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International Journal of Pharmaceutics 246 (2002) 203–206

international journal of pharmaceutics

www.elsevier.com/locate/ijpharm

Note

Solubilizing potential of submicron emulsions and aqueous dispersions of lecithin

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Received 22 October 2001; received in revised form 10 July 2002; accepted 15 July 2002

Abstract

Aqueous lecithin dispersions (WLD, water-lecithin-dispersion) were obtained by dispersing egg lecithin (1.2 or 2.4% w/w) in an isotonic mixture of glycerol and water. The solubilization potential of the pure phospholipid structures was investigated and compared with that of submicron emulsions containing the same amounts of lecithin and 10 or 20% (w/w) of soya-bean oil. The increase in solubility of the investigated lipophilic drugs in WLD was proportional to the lecithin concentration. Concentration of lecithin in the emulsion was the main factor determining solubility of drugs moderately lipophilic (log *P* below 2.5), while for more lipophilic compounds the presence of oil was a determinant and for such drugs solubility in submicron emulsion was better than in WLD. WLD obtained in a simple technological process may be considered as a carrier particularly for highly lipophilic drugs: solubility of estradiol in this system was 100-fold higher than in water.

Keywords: Lecithin; Submicron emulsions; Solubility

Lecithin is a mixture of phospholipids with phosphatidylcholine as a main component (up to 98% w/w). Egg or soya lecithin as well as purified phospholipids are used for pharmaceutical purposes as components of liposomes, mixed micelles and submicron emulsions. All these structures are good carriers for lipophilic drugs and it is well documented that phospholipids play a significant role in solubilization of drugs in mixed micelles (Rosoff and Serajuddin, 1980; Hammad and Müller, 1998a,b,c). However, increased solubility of drugs in submicron emulsions is generally explained with the presence of the oily phase while contribution of lecithin to this effect has not been evaluated yet. In the systems containing phospholipids many different structures like: liposomes, lamellar or discoidal micelles, nanoparticles or network-like structures are present (Polozova et al., 1995; Stoye et al., 1998) and most probably these structures can also be present in submicron emulsions stabilized with lecithin (Westesen and Wehler, 1992; Groves and Herman, 1993). Thus, solubilization of drugs in emulsions may occur not only in the oily droplets or interphase but also in

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0378-5173/02/$ - see front matter
PII: S0378-5173(02)00395-2

phospholipid structures present in the aqueous phase.

Aqueous lecithin dispersion (WLD, water-lecithin-dispersion) is a system obtained by dispersing lecithin in water or in an isotonic aqueous solution (e.g. mixture of glycerol and water) with means of extensive mixing at temperature 40–60 °C in order to obtain good hydration of lecithin. In contrast to the well-known formulations like liposomes or mixed micellar systems (Hammad and Müller, 1998a; Stoye et al., 1998; Peters et al., 1999; Kirby and Gregoriadis, 1999), neither special manufacturing procedure, nor additional lipids and surfactants are used. WLD has not been used as a drug carrier system yet and to our knowledge the solubilization potential of such system has not been studied.

The aim of our experiments was to compare the solubility of drugs in submicron emulsion and in WLD in order to determine the effect of lecithin on solubilization of drugs in these two systems in relation to drug lipophilicity. The results might allow considering WLD as a carrier for water-insoluble drugs.

Submicron emulsions used for the studies contained 10 or 20% (w/w) soya-bean oil (Lipoid, Ludwigshafen, Germany), 1.2 or 2.4% (w/w) egg lecithin (Lipoid E-80; Lipoid) and 2.3% glycerol (90% w/w; Pollena-Strem, Dabrowa, Poland) and were prepared by a standard method (Benita and Levy, 1993). Shortly, lecithin was dispersed in a mixture of water and glycerol and combined with soya-bean oil at 85 °C. A primary emulsion was stirred with a high shear mixer (Ultra Turrax, Janke & Kunkel, Staufen, Germany) and homogenized at 500 bar (APV Gaulin homogenizer, Hilversum, The Netherlands). After adjustment of pH to 8.5 the emulsion was filtered through a 0.45 μm Durapore filter (Millipore, Bedford, USA) and sterilized by autoclaving (121 °C, 15 min).

