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In vivo evaluation of tablets and capsules containing spray-dried o/w-emulsions for oral delivery of poorly soluble drugs

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Abstract

It is recognised that poorly soluble drugs may show an increased oral bioavailability when incorporated in o/w-emulsions. Encapsulating the emulsion lipid droplets in hydroxypropyl methylcellulose (HPMC) by spray drying has been demonstrated to preserve an improved bioavailability releasing lipid droplets from the powder in vivo. However, the spray-dried powder is cohesive and bulky requiring additional processing to improve handling. This was resolved in previous work where a directly compressible dry emulsion formulation was described. The purpose of the present study is to investigate the oral bioavailability resulting from administration of a directly compressible dry emulsion as a tablet and compare it with a HPMC dry emulsion powder and a simple lipid solution. Four female Beagle dogs received a single dose of each formulation containing the same amount of medium-chain triglycerides (MCT) and a model drug, Lu 28-179. Cyclodextrin solutions administered orally and intravenously were used as references. The absolute bioavailability decreased in the order cyclodextrin solution (0.14), HPMC dry emulsion (0.11), technically improved dry emulsion (0.10) and MCT solution (0.06). The directly compressible dry emulsion tablets were concluded to be comparable to a HPMC dry emulsion powder in terms of bioavailability. The lack of statistically significant differences relative to a MCT solution was ascribed to a low and variable absolute oral bioavailability of the model drug.

Keywords: Oral absorption; Poorly soluble drug; Dry emulsion; Lipid solution; Medium-chain triglycerides; Beagle dogs

1. Introduction

The use of high throughput screening in drug discovery has led to an increasing number of new drug substances having low aqueous solubilities and

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hence poor oral bioavailability when administered using a conventional tablet or capsule formulation. These drugs often have an improved bioavailability when co-administered with lipids, which has resulted in a growing interest in developing lipid formulations for oral administration (Charman, 2000; Pouton, 2000). Applying a lipid solution of a drug an increased bioavailability may arise due to the elimination of the dissolution step. Dispersing a drug in a lipid, an increased dissolution rate may be caused by a solubilising effect of the lipid digestion products. Furthermore, this has the potential to maintain the drug in a dissolved state during transport to the unstirred water layer of the intestinal membrane (Charman et al., 1997). Compared with a simple lipid solution or dispersion of a drug the incorporation of the lipid phase in an o/w-emulsion, increasing lipid surface area, may increase the bioavailability further (Carrigan and Bates, 1973; Chakrabarti and Belpaire, 1978). The effect is ascribed to an improved dispersion of the lipid phase resulting in a more efficient absorption (Humberstone and Charman, 1997). Unfortunately, the use of o/w-emulsions is complicated by their relatively large volume and thermodynamical instability. These problems have been attempted resolved by spray drying o/w-emulsions to obtain powders containing discrete stabilised lipid droplets. The o/w-emulsion can be reconstituted from the powder before dosing or on contact with the intestinal fluids, thereby, maintaining an improved bioavailability relative to a simple lipid solution or dispersion of the drug. The preservation of the initial emulsion lipid droplet size distribution can be achieved using various excipients. Formulations based on encapsulation using colloidal silica (Takeuchi et al., 1992), hydroxypropyl methylcellulose (HPMC) (Christensen et al., 2001a) or caseinate and water-soluble carrier material (Pedersen et al., 1998; Dollo et al., 2003) have been successfully applied. The ability of spray-dried emulsions to improve the oral bioavailability of poorly soluble drugs has been demonstrated for Vitamin E acetate (Takeuchi et al., 1991), 5-phenyl-1,2-dithiole-3-thione (Dollo et al., 2003) and 1′-[4-[1-(4-fluorophenyl)-1-*H*-indol-3-yl]-1-butyl]spiro[*iso*-benzofuran-1(3H), 4′ piperidine] (Lu 28-179) (Christensen, 2004).

