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Comparison of the lymphatic transport of a lipophilic drug from vehicles containing α-tocopherol and/or triglycerides in rats

P. B. Nielsen, A. Müllertz, T. Norling and H. G. Kristensen

Abstract

The applicability of α-tocopherol as a lymphotropic carrier for a highly lipophilic drug has been evaluated. Transport to the intestinal lymph of the highly lipophilic model drug, Lu28-179, in rats after administration to the stomach in an α-tocopherol emulsion was compared with lymphatic transport after administration of a sesame oil emulsion and an α-tocopherol/sesame oil emulsion. Lymphatic transport of the triglycerides and of α-tocopherol was determined. A conscious rat model was used, and the mesenteric lymph was collected. There was no significant difference between the cumulative masses of triglyceride from the two emulsions containing triglyceride 24 h after administration. Administration of an α-tocopherol emulsion seemed to induce mobilization of endogenous triglyceride. The lymphatic transport of α-tocopherol was less than 1 mg 24 h after administration of both emulsions containing α-tocopherol. The absorption of Lu28-179 from the α-tocopherol emulsion was very low, with a lymphatic recovery of 0.05 %. When administered in an α-tocopherol/sesame oil emulsion, the recovery of Lu28-179 increased sevenfold to 0.35 %. However, after administration of Lu28-179 in a sesame oil emulsion, the lymphatic recovery increased a further 13-fold to 4.5 %. In conclusion, the study showed that α-tocopherol did not promote lymphatic absorption of Lu28-179 and thus was not a good lymphotropic carrier, as compared with sesame oil. α-Tocopherol in combination with sesame oil was not a good lymphotropic carrier either. The non-absorbed α-tocopherol fraction in the intestine might be able to prevent the absorption of Lu28-179.

Dumex-Alpharma ApS, Dalslandsgade 11, 2300 Copenhagen S, Denmark

P. B. Nielsen, T. Norling

Department of Pharmaceutics, the Royal Danish School of Pharmacy, Universitetsparken 2, 2100 Copenhagen Ø, Denmark

A. Müllertz, H. G. Kristensen

Correspondence: A. Müllertz, Department of Pharmaceutics, The Royal Danish School of Pharmacy, Universitetsparken 2, 2100 Copenhagen Ø, Denmark.

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Introduction

Orally administered drugs are generally absorbed via the portal blood to the systemic circulation. Lipid digestion products, lipid soluble vitamins, cholesterol, and other lipophilic drugs are, however, mainly transported via the lymphatic system. Drugs transported by the intestinal lymphatic system circumvent the liver and hence hepatic first-pass metabolism. Moreover, the lymphatic route is the primary pathway for tumour metastases and therefore an important target for anticancer drugs (Muranishi 1991).

Lipophilic drugs or prodrugs may gain access to the lymph by entering the lipid digestion pathway and by incorporation into chylomicrons. As described by Charman & Stella (1986), highly lipophilic drugs (log P > 5, triglyceride solubility > 50 mg mL^{-1}) may associate with chylomicrons after absorption and as a result may gain access to the intestinal lymph. Triglycerides with long chain fatty acids are generally used as co-administered lipid or vehicle. These are relatively good solvents

for many lipophilic drugs and they are themselves incorporated into chylomicrons and transported by the lymphatic system. α-Tocopherol is also a very good solvent for many lipophilic drugs (Sonne 1995). It is absorbed by passive diffusion through the intestinal wall, incorporated into chylomicrons, and is then transported via the lymph to the systemic circulation. The absorption of α-tocopherol to the lymph is increased by co-administration of triglycerides (Gallo-Torres et al 1971).

The aim of this study was to investigate the applicability of α-tocopherol or α-tocopherol in combination with a triglyceride as a lymphotropic carrier for a highly lipophilic drug, as compared with triglycerides alone. The lymphatic absorption of the highly lipophilic model drug, Lu28-179, from an α-tocopherol, a sesame oil, and an α-tocopherol/sesame oil emulsion was investigated in a restrained conscious rat model. Mesenteric lymph was collected.

