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Research paper

Solution or suspension – Does it matter for lipid based systems? In vivo studies of chase dosing lipid vehicles with aqueous suspensions of a poorly soluble drug

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ABSTRACT

In this study, the potential of co-administering an aqueous suspension with a placebo lipid vehicle, i.e. chase dosing, was investigated in rats relative to the aqueous suspension alone or a solution of the drug in the lipid vehicle. The lipid investigated in the present study was Labrafil M2125CS and three evaluated poorly soluble model compounds, danazol, cinnarizine and halofantrine. For cinnarizine and danazol the oral bioavailability in rats after chase dosing or dosing the compound dissolved in Labrafil M21515CS was similar and significantly higher than for the aqueous suspension. For halofantrine the chase dosed group had a tendency towards a low bioavailability relative to the Labrafil M2125CS solution, but still a significant higher bioavailability relative to the aqueous suspension. This could be due to factors such as a slower dissolution rate in the intestinal phase of halofantrine or a lower solubility in the colloidal structures formed during digestion, but other mechanisms may also be involved. The study thereby supported the potential of chase dosing as a potential dosing regimen in situations where it is beneficial to have a drug in the solid state, e.g. due to chemical stability issues in the lipid vehicle.

1. Introduction

Enabling oral formulation approaches, rather than conventional formulations, may be needed to facilitate satisfactory oral bioavailability for the increasing number of poorly water soluble drug compounds generated in the pharmaceutical industry. Oral lipid-based drug delivery systems (LbDDS) are an approach to increase the bioavailability of poorly water soluble compounds. LbDDS covers a diverse group of delivery systems containing lipids in a broad context [1,2]. In general, the drug is dosed pre-dissolved in the oral LbDDS thereby presenting the drug solubilised to the small intestine, which have been related to LbDDS's ability to enhance oral bioavailability for difficult to formulate compounds [3]. However, besides the ability of the lipids to solubilise the compound, additional physiological responses to the presence of lipids can also facilitate the absorption of poorly soluble compounds, e.g. increased secretion of bile salts, increased gastric emptying time, and facilitation of lymphatic transport [4–7,1,8]. A frequently encountered problem when desiring to employ LbDDS, is the inadequate solubility of many poorly soluble drugs in pharmaceutically relevant lipids, however, alternatively a suspension of the drug compound in the lipid vehicle can be prepared [9–11]. The use of lipid-based suspensions has previously been found beneficial for a number of compounds [8], including a study where the poorly water soluble compound danazol was demonstrated to have equal bioavailability when administered as either a solution or suspension in Labrafil M2125CS [12]. Labrafil M2125CS is a macrogolglyceride, which is a mixture composed of mono-, di- and tri-glycerides and mono-, and di-fatty acid esters of polyethylene glycol (PEG) 300 [13]. The fatty acid moieties are mainly linoleic acid (C18:2) and oleic acid (C18:1). Labrafil M2125CS is a substrate for lipolytic enzymes in the gastro-intestinal tract [12,14,15].

Though the biopharmaceutical use for application of a lipid suspension may be valid, the use of LbDDS can potentially be limited for compounds, which are sensitive to oxidation. In this case, it could be relevant to work with co-administration of a conventional formulation with a placebo lipid based capsule or a capsule containing the solid API in a capsule containing the lipid, i.e. a capsule in a capsule like the nutraceutical Prolive®, where the inner capsule contains the active compound and the outer the lipid vehicle.

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In a recent human study, the co-administration of cinnarizine with a placebo self-nanoemulsifying drug delivery system (SNEDDS) did not lead to a higher bioavailability than in the fasted state [16]. This observation is in contrast to previous studies with lipid suspensions [8,12] and could be compound specific or an effect of the lipid formulation chosen for the chase dosing. The SNEDDS may have been suboptimal to ensure solubilisation of the compound after the formation of the nanoemulsion. Given that Labrafil M2125CS have previously shown to be an effective vehicle for lipid suspensions it could be relevant to investigate if various model drugs as a Labrafil M2125CS solution or as dosing of the Labrafil M2125CS vehicle followed by an aqueous suspension containing the drug, would perform similarly from a bioavailability perspective. The purpose of the current study was therefore to investigate if similar oral bioavailability could be obtained by dosing three different poorly water soluble compounds belonging to the biopharmaceutical system class II, danazol (DAN) [17], cinnarizine (CIN) [18] and halofantrine (HF) [19] (see Table 1), when solubilised in Labrafil M2125CS or when dosed by a chasing regime, i.e. dosing first the Labrafil M2125CS immediately followed by an aqueous suspension containing the compound.