From a dosing and handling point of view it may be considered advantageous if the dry emulsion is suitable for dosing as tablets or capsules. Of the formulations mentioned above, only the HPMC dry emulsion (Christensen et al., 2001b) has been investigated in this respect. In order to be effectively incorporated in tablets this spray-dried powder had to be granulated to overcome its poor flowability. In previous work, a technically improved spray-dried emulsion, which is directly compressible; thus, easing the manufacture of tablets was described (Hansen et al., 2004). However, in terms of lipid droplet size following disintegration the tablets prepared using this formulation may be inferior to a HPMC dry emulsion tablet or powder. References are often made to the observations on absorption of cyclosporin in a rat perfused intestine model of absorption (Tarr and Yalkowsky, 1989) to conclude that a reduction in lipid droplet size causes a further increase in bioavailability. But perfusion does not account for the intestinal processing of lipids, which has the potential to reduce the droplet size of an ingested emulsion. Thus, a dog study conducted by Porter et al. (1996) indicated that oral absorption of cyclosporin might not be very sensitive to the degree of lipid dispersion if a self-emulsifying formulation is applied. In contrast, the lipid droplet size was found important for oral absorption of penclomidine in rats whereas digestion of the droplets was not (De Smidt et al., 2004). It was noted that drugs having higher log *P*-values might depend differently on the absorptive pathways. Thus, indicating that an effect of lipid dispersion might depend on the drug in question requiring individual in vivo evaluation.

A previous study on Lu 28-179 showed that the oral bioavailability in dogs from HPMC dry emulsions was higher than from a cyclodextrin solution (Christensen, 2004). Furthermore, the bioavailability relative to the cyclodextrin solution did not increase when the emulsion droplet size decreased from the micron to the submicron range applying a self-micro-emulsifying formulation. However, the amount of triglycerides was lower in the formulations yielding the smallest droplets. Thus, an effect of dispersion to increase bioavailability might have been counteracted by the concurrent reduction in lipid content. The objective of this study is to further investigate the bioavailability from spray-dried emulsions applying Lu 28-179 as a poorly soluble model drug. Tablets prepared using a directly compressible dry emulsion were compared to a HPMC dry emulsion powder, which preserved the initial lipid droplet size. The effect of lipid dispersion on the bioavailability was, furthermore, evaluated applying a

solution of the drug in the same amount of lipid. A cyclodextrin solution was included in the study as a reference. The formulations were administered orally to fasted Beagle dogs. Additionally, an i.v. dose was included to obtain the absolute bioavailabilities, which have not previously been reported.

2. Materials and methods

2.1. Materials

All formulations contained the base or the hydrochloride salt of a model drug 1′-[4-[1-(4-fluorophenyl)-1-*H*-indol- 3 -yl]-1-butyl]spiro[*iso*-benzofuran-1(3H), 4′ piperidine] (Lu 28-179, solubility of base in medium-chain triglycerides (MCT) ∼ 49 mg/g, intrinsic solubility in water ∼ 0.03 μg/ml, solubility of the hydrochloride salt in water 150 μg/ml, pKa ∼ 9, log *P* ∼ 8.5, H. Lundbeck A/S, Denmark). The lipid formulations were prepared using MCT (Ph. Eur. grade, Delios V, Grünau Illertissen, Germany), hydroxypropyl methylcellulose (Ph. Eur. grade, Methocel E3, DOW Chemicals, USA), gelatine (Ph. Eur. grade, Rousselot Gelatin 275 FG 8, Rousselot, France), trehalose dihydrate (High Purity grade, Hayashibara Company, Japan) and magnesium alumino metasilicate (Neusilin US2, Fuji Chemical Industry Company, Japan). Inclusion complexes were made using hydroxypropyl-β-cyclodextrin (average MW 1300, degree of substitution, 0.62, Ph. Eur. grade, Roquette Freres, France) and sodium chloride (analysis grade, Merck KGaA, Germany). Hard gelatine capsules (size 000, Capsugel, France) were used for the dosing of the lipid formulations.