Materials and Methods

Chemicals and reagents

Lu28-179 (base) (H. Lundbeck A/S, Denmark), α-tocopherol (BASF, Norway), tocopherol polyethylene glycol 1000 succinate (TPGS) (BASF, Norway), Lutrol F68 (poloxamer, BASF, Germany), mono-olein (Rylo MG15, Danisco, Denmark), Hypnorm (Janssen), Dormicum (Roche), Torbugesic Vet. (American Home Products), sodium pentobarbital (Lyngby Svane Apotek), D-glucose, sodium chloride, potassium chloride, Titriplex III (EDTA), hexane, methanol (all Merck), MPR2 Triglycerides GPO-PAP 701912 (kit for the analysis of triglycerides) (Roche), sesame oil (Henry Lamotte, Germany). The sesame oil used in the study contained triglycerides with the following content of fatty acids: C16:0 (8.5%), C18:0 (5.5%), C18:1 (39.2%), C18:2 (45.2%), C20:0 (0.8%).

Animals

Sprague-Dawley male rats (Mol:SPRD) (300–350 g on the day of surgery) from M&B (Lille Skensved, Denmark) were used. The animals were subject to health monitoring according to the Federation of European Laboratory Animal Science Associations guidelines and acclimatized for 10–12 days in separate rooms before surgery. Each room had its own ventilation system. The temperature was kept at 19–23°C with a relative humidity of 50–60%. The animals were held in transparent Techni-plastic macrolone cages type III (180 × 320 × 450 mm) with two rats in each cage. Tapvei aspen was used as bedding, and the feed was Altromin 1324 pellets, from Chr. Petersen, Ringsted, Denmark. Fresh drinking water was freely available.

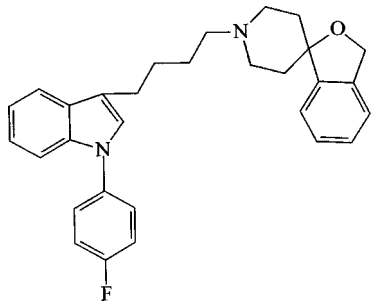

Figure 1 The structure of Lu28-179.

The model drug

The model drug used was a newly developed compound called Lu28-179 (Figure 1), kindly provided by H. Lundbeck A/S, Denmark. The molecular weight of Lu28-179 was 454.6 g mol^{-1}, with an estimated log P value of approximately 8, and a pK_a value of 8.5. The aqueous solubility of Lu28-179 was 4 ng mL^{-1}. The solubility of Lu28-179 in α-tocopherol and α-tocopherol/sesame oil (1:1, w/w) was 58 and 95 mg g^{-1}, respectively. The solubility of Lu28-179 in soybean oil and sesame oil was approximately 50 mg g^{-1}. It therefore complied with the demands for a drug likely to be transported by the lymphatic route, but unfortunately Lu28-179 was not a drug whose solubility in α-tocopherol was better than its solubility in triglyceride.

Manufacture of preparations

Three different preparations (emulsions) representing three different treatments were used. Preparation A was an α-tocopherol emulsion, preparation B was a sesame oil emulsion, and preparation C was an α-tocopherol/sesame oil (1:1) emulsion. The oily phase of the emulsions accounted for 40% of the total volume. All three emulsions contained the same amount (10 mg g^{-1}) of dissolved drug, and it was therefore possible to administer the same dose (5 mg) with the same volume (0.5 g) with all treatments. The choice of concentration in the emulsion was based on results from previous in-vivo studies performed by H. Lundbeck A/S (unpublished data). All the emulsions contained the same emulsifying system (2.5% TPGS, 2.5% mono-olein,

and 5% Lutrol) and were prepared by mixing the aqueous phase (water and Lutrol), adjusting the pH (8.5), and heating it to approximately 60°C. The oily phase (α-tocopherol and/or sesame oil and TPGS, mono-olein and Lu28-179) was mixed and heated. The aqueous phase was added to the oil phase by use of a pump (approximately 8 mL min^{-1}) under stirring on a Heidolph stirrer (130 rev min^{-1}). The mixture was stirred for approximately 15 min at 40 rev min^{-1}. The emulsion was homogenized on ice with an Ultra Turrax at 24000 rev min^{-1} for 10 min. All emulsions had an average particle size diameter of approximately 5 μm. All emulsions were physically stabile for the duration of the experimental studies.

