log P-values of 4.8 and approximately 8, respectively, whereas griseofulvin has a log P of 2.2. This difference might explain why felodipine and Lu28-179 were more easily solubilised by long chain LDP, and why LDP had a much greater impact on the solubility of felodipine and Lu28-179 than on that of griseofulvin.

Addition of α-tocopherol into simple bile salt micelles (simulating the fasted state) had no positive effect on the solubility of the drugs. This might be explained by a poor incorporation of α-tocopherol into simple bile salt micelles. Addition of α-tocopherol into the mixed micelles had a positive effect on the solubility of griseofulvin in all the media tested, whereas no effect was found on the solubility of felodipine, as compared to media without co-solubilised α-tocopherol. α-Tocopherol had a strong positive effect on the solubility of Lu28-179 in medium chain media, which on their own, provided relatively poor solubilities, but no (or in fact a negative) effect in long chain media, which on their own, provided good solubilities.

These investigations give a static picture of the solubilising capacity of mixed micelles towards poorly water-soluble drugs. The actual impact of mixed micelles on the bioavailability of drugs is hard to predict, since drugs distribute between all the different colloidal phases in the gastrointestinal tract. These phases are subject to changes as a function of the fed/fasted cycle and the kinetics of lipid digestion (Charman et al., 1997).

3.3. Sizes of the micelles

Table 3 shows the sizes of the micelles formed in five of the SIF (Table 1, media in bold).

According to Carey and Small (1970), mixed micellar solutions contain particles of sub-micron size (3–10 nm in diameter). The sizes of the particles in the present media were approximately

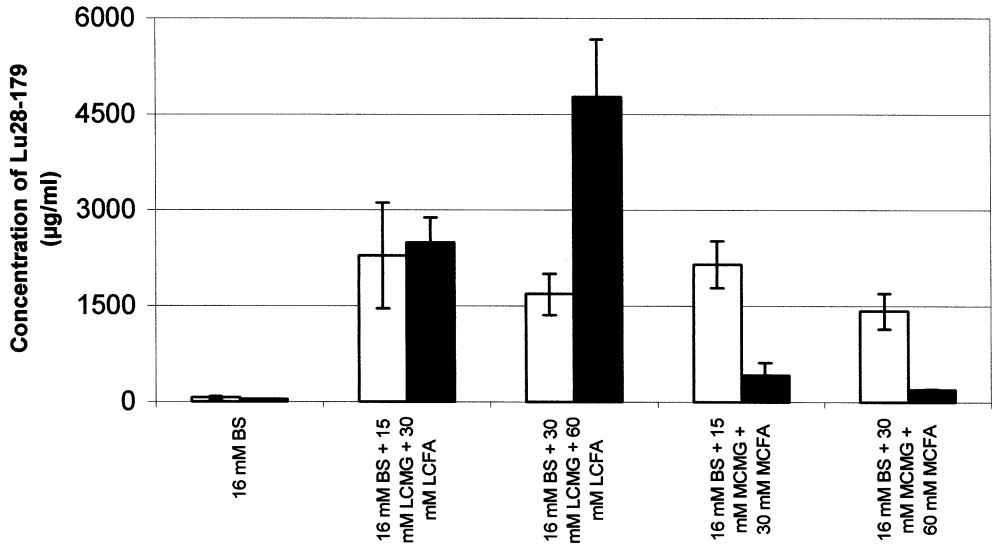

Fig. 3. The solubilisation of Lu28-179 in simulated intestinal fluids with (□) and without (■) solubilised α-tocopherol ($n = 3$) (see also Table 1).

10-fold larger. The solution containing bile salts only (medium 2a) had an average particle diameter of 33 nm. The relatively large size might be due to the presence of molecules other than bile salts in the bile extract from which this solution was made.

The particle sizes in the two media containing long chain LDP (media 10a and 11a) were 55 and 50 nm, respectively. The particle size did not increase with the increase in the LDP concentration. Probably, only the number of mixed micelles increased. The particle size in the medium containing medium chain LDP was 101 nm. It is not known why mixed micelles of medium chain LDP were larger than mixed micelles of long chain LDP.

The presence of α-tocopherol in the micelles and mixed micelles did not alter the particle size significantly, except for the medium chain medium (7b), where the presence of α-tocopherol seemed to decrease the particle size to the same size as in the other media.