Acetonitrile (gradient grade, Riedel-deHaën, Germany) and citric acid monohydrate (pro analysis, Merck KGaA, Germany) were applied in the analysis of the spray-dried powders using high performance liquid chromatography (HPLC). Acetonitrile, (HPLC quality, Labscan, Ireland), ethanol 96% (Ph. Eur., Danish Distillers, Denmark), formic acid 100%, (pro analysis, Merck KGaA), *n*-pentane (HPLC quality, Labscan, Ireland), sodium hydroxide (pro analysis, Merck KGaA) were used for serum sample preparation and analysis by HPLC coupled to a tandem mass spectrometer (LC-MS/MS). The deionised water used in the analyses was purified (Elgastat Maxima, Elga Labwaters, England).

2.2. Preparation of formulations

The compositions of the lipid formulations are listed in Table 1. The lipid formulations were prepared using a 45 mg/g solution of Lu 28-179 base in MCT resulting in co-administration of 424 mg MCT in each case. The solution was either filled into hard gelatine capsules, which were subsequently sealed, or included in the spray-dried formulations. Spray drying was performed in a pilot plant spray dryer (Mobile Minor, GEA Niro A/S, Denmark) equipped with a chamber extension section to increase the height of the drying chamber. The total dimensions of the drying chamber were 0.84 m cylindrical height with a diameter of 0.80 m and a 60° conical base. Drying airflow was 80 kg/h at a chamber pressure of −5 mbar. A 1.5 mm two-fluid nozzle operating at an airflow of 4.2 kg/h was used to atomise the feed in mixed-flow mode. The inlet air temperature was constant and the emulsion feed-rate was regulated by a programmable logic controller to maintain a constant outlet air temperature. A cyclone was used to collect the spray-dried particles from the outlet air.

The HPMC o/w-emulsion was prepared using the method of Christensen et al. (2001a). The highest MCT-solution content allowing preparation of a redispersible dry emulsion, 40% (w/w), was chosen. The dry emulsion powder was obtained by spray drying the emulsion at an inlet air temperature of 120 °C and an out-

Table 1
Compositions of the lipid formulations evaluated in the in vivo absorption study, % (w/w)

Formulation	Lu 28-179 base	MCT	HPMC	Trehalose dihydrate	Gelatine	Magnesium alumino metasilicate
MCT solution	4.50	95.50	–	–	–	–
HPMC dry emulsion	1.80	38.20	60.00	–	–	–
DC dry emulsion[a]	1.77	37.55	–	35.90	6.84	17.94

[a] Directly compressible dry emulsion.

let air temperature of 75 °C. The preparation of the directly compressible dry emulsion was initiated by dissolving 20 g gelatine and 105 g trehalose dihydrate in 385 g water at 50 °C by stirring. Next, the pH in the aqueous solution was adjusted to the isoelectrical point of the gelatine before mixing with 115 g Lu 28-179 base MCT solution. A crude emulsion was formed by stirring the mixture using a dispersing unit (Ultra-Turrax T 25 basic equipped with a S 25 N – 25 G dispersing head, IKA Labortechnik, Germany) for 3 min at 19,000 rpm. Further homogenisation was subsequently performed at a temperature of approximately 50 °C with a high-pressure homogeniser (EmulsiFlex C5, Avestin, Canada) applying two passages at a pressure of 138–152 MPa. 52.5 g magnesium alumino metasilicate was added to the emulsion and gentle stirring was performed for 15 min to complete the preparation before spray drying started. The stirring continued during the spray drying process to avoid sedimentation of the insoluble magnesium alumino metasilicate. Spray drying was performed at an inlet air temperature of 200 °C and an outlet air temperature of 115 °C.