Surgical procedures

The Danish Animal Experiments Inspectorate approved all surgical and experimental procedures. The rats were anaesthetised by intraperitoneal injection of an 0.8-mL mixture of Hypnorm, Dormicum, and water (1:1:2). The mesenteric lymph duct was cannulated by the method of Bollman et al (1948), with some modification. Polyvinyl chloride tubing (i.d. 0.5 mm, o.d. 0.8 mm; Critchley Electrical Products, Australia), rinsed with heparin-saline solution (200 U mL^{-1}) was used for the lymph cannulation. The cannula was kept in place with a drop of instant cyanoacrylate adhesive instead of a silk ligature. The cannula was externalized through the abdominal wall. A silicone tube (i.d. 1.0 mm, o.d. 3.0 mm; Critchley Electrical Products, Australia) was led through the abdominal wall on the left side of the rat to the non-glandular part of the stomach, and sutured. The rats received a solution of sugar and salts (55 g L^{-1} D-glucose, 9 g L^{-1} sodium chloride, 0.15 g L^{-1} potassium chloride) at a rate of 2 mL h^{-1} through the stomach cannula from the end of surgery until the end of the experiment. After completion of the surgical procedures, and just before arousal from the anaesthetic, the rats were placed and fixed in Bollman cages (Bollman 1948). The rats were stabilized for 16–24 h while fasting and received 0.2 mL of a 1:10 dilution of Torbugesic Vet. (analgesic) once during stabilization. At the end of each experiment, the rats were killed with an overdose of sodium pentobarbital through the stomach cannula.

Lymphatic absorption studies

Dosing

One treatment was given to each rat. Each treatment (A–C) was given in a randomized order to seven rats, giving a total of 21 studies. The emulsions were given through the stomach cannula by means of a syringe and needle. The rats received 0.5 g of the emulsions. Table 1 summarizes the amount of triglycerides, α-tocopherol, and Lu28-179 given to each rat with the dose. Additionally 0.5 mL of the sugar/salt solution was given through the cannula.

Sampling

The lymph was collected in 5-mL tubes containing 100 μL of a 0.26 M EDTA solution. (Sample No. 10 contained 500 μL EDTA in an Erlenmeyer flask). The lymph was collected at 1-h intervals from 1 h before dosing to 8 h after dosing. One sample from 8 h to 23 h after dosing and one sample from 23 h to 24 h post dosing were collected, making a total of 11 samples per experiment. The collected lymph was weighed. The lymph samples were kept at −20°C until analysed.

Analyses

The concentration of Lu28-179, the total amount of triglyceride and the concentration of α-tocopherol were determined in all lymph samples, provided that the amount of sample collected was sufficiently large for all analyses. Analyses were prioritized in the order mentioned.

Concentration of Lu28-179

A specific HPLC method for quantitative determination of Lu28-179 in the range 2–250 ng/sample in rat serum and lymph was used. The method involved liquid–liquid extraction of the test compound and internal standard followed by HPLC analysis and quantification by fluorescence detection.

Before analysis the method was validated as a full six-day validation in serum and a reduced two-day validation in rat lymph. The method was found valid for accurate, precise and specific determination of Lu28-179 in rat serum and lymph in the range 0–250 ng/sample with an LOQ (limit of quantitation) of 2 ng/sample using 500-μL samples. The overall performance of the analytical method was found to be satisfactory for the purpose of determining concentration levels in rat lymph samples.