WLD also contained 1.2 or 2.4% (w/w) lecithin and lack of the oil was the only difference in composition between WLD and emulsions. Egg lecithin, Lipoid E-80, was added to a water-glycerol mixture and stirred at 40 °C with a magnetic stirrer followed by a high shear mixer. The warm dispersion was filtered and sterilized as above.

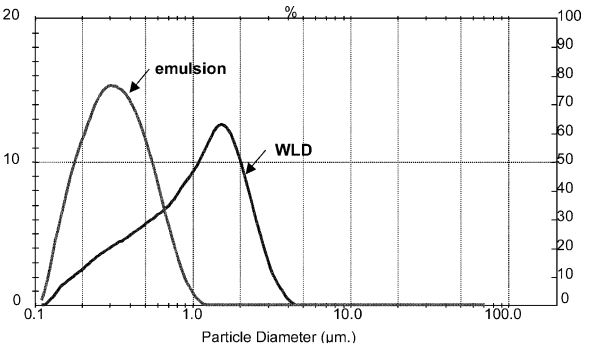

Fig. 1. Size distribution profiles of dispersed particles in WLD and submicron emulsion containing 1.2% (w/w) lecithin.

Evaluation of size of dispersed particles was performed using a laser diffractometer (Mastersizer E, Malvern Instr., Malvern, UK). Fig. 1 presents the particle size distribution in the formulations containing 1.2% lecithin. The mean droplet size in the emulsion was 0.32–0.37 μm with largest particles 4.3 μm, while the phospholipid particles in WLD were in the range 0.05–5 μm with the mean diameter 1.5 μm. The same particle size profile was observed for systems containing 2.4% lecithin. Worth of noting is a fact that larger samples of WLD were required for the size distribution measurements: nearly 20 ml of WLD had to be used for each measurement while only 0.5 ml of submicron emulsion was sufficient under the same conditions. This may be explained by different optical characteristics, particle number, size and nature of both systems.

The following drugs were used for solubility studies: hydrocortisone (Deutsche, Sinochem, Germany and Polfa, Pabianice, Poland), testosterone (Sigma, USA), dexamethasone (Polfa, Warsaw, Poland), estradiol (Jelfa, Jelenia Gora, Poland), carbamazepine (Polpharma, Starogard, Poland), diazepam (Polfa, Poznan, Poland). Drugs were added in excess to water, soya-bean oil, aqueous lecithin dispersion or to emulsion and shaken for at least 18 h at 20±2 °C. The suspensions were filtered through 0.45 μm cellulose acetate filter (Millipore). Drug concentration in the filtrate was analyzed using RP-HPLC method with UV detection (Merck-Hitachi HPLC system, Darmstadt, Germany). A mobile phase consisting of water,

Table 1
Drug solubility (±sd) in the investigated systems (mg/ml)

Drug	log *P*	WLD		Submicron emulsion			Water	Soya-bean oil
		1.2%	2.4%	10% oil		20% oil		
				1.2% lecithin	2.4% lecithin	1.2% lecithin		
Hydrocortisone (H)	1.61	0.76±0.03	1.19±0.12	0.89±0.07	1.37±0.08	0.96±0.04	0.38±0.01	0.18±0.01
Dexametasone (DEX)	1.83	0.23±0.03	0.51±0.01	0.40±0.01	n.d.	0.39±0.02	0.07±0.002	0.055±0.004
Carbamazepine (C)	2.45	0.42±0.01	0.73±0.01	0.60±0.01	n.d.	0.63±0.06	0.12±0.01	0.93±0.04
Diazepam (D)	2.7	0.39±0.03	0.80±0.03	2.05±0.03	n.d.	4.0±0.03	0.05±0.03	13.5±0.03
Testosterone (T)	3.32	0.15±0.01	0.32±0.01	0.41±0.02	0.49±0.02	0.63±0.05	0.021±0.001	4.30±0.13
Estradiol (E)	4.01	0.060±0.010	0.191±0.012	0.102±0.005	n.d.	0.235±0.030	0.001±0.000	0.796±0.01

WLD, aqueous lecithin dispersion; n.d., not determined.

methanol and acetonitrile (Merck, Darmstadt, Germany) in the ratio of 50:25:25 (v/v) was used for the HPLC analysis of hydrocortisone and dexamethasone. For the analysis of carbamazepine and estradiol 28 and 45% v/v acetonitrile were used, respectively, while 65% v/v methanol was used in case of diazepam and testosterone.