The content of Lu 28-179 in the spray-dried powders was determined by reversed phase HPLC-analysis using an UV-detector operating at $\lambda = 220$ nm. The column (YMC-Pack Pro C18, particle size 5 μm, 250 by 4.6 mm internal diameter) was heated to a temperature of 45 °C. The mobile phase (35% (v/v) 25 mM citrate buffer, pH 6.2 and 65% (v/v) acetonitrile) had a flow of 1.5 ml/min. The values obtained were used to calculate the amount of spray-dried powders needed for doses of 20 mg Lu 28-179 base. An excentric press (Korsch EK 0, Korsch AG, Germany) was used to prepare 8 mm tablets of the directly compressible dry emulsion. A mean pressure of 1000 Newton was applied to the upper punch. The HPMC dry emulsion powder and the dry emulsion tablets were filled into hard gelatine capsules before dosing.

The cyclodextrin solutions were prepared by adding the hydrochloride salt of Lu 28-179 to aqueous solutions of hydroxypropyl-β-cyclodextrin. Following stirring clear solutions were obtained. The cyclodextrin solution for oral administration contained 15% (w/v) hydroxypropyl-β-cyclodextrin and had a Lu 28-179 base concentration of 2.5 mg/ml. The cyclodextrin solution for i.v. administration contained 0.5 mg/ml Lu 28-179 base, 0.8% (w/v) sodium chloride and 5% (w/v) hydroxypropyl-β-cyclodextrin. This solution was passed through a 0.22 μm filter and sterilized for 16 min at 121 °C in an autoclave. The solutions were administered using a syringe fitted with a plastic tube (oral administration) or a hypodermic needle (i.v. administration).

2.3. Characterisation of the spray-dried formulations

2.3.1. Emulsion droplet size distribution before spray drying

The emulsion lipid droplet volume size distributions were determined using laser diffraction and wet dispersion (HELOS KF with CUVETTE, Sympatec, Germany) applying the Fraunhofer theory. The emulsion used for the preparation of the directly compressible dry emulsion was measured before the addition of the insoluble magnesium alumino metasilicate. The emulsions were diluted with water prior to the measurements and the mean of two determinations calculated. The median of the volume size distribution ($d_{50\%}$) was used to describe the average droplet size. The width of the volume size distribution was described using SPAN calculated according to Eq. (1):

$$\text{SPAN} = \frac{(d_{90\%} - d_{10\%})}{d_{50\%}} \quad (1)$$

where $d_{10\%}$ and $d_{90\%}$ represents the 10% and 90% quantiles, respectively.

2.3.2. Particle size distribution

The particle size distributions were determined using the laser diffraction apparatus as described for emulsion droplet size. Due to cohesiveness the HPMC dry emulsion was measured using wet dispersion in MCT. The directly compressible dry emulsion was analysed applying a dry powder feeder (RODOS/VIBRI, Sympatec, Germany) and an injector pressure of 0.2 bar.

2.3.3. Density

Pycnometric density was determined with five purges and five runs on a helium gas displacement pycnometer (AccuPyc 1330, Micromeritics, USA). Bulk density was determined by pouring approximately 50 ml powder into a tared graduated 50:1 ml cylinder and measuring the volume and mass. Three determina-

tions were performed and used to calculate the mean pycnometric density and bulk density.

2.3.4. Tablet hardness

The mechanical strength of the tablets prepared using the directly compressible dry emulsion was determined using a tablet hardness tester (Model 6D, Dr. Schleuniger Pharmatron AG, Switzerland). Twenty tablets were measured individually and the results used to calculate the mean tablet hardness.

2.3.5. Lipid droplet size on reconstitution of the spray-dried formulations

The emulsion lipid droplet size distributions resulting from reconstitution in water were determined using the laser diffraction apparatus as described for emulsion droplet size. The HPMC dry emulsion was redispersed in water using the method of Christensen et al. (2001a). The resulting emulsion was measured following dilution with water. The dry emulsion tablets were subjected to disintegration in water according to Ph. Eur. using a disintegration tester (DES-1A, Kramer, Germany). The resulting lipid droplet size distribution was measured withdrawing samples from the disintegration vessel at the end of the test.