4. Conclusion

The solubilisation of α-tocopherol in an aqueous micellar phase increases with the addition of MG and FFA, preferably of medium chain length, as compared to the simple bile salt solution. The sizes of the particles formed in the

Table 3
Hydrodynamic radius, R_h, of micelles formed in simulated intestinal fluids with and without solubilised α-tocopherol (mean ± S.D)

Media	Content of media	R_h (nm)
2a	16 mM BS	16.7 ± 1.9
2b	16 mM BS + tocopherol	18.0 ± 2.2
6a	16 mM BS, 15 mM MCMG, 30 mM MCFFA	–
6b	16 mM BS, 15 mM MCMG, 30 mM MCFFA + tocopherol	–
7a	16 mM BS, 30 mM MCMG, 60 mM MCFFA	50.6 ± 0.9
7b	16 mM BS, 30 mM MCMG, 60 mM MCFFA + tocopherol	29.4 ± 1.4
10a	16 mM BS, 15 mM LCMG, 30 mM LCFFA	27.5 ± 0.8
10b	16 mM BS, 15 mM LCMG, 30 mM LCFFA + tocopherol	28.5 ± 1.2
11a	16 mM BS, 30 mM LCMG, 60 mM LCFFA	25.0 ± 0.6
11b	16 mM BS, 30 mM LCMG, 60 mM LCFFA + tocopherol	28.0 ± 2.0

–, not determined. For further reference, see Table 1.

different media are generally not affected by the presence of α-tocopherol.

The solubilising capacity of mixed micelles is significantly higher than that of simple bile salt micelles, but depends on the drug to be solubilised and on the chain length of LDP. The solubilising capacity of mixed micelles increases as the log *P* of the drug increases. Medium chain LDP seem to have a larger solubilising capacity toward drug molecules with relatively low log *P* values (griseofulvin), whereas long chain LDP have larger effects on drugs with high log *P* values (felodipine and Lu28-179).

Addition of α-tocopherol to simple bile salt solutions (simulating the fasted state) has no effect on the solubilising capacity. Addition of α-tocopherol to mixed micellar solutions has a positive effect on the solubility of griseofulvin, but no significant effect on the solubility of felodipine. α-Tocopherol has a positive effect on the solubility of Lu28-179 in medium chain media, which on their own, provide relatively poor solubilities. The results from the study of solubilising capacity of mixed micellar solutions underline the compound-specific nature of the interaction.

In general, α-tocopherol cannot be considered an important factor for the solubilisation of highly lipophilic drugs in intestinal fluids. The presence of LDP of the proper chain length in relation to the drug to be solubilised is much more important.

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References

Bates, T.R., Sequeira, J.A., 1975. Bioavailability of micronized griseofulvin from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms in humans. J. Pharm. Sci. 64 (5), 793–797.

Borgström, B., 1967. Partition of lipids between emulsified oil and micellar phases of glyceride-bile salt dispersion. J. Lipid Res. 8, 598–608.

Carey, C.M., Small, D.M., 1970. The characteristics of mixed micellar solutions with particular reference to bile. Am. J. Med. 49, 590–608.

Charman, W.N., Porter, C.J.H., Mithani, S., Dressman, J.B., 1997. Physicochemical and physiological mechanisms of the effects of food on drug absorption: the role of lipids and pH. J. Pharm. Sci. 86 (3), 269–282.

Cohn, W., Gross, P., Grun, H., Loechleiter, F., Muller, D.R.P., Zulauf, M., 1992. Tocopherol transport and absorption. Symposium on micronutrient transport processes. Proc. Nutr. Soc. 51, 179–188.

Gallo-Torres, H.E., 1970. Obligatory role of bile for the intestinal absorption of Vitamin E. Lipids 5 (4), 379–384.

Gallo-Torres, H.E., Ludrof, J., Brin, M., 1978. The effect of medium-chain triglycerides on the bioavailability of Vitamin E. Int. J. Vit. Nutr. Res. 45, 240–249.

Hernell, O., Staggers, J.E., Carey, M.C., 1990. Physical-chemical behaviour of dietary and biliary lipids during intestinal digestion and absorption. 2. Phase analysis and aggregation states of luminal lipids during duodenal fat digestion in healthy adult human beings. Biochemistry 29, 2041–2056.

Humberstone, A.J., Charman, W.N., 1997. Lipid-based vehicles for the oral delivery of poorly water-soluble drugs. Adv. Drug Del. Rev. 25, 103–108.

Kararli, T.T., 1995. Comparison of the gastrointestinal anatomy, physiology, and biochemistry of humans and commonly used laboratory animals. Biopharm. Drug Disp. 16, 351–380.

Mithani, S.D., Bakatselou, V., TenHoor, C.N., Dressman, J.B., 1996. Estimation of the increase in solubility of drugs as a function of the bile salt concentration. Pharm. Res. 13 (1), 163–167.

Müllertz, A., 1991. Langkædede polyumættede (n-3) fedtsyrer og deres betydning for lipid peroxidation. Afdelingen for Biokemi og Ernæring; Danmarks Tekniske Højskole, 85.

Sonne, M., 1995. Tocopherol compositions for delivery of biologically active agents International application published under the patent cooperation treaty; WO 95/31217, EP95-01835.

Takahashi, Y.I., Underwood, B.A., 1974. Effect of long and medium chain length lipids upon aqueous solubility of alpha-tocopherol. Lipids 9 (11), 855–859.

Tur, K.M., Ch'ng, H.-S., Baie, S., 1997. Use of bioadhesive polymer to improve the bioavailability of griseofulvin. Int. J. Pharm. 148, 63–71.