Unknown samples, QC (quantification control) samples and calibration standards were shaken for 15 min on a shaking apparatus, after addition of internal standard, 100 μL 2 M NaOH and 4.0 mL n-heptan containing 1% isobutanol. The samples were then centrifuged for 5 min at approximately 1900 *g* and frozen in a mixture of ethanol and dry ice. The organic phase was

Table 1 The amount of triglycerides, α-tocopherol, and Lu28-179 given to each rat with one dose of 0.5 g.

Treatment	Amount per dose (mg)		
	Triglycerides	α-Tocopherol	Lu28-179
α-Tocopherol emulsion (A)	0	200	5
Sesame oil emulsion (B)	200	0	5
α-Tocopherol/sesame oil emulsion (C)	100	100	5

transferred to a 10-mL test tube and aspirated off under nitrogen in a Zymac, TurboVap LV evaporator. The residue was dissolved in 150 μL of the mobile phase and injected on the HPLC-system. Analyses were performed on 500 μL lymph. If the content of Lu28-179 exceeded 250 ng a reduced volume of lymph was used and the samples were made to 500 μL using control rat serum.

An HPLC system consisting of the following components, all from (Merck) Hitachi (Tokyo, Japan), was used: L-7100 pump, L-7250 autosampler, L-7480 fluorescence detector, L-7300 column oven, D-7000 interface and HSM Data System. Separation was performed on an HP Hypersil column (100 × 4.6 mm i.d., 5-μm particles) from Hewlett-Packard. The mobile phase for the pseudo-normal phase chromatographic method consisted of a mixture of acetonitrile and a solution containing 0.15 M ammonium acetate (98.5/1.5, v/v). The flow rate was 1.5 mL min^{-1}. The injection volume was 75 μL. The column oven temperature was 35°C. The wavelengths of excitation and emission were respectively 257 nm and 380 nm. H. Lundbeck A/S performed the analyses.

Total amount of triglycerides

Lymph triglyceride concentrations were determined by an enzymatic colorimetric method and assayed at 500 nm on a Cary 1Bio UV spectrophotometer (Varian Instruments, Victoria, Australia).

Concentration of α-tocopherol

A specific HPLC method for quantitative determination of α-tocopherol in the range 5–125 μg mL^{-1} in rat lymph was used. The method was modified from Müllertz (1991). The method involved liquid–liquid extraction of the test compound followed by HPLC analysis and quantification by fluorescence detection. The method was found valid for accurate and specific determination of α-tocopherol in the range 0–125 μg mL^{-1} with an LOQ of 1 μg mL^{-1} using 0.6-mL samples.

α-Tocopherol was extracted from the lymph samples in the following way: 300 μL of a α-tocopherol standard solution (5–100 μg mL^{-1}) in a tube was aspirated off under nitrogen and 300 μL of blind lymph was added. From here on, samples and standards were treated equally. A 300-μL lymph sample and 3 mL hexane were whirly mixed for 30 s. The mixture was centrifuged for 5 min at 20°C and 3000 rev min^{-1} and 2.4 mL of the hexane phase was collected. An additional 3 mL hexane was added to the lymph samples, then whirly mixed and centrifuged as described above. A 3.0-mL sample of the hexane phase was collected. The 5.4-mL hexane phases were aspirated off under nitrogen in a Zymac, TurboVap LV evaporator. The samples were redissolved in 0.6 mL mobile phase, whirly mixed, and transferred to vials.

The HPLC system for the α-tocopherol analysis consisted of a Waters 510 pump, a Waters Scanning Fluorescence Detector 470, a Waters WISP injector 712, and a HP 3390 A integrator. The column was a 250 × 4.6 mm Spherisorb S5 ODS1, maintained at 30°C by a column oven. The wavelengths of excitation and emission were 290 nm and 330 nm, respectively. The mobile phase consisted of methanol/hexane/water (90:5:5, v/v). The flow rate was 1.0 mL min^{-1} and the injection volume 20 μL. The area was used as a measure for the concentration of α-tocopherol.