2.4. In vivo evaluation of the formulations

The freshly prepared formulations listed in Table 2 were administered to four fasted female Beagle dogs (15–17 kg) in a non-randomised single dose cross-over study. Each dog received a single dose of each formulation. The dogs were fed approximately 5 h after dosing. A washout period of 1 week between the doses was applied. Blood samples were obtained pre-dose and 0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 24 and 48 h after dose. Vials containing EDTA as coagulation activator were used for the collection of blood samples obtained from the vena jugularis. The serum was isolated by centrifugation and the content of Lu 28-179 analysed by LC-MS/MS following liquid–liquid extraction. The lower limit of quantification was 0.44 nmol/l. The protocol of the study was complied with the guidelines of the local ethics committee and was approved by the veterinarian in charge of animal welfare.

Table 2
Formulations evaluated in the in vivo absorption study applying 20 mg oral and 5 mg i.v. doses of Lu 28-179 base

Formulation	Concentration of Lu 28-179	Number of capsules dosed[a]
MCT solution	45 mg/g	1
HPMC dry emulsion powder	18.3 mg/g	4
Directly compressible dry emulsion tablets	13.7 mg/g	2[b]
Cyclodextrin solution, oral	2.5 mg/ml	–
Cyclodextrin solution, i.v.	0.5 mg/ml	–

[a] Corresponding to a dose of 20 mg Lu 28-179 base dissolved in 424 mg MCT.
[b] Each capsule containing three tablets.

2.5. Pharmacokinetical and statistical analysis

Non-compartmental pharmacokinetical analysis was performed using PC software (WinNonlin 3.2, Pharsight Corporation, USA) to obtain maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}) and the area under the plasma concentration curve from the time of administration to infinity ($AUC_{0-\infty}$). $AUC_{0-\infty}$ was calculated using the linear up logarithmic down method. The relative (F_{rel}) and absolute (F_{abs}) oral bioavailabilities were calculated and corrected for changes in the weight of the dogs at the days of dosing according to Eq. (2):

$$F = \frac{\text{dose}_{\text{reference}} \times \text{AUC}_{\text{oral}} \times \text{weight}_{\text{at reference dosing}}}{\text{dose}_{\text{oral}} \times \text{AUC}_{\text{reference}} \times \text{weight}_{\text{at oral dosing}}} \quad (2)$$

The differences in the mean pharmacokinetic parameters were evaluated statistically using one-way analysis of variance.

3. Results

3.1. Characterisation of the spray-dried formulations

The results of the physical characterisation of the spray-dried emulsion powders are listed in Table 3. Comparing the initial emulsion lipid droplet size distributions a slightly increased median droplet size resulted from the preparation of the directly compressible dry emulsion. In both instances, the spray drying process converted the emulsion into a dry powder. The highest process yield was observed for the HPMC dry emulsion. In contrast, the directly compressible dry

Table 3
Characteristics of the spray-dried emulsion formulations

Formulation	Emulsion droplet size (μm) and SPAN[a]	Drying process yield (%)	Pycnometric density (g/cm^3)[b]	Bulk density (g/ml)[b]	Particle size (μm)[a]	Redispersed emulsion droplet size (μm) and SPAN[a]
HPMC dry emulsion	1.2 (1.1)	66	1.15	0.19	43	1.4 (1.4)
DC dry emulsion[c]	1.9 (1.2)	54	1.39	0.39	113	19 (2.6)[d]

[a] Mean values ($n = 2$) of volume size distribution medians. SPAN values are listed in parenthesis for the emulsion droplet size distributions.
[b] Mean values ($n = 3$).
[c] Directly compressible dry emulsion tablets.
[d] Partial lipid coalescence was observed and a small amount of insoluble particles were present during measurement.