The results of the solubility studies are presented in Table 1. The numbers were obtained from at least four (4–8) independent experiments and Student's *t*-test was performed to evaluate results statistically.

In comparison to water all investigated formulations provided increased solubility of drugs ($P < 0.05$) selected from the range of log *P* 1.6–4.0. For all investigated drugs but estradiol the solubility in 2.4% WLD was 1.6–2.2 times higher than in 1.2% WLD. In the case of estradiol more than 3-fold increase of solubility was achieved with increase of lecithin concentration from 1.2 to 2.4%. In contrast, solubility of drugs in submicron emulsions can not be correlated with lecithin concentration. Although 2 times increase of lecithin concentration in 10% emulsion resulted in 2 times higher solubility of less lipophilic hydrocortisone, but solubility of testosterone increased only by 25%. For more lipophilic compounds (log *P* 2.7 or larger), the presence of oil, not lecithin, is the main factor determining solubility. An increase in solubility of such drugs by 50% (testosterone) or 100% (diazepam, estradiol) was achieved increasing oil content from 10 to 20%.

On the other hand the presence of the oily phase does not influence solubility of less lipophilic drugs (log $P < 2.5$). For those compounds better solubility was achieved in WLD containing 2.4% lecithin than in emulsion containing 20% oil and 1.2% lecithin ($P < 0.05$). Such observation was true even for carbamazepine, whose solubility in soya oil was 8 times higher than in water. This supports a hypothesis that less lipophilic drugs are solubilized in submicron emulsion mainly by phospholipids.

Fig. 2 presents the relationship between drug lipophilicity and solubilization potential of sub-

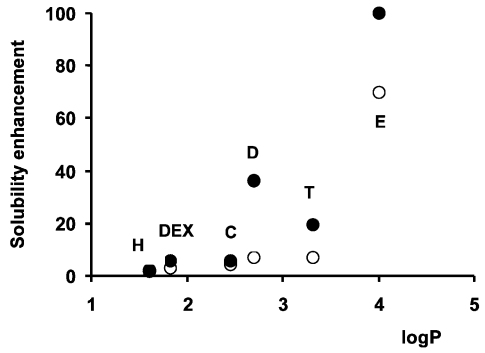

Fig. 2. Relationship between log *P* and solubility enhancement of drugs in 10% submicron emulsion (●) or WLD (○) containing 1.2% lecithin. (For abbreviations of drugs refer to Table 1).

micron emulsions and WLD expressed as a multiple of the solubility in water. The increase of solubility by 2–4 times with emulsion or WLD for less lipophilic drugs is too low to consider these systems as good solubilizing carriers. However solubility of the most lipophilic drug, estradiol, is increased 60–100 times, although the final solubility of estradiol is still not very high, namely 0.02% w/v. Increase of solubility of diazepam in submicron emulsion is higher than predicted from the observed correlation, what results from a very good solubility of diazepam in soya-bean oil (Table 1). Interestingly, the solubility of diazepam in WLD was only slightly lower than in dispersions of mixed micelles with 5% content of the surfactants. Hammad and Müller (1998a) found that solubility of diazepam in such system was 1.0–1.1 mg/ml.

WLD obtained in a simple technological process may become an alternative carrier for drugs poorly soluble in water. Our preliminary results indicate that physical stability of the system is satisfactory and chemical stability may be accomplished under condition of protection against oxidation by saturation with nitrogen. The studies on the internal structure of these systems are in progress.

Acknowledgements

This research was financially supported by the State Committee for Scientific Research, Poland (Grant 6 P05F 021 20).

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