Data handling

The amount of total triglyceride, α-tocopherol, and Lu28-179 in each sample was calculated by multiplication of the concentration and volume of each sample. These values were then accumulated and expressed as a percentage (w/w) of the orally administered dose. Statistical significance for the comparison of formulations was tested by Turkeys honestly significant difference (HSD) procedure.

Results and Discussion

Table 2 summarizes the cumulative mass and % dose found for total triglyceride, α-tocopherol, and Lu28-179 for each of the three emulsions.

Table 2 Cumulative masses and % dose of total triglycerides, α-tocopherol, and Lu28-179, as mean ± s.e. for each treatment 24 h after gastric administration.

	Total triglyceride		α-Tocopherol		Lu28-179	
Treatment	Cumulative mass (mg)	Cumulative dose (%)	Cumulative mass (mg)	Cumulative dose (%)	Cumulative mass (μg)	Cumulative dose (%)
α-Tocopherol emulsion	28.6 ± 30.7 (n = 7)	–	1.0 ± 0.2 (n = 5)	0.5 ± 0.1(n = 5)	2.5 ± 0.5 (n = 7)	0.05 ± 0.01 (n = 7)
Sesame oil emulsion	273.9 ± 28.5 (n = 7)	136.9 ± 14.3 (n = 7)	0.2 ± 0.05 (n = 6)	–	227.1 ± 34.3 (n = 7)	4.5 ± 0.7 (n = 7)
α-Tocopherol/sesame oil emulsion	230.1 ± 49.3 (n = 5)	230.1 ± 49.3 (n = 5)	0.8 ± 0.1 (n = 5)	0.8 ± 0.1 (n = 5)	17.5 ± 5.1 (n = 7)	0.4 ± 0.1 (n = 7)

Lymphatic transport of triglycerides

Figure 2 shows the mean (± s.e.) cumulative mass of total triglycerides transported in the lymph after oral administration of the three emulsions as a function of time. No correction for endogenous triglyceride concentrations in the mesenteric lymph was made.

The α-tocopherol emulsion did not contain triglycerides, and thus the lymphatic triglyceride flow in this group reflected the endogenous triglyceride production. The initial triglyceride flow (from 0 to 8 h) was approximately 9 mg h^{-1}. In the literature, the average endogenous triglyceride output in conscious rats has been reported to vary between 1.06 and 5.64 mg h^{-1} (Porter et al 1996; Caliph et al 2000). Even though the apparent triglyceride flow in this study seemed to be higher than other published data it was not possible to conclude that α-tocopherol induced endogenous triglyceride production.

There was no significant difference between the cumulative masses of total triglycerides 24 h after administration of the two emulsions containing triglyceride, even though different amounts of triglyceride were given with the emulsions (see Table 1). This might be explained by endogenously formed triglycerides induced by α-tocopherol. However, it has been suggested that exogenous lipid is able to stimulate the turnover of endogenous lipid (Caliph et al 2000). Cumulative % dose values above 100% were attained (Table 2), as no correction for endogenous levels of triglycerides was made. There was a significant difference ($P < 0.05$) between the cumulative masses of total triglycerides 24 h after administration of the tocopherol emulsion and the triglyceride emulsion.

Lymphatic transport of α-tocopherol

Figure 3 shows the mean (± s.e.) cumulative mass of α-tocopherol transported in the lymph after administration of the three emulsions as a function of time. No values on endogenous output of α-tocopherol in conscious rats have been found in the literature, hence, no correction for these values has been made. The amount of α-tocopherol found in the lymph after administration of the sesame oil emulsion might reflect the endogenous level of α-tocopherol.