emulsion powder had the highest particle size as well as bulk and pycnometric densities. Whereas the HPMC dry emulsion was cohesive the flowability of the directly compressible dry emulsion allowed tablets to be prepared without additional processing. The relative standard deviation of the tablet mass was 0.9% and the tablets, having a mean crushing strength of 50 N, disintegrated within 6 min. Following disintegration, coalesced lipid droplets could be observed on the surface of the water in the disintegration vessel. Additionally, a small amount of the insoluble magnesium alumino metasilicate particles were observed to be present in the samples withdrawn for the determination of redispersed emulsion droplet size. During redispersion of the HPMC dry emulsion the powder initially got lumpy and, only slowly, a complete dispersion was obtained. However, the redispersed emulsion median droplet size and SPAN were near identical to the values measured before drying, Table 3.

3.2. In vivo evaluation of the formulations

The pharmacokinetic data obtained following administration of the formulations described in Tables 1–3 are listed in Table 4. Further, the mean plasma profiles following administration of each formulation are depicted in Fig. 1. It is noted that there was a tendency of the oral formulations to cause different rate and extent of Lu 28-179 absorption. The observed differences in C_{max}, t_{max} and $AUC_{0-\infty}$ were not statistically significant using $P < 0.05$. However, comparing the t_{max} values the initial rate of absorption from the cyclodextrin solution and the MCT solution tended to be higher than from the spray-dried formulations. The plasma concentration following dosing of the dry emulsions indicated an increasing concentration for a longer period of time than the MCT solution. Eventually, this resulted in a trend to higher C_{max} values compared with the MCT solution. The dry emulsion formulations only resulted in a moderately lower absolute bioavailability than the cyclodextrin solution. In contrast, the absolute bioavailability of the MCT solution was approximately less than 60% of the other lipid formulations. None of the differences between the orally administered formulations were statistically significant using one-way analysis of variance and $P < 0.05$. However, applying a paired Student's t-test a P-value of 0.054 was obtained comparing the MCT solution and

Table 4
Pharmacokinetic parameters of Lu 28-179 following oral administration to fasted Beagle dogs in different formulations[a]

Treatment	t_{max} (h)	C_{max} (nmol/l)	$AUC_{0-\infty}$ (nmol h/l)	$F_{abs,\ 0-\infty}$[b]	$F_{rel,\ 0-\infty}$[c]
MCT solution	2.0 (41)	9.61 (53)	104 (45)	0.06 (62)	0.50 (70)
HPMC dry emulsion powder	3.3 (39)	18.2 (48)	187 (47)	0.11 (54)	0.83 (61)
DC dry emulsion tablet	3.5 (37)	12.7 (53)	160 (45)	0.10 (54)	0.86 (72)
Cyclodextrin solution, oral	1.8 (55)	27.3 (47)	250.5 (51)	0.14 (33)	–
Cyclodextrin solution, i.v.	–	–	431.8 (22)	–	–

[a] Mean values ($n = 4$) and relative standard deviations (in parenthesis, %) following administration of either 20 mg oral or 5 mg i.v. doses calculated as Lu 28-179 base.
[b] Relative to the i.v. cyclodextrin solution and corrected for changes in the weight of the dogs at the days of dosing.
[c] Relative to the oral cyclodextrin solution and corrected for changes in the weight of the dogs at the days of dosing.