2. Materials and methods

2.1. Materials

Danazol USP was purchased from Unikem A/S (Copenhagen, Denmark) and Halofantrine crystalline base and the internal standard 2,4-dichloro-6-trifluoromethyl-9[1-[2-(dibutylamino)ethyl]]-phenathrenemethanol hydrochloride were kindly donated by GlaxoSmithKline (West Sussex, UK). Labrafil M2125CS was kindly donated by Gattefossé (Saint-Priest, France). Sulfobutylether-β-cyclodextrin (SBE7-β-CD) were purchased from Ligand (La Jolla, CA, USA). Cinnarizine, soybean oil, and methylcellulose USP grade were all purchased from Sigma-Aldrich (St. Louis, MO, USA). 99.9% ethanol, acetonitrile HPLC grade and methanol HPLC grade were purchased from VWR (Copenhagen, Denmark). All other chemicals were of analytical grade. Water was obtained from a Millipore purification system (Billerica, MA, USA).

2.2. Saturated solubility of danazol, cinnarizine and halofantrine in Labrafil M2125CS

The solubility of DAN was determined in a previous study [12].

Excess of CIN was added to Labrafil M2125CS in glass vials and the mixtures were placed on an end-over-end rotational device at ambient temperature or 37 °C. After 22 and 48 h samples were taken and centrifuged at 15,000 rpm for 30 min (Biofuge 15, Heraeus, Oterode, Germany), equal to 21,900*g*. A few drops of the supernatant were weighed into a 10 mL volumetric flask and diluted with ethanol after recording of the weight. This solution was further diluted mobile phase and the quantification of CIN was performed as described in the analytical section. The equilibrium was considered obtained when two consecutive samples varied by less than 5%. All solubilities were determined in triplicate.

Excess of HF was added to Labrafil M2125CS in a glass vial with Teflon-lined caps. This mixture was treated on a Covaris S1 acoustic transducer (Covaris Inc., Woburn, MA, USA) for 100 s with the following settings: duty cycle 20, intensity 10 and cycles/bursts 1000. This was done to bring the suspension close to equilibrium solubility faster, as HF can have a slow dissolution process in lipids (unpublished data). Subsequently the glass vials were placed on an end-over-end rotational device for 24 h at ambient temperature and at 37 °C. After 24 h the samples were filtered through a 0.20 μm filter (Millex-FG, Millipore Corporation, Billerica, MA, USA), diluted with acetonitrile to an appropriate concentration and the HF content determined as described in the analytical section.

2.3. Preparation of formulations

DAN, CIN and HF solutions in Labrafil M2125CS were prepared by weighing the compound and subsequently adding sufficient amounts of Labrafil M2125CS to make the final concentration 7 mg/mL. These mixtures were left overnight on a magnetic stirrer until the compounds were completely dissolved.

Aqueous suspensions containing 28 mg/mL of DAN, CIN and HF, respectively, were prepared by mixing the compounds with a 0.5% (w/v) methylcellulose solution. The particle sizes in the crude suspensions were reduced by means of a Sonifier Cell Disrupter, model B15, equipped with a standard microtip from Branson (Pusan, Korea). The suspensions were placed on ice and treated with the power output on 5 three times for 10 min.

The intravenous data for DAN was obtained from Larsen et al. [12]. The intravenous CIN formulation containing 1.25 mg/mL was prepared by weighing 25 mg CIN in a 20 mL volumetric flask and subsequently adding approximately 17 mL 10% (w/v) SBE7-β-CD solution (pH 3.5). The mixture was stirred overnight and pH was adjusted to 3.5 with methane sulfonic acid and the volume was adjusted to 20 mL with 10% (w/v) SBE7-β-CD solution (pH 3.5). The formulation was filtered through a 0.22 μm filter before use. The intravenous HF formulation, was an intravenous oil-in water (o/w) emulsion, contained 0.1% halofantrine (1 mg/mL), 20% soybean oil, 2% lecithin, 2.4% glycerol and 75.5% water (w/w). The emulsion was prepared as previously described [17].

Table 1
Physical-chemical data and structures of halofantrine, cinnarizine and danazol.

Compound	Halofantrine	Cinnarizine	Danazol
M_w (g/mol)	500	369	337
pk_a	5.58 [20]	1.95 [21] and 7.47 [22]	NA
Log P	8.86 [20]	5.77 [23]	4.53 [24]
Aqueous solubility	2 μg/ml (pH 2.5–3.5, 28 °C) [25]	0.47 μg/ml (pH 6.5, 37 °C) [26]	0.61 μg/ml (37 °C) [27]
Labrafil solubility at ambient temperature	44.1 ± 6.4 mg/mL (n = 3)	25.4 ± 0.40 mg/mL (n = 3)	8.3 ± 0.2 mg/mL (n = 3) [12]
Labrafil solubility at 37 °C.	73.3 ± 1.7 mg/mL (n = 3)	36.6 ± 0.58 mg/mL (n = 3)	10.3 ± 0.3 mg/mL (n = 3) [12]
Structure