Twenty-four hours after administration of the two emulsions containing α-tocopherol less than 1 mg α-tocopherol was recovered in the lymph, corresponding

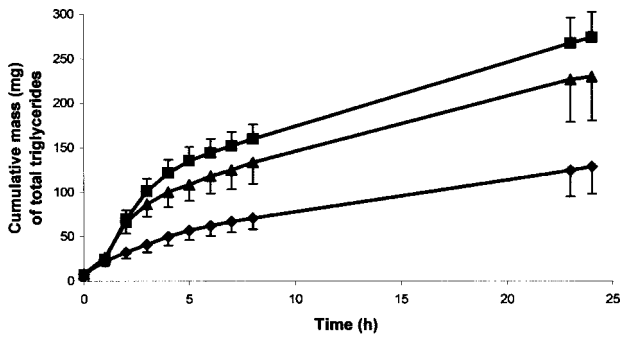

Figure 2 Cumulative mass of total triglycerides (mean ± s.e.) recovered in the lymph. Administered preparations were: ◆ α-tocopherol emulsion (n = 7); ■ sesame oil emulsion (n = 7); ▲ α-tocopherol/sesame oil emulsion (n = 5).

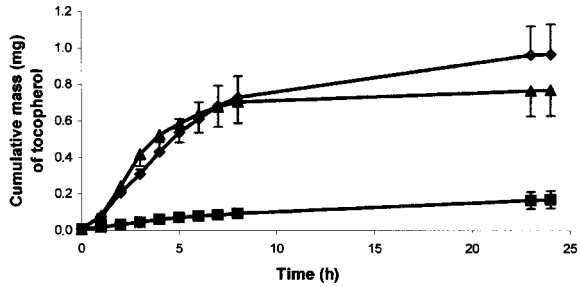

Figure 3 Cumulative amount of α-tocopherol (mean ± s.e.) recovered in the lymph. Administered preparations were: ◆ α-tocopherol emulsion (n = 5); ■ sesame oil emulsion (n = 6); ▲ α-tocopherol/sesame oil emulsion (n = 5).

to less than 1% of the administered dose. Gallo-Torres et al (1971) found that the absorption of α-tocopherol was enhanced by co-administration of triglycerides. This effect was not obvious in this study.

There was no significant difference in the cumulative masses of α-tocopherol 24 h after administration of the two emulsions containing α-tocopherol, even though the α-tocopherol emulsion contained twice the amount of α-tocopherol as compared with the α-tocopherol/sesame oil emulsion. On the other hand, when recoveries of administered amounts of α-tocopherol were compared, the α-tocopherol emulsion showed the lowest recovery indicating that the absorption efficiency decreased with a high content of α-tocopherol in the emulsion. The cumulative mass of α-tocopherol 24 h after administration of the triglyceride emulsion was significantly lower ($P < 0.05$) than after administration of the two emulsions containing α-tocopherol. Porsgaard & Høy (2000) investigated the absorption efficiencies of tocopherols in naturally occurring concentrations from rapeseed, soybean and sunflower oil. They found that the lymphatic recoveries 24 h after oil administrations decreased when the α-tocopherol concentration increased, although there still was a positive correlation between the amounts of α-tocopherol transported via the lymph and the concentrations in the oils: 78.8% (25.2 μg) was recovered from the soybean oil that contained 32 μg α-tocopherol per dose, whereas only 21.4% (41.5 μg) was recovered from the sunflower oil that contained 194 μg α-tocopherol per dose. Higher concentrations of α-tocopherol in the lymph were obtained in this study, as compared with the study by Porsgaard & Høy (2000), but our recoveries were lower.

α-Tocopherol recovery in rats varies widely between different studies. Kellerher et al (1972) found that increases in the administered dose of α-tocopherol to rats from 40 μg to 20 mg (in an arachis oil solution) led to a marked decrease in the lymphatic recovery of α-tocopherol, from 67.5% (27 μg) to 31.5% (6.3 mg). MacMahon et al (1971) reported a lymphatic recovery of α-tocopherol of 42% (109 μg) after the administration of 260 μg α-tocopherol in a mixed miceller solution. Bjørneboe et al (1986) found lymphatic recoveries of α-tocopherol of 22% (220 μg) and 15% (1.5 mg) after administration of respectively 1 and 10 mg α-tocopherol in 300 μL soybean oil. The results presented in those studies and those obtained in this study seem to indicate that the lymphatic transport of α-tocopherol is a saturable process, and that the recovery of α-tocopherol depends on the amount and the form in which it is administered, the amount of co-administered triglycerides, and the methodologies used.