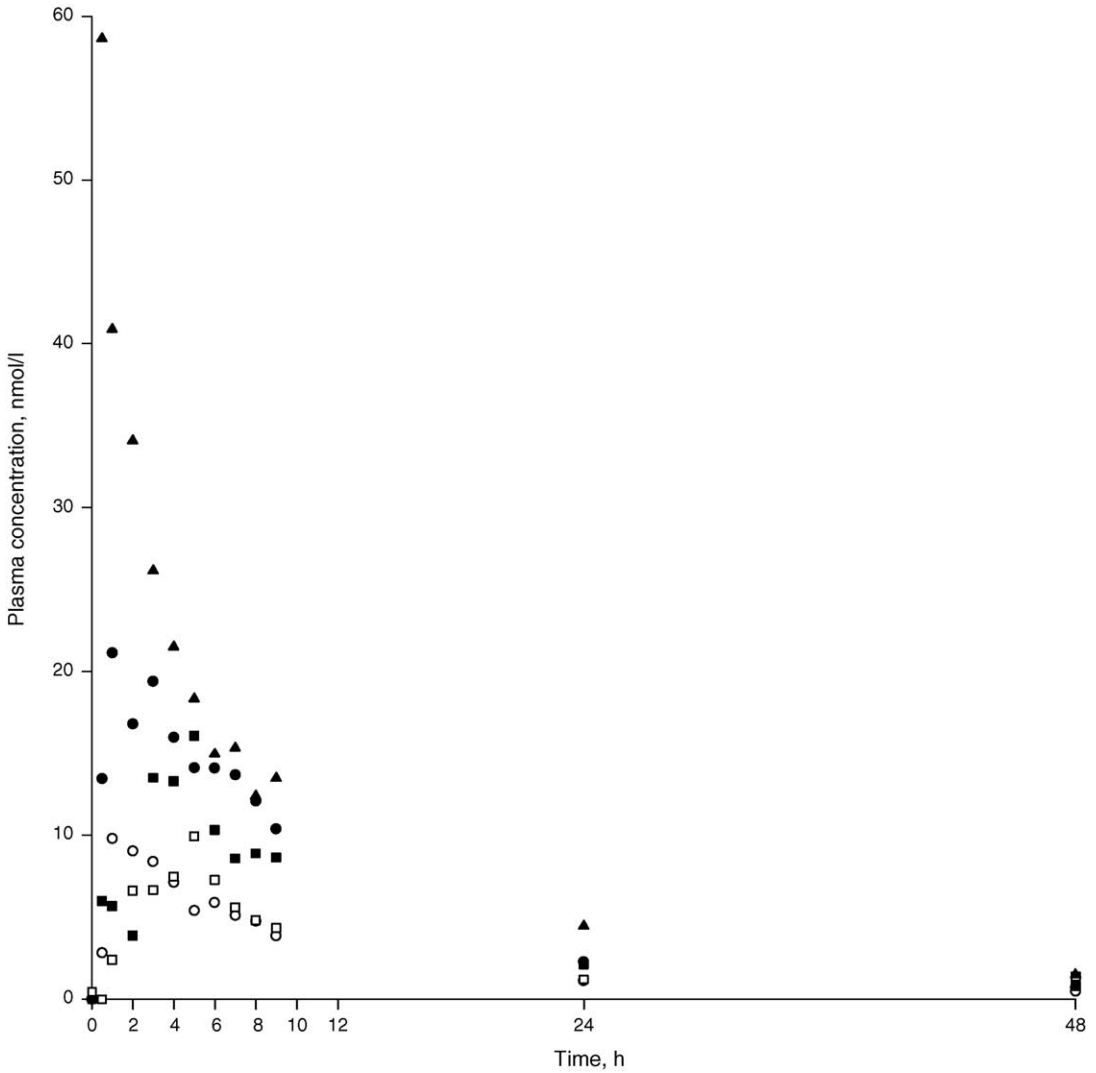

Fig. 1. Mean plasma concentrations of Lu 28-179 following administration of 5 mg (i.v. dose) or 20 mg (oral doses) to fasted female Beagle dogs ($n = 4$). Cylcodextrin solution, i.v. (▲); cyclodextrin solution, oral (●); HPMC dry emulsion powder, oral (■); directly compressible dry emulsion tablets, oral (□); MCT solution, oral (◯).

the oral reference. Thereby, further indicating a difference relative to the dry emulsions. Statistical analysis of the bioavailabilities of the lipid formulations relative to the oral cyclodextrin solution did not lead to a different result. A high intra subject variability in $AUC_{0-\infty}$ following oral dosing compared to i.v. dosing could be observed even though the oral doses were four-fold higher.

4. Discussion

4.1. Characterisation of the spray-dried formulations

The spray drying process yields were comparable to previous reports on similar formulations using the same spray dryer and process conditions (Christensen, 2004;

Hansen et al., 2004). The bulk density of the HPMC dry emulsion was only slightly lower than reported by Christensen (2004). This is in accordance with the dry emulsions having comparable lipid phase contents of 41.7% (w/w) and 40% (w/w), respectively. The dry emulsions were, furthermore, alike in terms of particle size. In the previous study a slightly lower emulsion median droplet size, 0.9 μm (volume weighted median diameter), was obtained before drying and after reconstitution in vitro whereas the droplet size distribution SPANs were comparable. The difference is not related to the difference in lipid phase content as lowering HPMC dry emulsion lipid content would be expected to decrease median droplet size (Christensen et al., 2001a). Comparing the dry emulsions, the dosing of the poorly soluble drug was facilitated applying the directly compressible formulation reducing the number of capsules needed for a 20 mg dose of Lu 28-179 base, Table 2. In part, this was due to the reduction in volume associated with the compression of the powder to form tablets. However, even in the powdery state the handling was substantially improved. This was ascribed to a combined effect of the increased density and the increased median particle size. The tablets had a higher content of lipid phase than reported for the tablets containing granulated HPMC dry emulsion, 20% (w/w) (Christensen et al., 2001b). The higher median droplet size observed following disintegration of the tablets prepared using the directly compressible dry emulsion could in part be due to the presence of magnesium alumino metasilicate. The median particle size of this insoluble material is approximately 112 μm (Hansen et al., 2004). Therefore, the particles present in the samples may have interfered with the measurement of lipid droplet size. Accordingly, the actual difference in mean lipid droplet size between the dry emulsion formulations might have been lower than observed. But the presence of coalesced surface droplets observed following disintegration of the tablets justifies the assumption that the initial in vivo lipid surface area decreased in the order: HPMC dry emulsion powder > directly compressible dry emulsion tablets ≫ MCT solution.

4.2. In vivo evaluation of the formulations

The lack of statistically significant differences in the pharmacokinetic parameters was probably due to the high intra-individual variability caused by the low absolute bioavailability and the fact that only four dogs were included in the study. A highly variable $AUC_{0-\infty}$ was observed even for the cyclodextrin solution, which was expected to result in a low variability based on the findings in the previous study on Lu 28-179 (Christensen, 2004). Here, the mean $AUC_{0-\infty}$ was 206 nmol h/l having a relative standard deviation of 12.5% ($n = 4$) using the same dose of Lu 28-179 base. The low oral bioavailability of the cyclodextrin solution might be due to displacement of Lu 28-179 by bile salts, resulting in precipitation of crystalline Lu 28-179, as proposed by Christensen (2004). However, it cannot be ruled out that factors related to the intestinal absorption process and metabolism also serves to reduce the oral bioavailability of Lu 28-179.

Applying the same amount of lipid in the formulations the C_{max} and the $AUC_{0-\infty}$, Table 4, tended to reflect the observed in vitro lipid dispersion. Both parameters increased when the lipid dispersion was enhanced thereby increasing lipid surface area. The gastrointestinal processing of the lipid formulations probably served to reduce the differences between the dry emulsions, which is in accordance with the results of Christensen (2004). Further, the HPMC dry emulsion resulted in a lower $AUC_{0-\infty}$ and F_{rel} in the present study.

In summary, the spray-dried formulations showed a tendency to improve the oral bioavailability of Lu 28-179 relative to a solution of the drug in the same amount of MCT. Thereby, the absolute bioavailability was approaching the level of the oral cyclodextrin solution. The data suggested that the difference in dry emulsion in vitro lipid dispersion did not affect the absolute bioavailability of Lu 28-179. Thus, tablets prepared using the directly compressible dry emulsion may be an alternative to the cohesive HPMC dry emulsion powder or a liquid lipid solution for oral delivery of a poorly soluble drug.

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