Lymphatic transport of Lu28-179

Figure 4 shows the mean (±s.e.) cumulative % dose of Lu28-179 transported in the lymph after administration of the three emulsions as a function of time. The lymphatic recovery of Lu28-179 from the sesame oil emulsion was 4.5%, whereas recovery from the α-tocopherol/sesame oil emulsion was 0.35%, and recovery from the α-tocopherol emulsion was only approximately 0.05% 24 h after administration. There was a significant difference ($P < 0.05$) between the cumulative mass 24 h after administration of the triglyceride emulsion as compared with the cumulative mass after administration of the α-tocopherol/sesame oil emulsion and the α-tocopherol emulsion.

As shown in Figure 2, approximately the same amount of triglyceride was absorbed with the sesame oil emulsion and the α-tocopherol/sesame oil emulsion. It is therefore remarkable that the lymphatic recovery of Lu28-179 from the α-tocopherol/sesame oil emulsion was 13-fold lower compared with the sesame oil emulsion. This difference might be because of the presence of non-absorbed α-tocopherol administered with the α-tocopherol/sesame oil emulsion in the intestine. This relatively large amount of non-absorbed α-tocopherol might prevent the absorption of Lu28-179, owing to unfavourable partitioning between the oily phase and the miceller phases in the intestine. It might also be due to competition between Lu28-179 and α-tocopherol for incorporation into chylomicrons. The difference in recovery of Lu28-179 between the α-tocopherol emulsion and the α-tocopherol/sesame oil emulsion was attributed to the presence of triglyceride, which is a good lymphotropic carrier.

It was not possible to collect simultaneous blood samples. Therefore, it is not known to what extent lymphatic absorption of Lu28-179 contributed to the

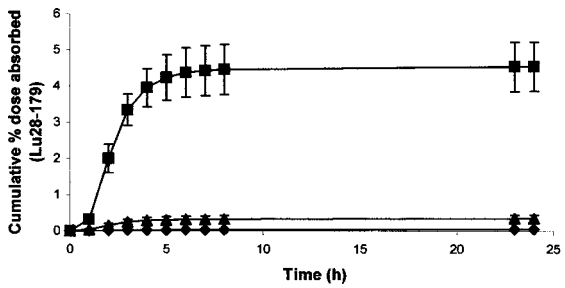

Figure 4 Cumulative % dose of Lu28-179 (mean ± s.e.) recovered in the lymph. Administered preparations were: ◆ α-tocopherol emulsion (n = 7); ■ sesame oil emulsion (n = 7); ▲ α-tocopherol/sesame oil emulsion (n = 7).

overall absorption of Lu28-179. Noguchi et al (1985) reported lymphatic recoveries of testosterone and four prodrugs administered in oleic acid to be less than 1%. The recoveries increased with an increasing log P of the prodrugs (log P from 1 to 9). The lymphatic recovery of halofantrine (log P 8.5) has been found to be 17% after administration as a triglyceride solution (Porter et al 1996). The lymphatic recoveries of DDT (log P 6.2) from an oleic acid and a peanut oil solution were respectively 36% and 18% (Charman et al 1986). These examples show that lymphatic recoveries of drugs depend on the physicochemical properties of the drug itself (e.g. log P, triglyceride solubility), on the structure of the co-administered lipids (chain length and degree of saturation), and on dosage form factors.

Conclusion

This study showed that α-tocopherol was not a good lymphotropic carrier for Lu28-179 as compared with sesame oil. α-Tocopherol in combination with sesame oil was not a good lymphotropic carrier either, even though it yielded a lymphatic recovery that was seven times better than the simple α-tocopherol preparation, but still 13-times lower than the sesame oil preparation. The non-absorbed α-tocopherol fraction in the intestine might have been able to prevent the absorption of Lu28-179. This might have been different for other substances, especially if the solubility of the substance was sufficiently high in order to reduce the amount of tocopherol needed for delivery.

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