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Effect of food intake and co-administration of placebo self-nanoemulsifying drug delivery systems on the absorption of cinnarizine in healthy human volunteers

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ABSTRACT

Positive food effects may be observed for low aqueous soluble compounds, these effects could potentially be circumvented using lipid based formulations. However, as all compounds are not chemically stable in lipid based systems, alternative dosage regimes could be investigated to evade the stability issue. The two aims for this present study were therefore; i) to investigate if a nutritional drink, Fresubin Energy®, could induce food effect in humans for the poorly soluble compound cinnarizine; and ii) to investigate if co-administration of a self-nano-emulsifying drug delivery systems (SNEDDS) with a conventional cinnarizine tablet could reduce the observed food-effect.

A commercial conventional cinnarizine tablet was dosed to 10 healthy volunteers in a cross-over design in both fasted and fed state, with and without co-administration of a SNEDDS, with a one week wash-out period between dosing. The fed state was induced using a nutritional drink (Fresubin Energy®) and gastric emptying was assessed by administration of paracetamol as a marker.

The pharmacokinetic analysis showed that the nutritional drink delayed the uptake and increased the fraction of absorbed cinnarizine, indicative of a food effect on the compound. This was in agreement with a previous dog study and indicates that the nutritional drink can be used for inducing the same level of food effect in humans. Though not statistically significant, the co-administration of SNEDDS exhibited a tendency towards a reduction of the observed food effect and an increased absorption of cinnarizine in the fasted state; based upon the individual ratios, which was not reflected in the mean data. However, the co-administration of SNEEDS in the fasted state, also induce a slower gastric emptying rate, which was observed as a delayed t_{max} for both cinnarizine and paracetamol.

1. Introduction

It is well described that concomitant food intake can change the pharmacokinetic profile of drugs as a consequence of the physiological and chemical changes in the gastrointestinal (GI) tract induced by food (Fleisher et al., 1999; Levy and Jusko, 1965; Welling et al., 1977).

The Biopharmaceutics Classification System (BCS) classifies a drug compound with low aqueous solubility and high permeability, as a Class II compound (Amidon et al., 1995). For BCS Class II compounds, solubilisation and dissolution rate in the GI-tract is often the limiting factor for absorption. Simultaneous food intake increases the residence time of the drug in the stomach, which in turn increases the time available for solubilisation. The solubilisation is further increased by the increased volume that is obtained by intake of food. Unpublished data from the OrBiTo consortium showed that intake of a full FDA-breakfast increased the gastric volume to comparable volumes in men and women. After 60 min, the gastric volume was approximately 700 mL. Sunesen et al. (2005) showed that intake of 800 mL water and thereby gastric volume had a positive effect on oral absorption of danazol. Furthermore, the postprandial increase in levels of bile salts, phospholipids and digestion products in the small intestine will increase the solubilisation capacity of the GI fluids through the creation of mixed micelles, uni-lamellar and multi-lamellar vesicles (Hernell et al., 1990; Fatouros et al., 2009; Persson et al., 2005, Kleberg et al., 2010). Consequently, for many BCS class II compounds the increased

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solubilisation level will increase the absorption and bioavailability in the fed state (Lue et al., 2008; Gu et al., 2007). This increase in absorption can therefore cause variations in plasma concentration, which can result in a different pharmacological effect in fasted compared to fed state.

Several studies have shown that SNEDDS (Self-Nano Emulsifying Drug Delivery systems) can improve the bioavailability of a number of BCS Class II compounds (Patel and Vavia, 2007; Kommuru et al., 2001; Thomas et al., 2013). It is believed that this increase in bioavailability is achieved by presenting the API in a solubilised state (Kadu et al., 2011; Bates and Sequeria, 1975; Mohsin et al., 2009). Furthermore, some studies have shown that compounds administered in SNEDDS were less sensitive to food effects. Woo et al. (2008), administered itraconazole to eight healthy volunteers in both the fasted and fed state. Itraconazole was formulated in a self-microemulsifying drug delivery system (SMEDDS) and compared to commercial Sporanox tablets. A pronounced food effect was reported for the Sporanox tablets, whereas the SMEDDS showed a significantly higher absorption than Sporanox in the fasted state and was less sensitive to food (Woo et al., 2008). In accordance, Nielsen et al. (2008), found a reduced food effect of probucol in mini-pigs, when dosed in different lipid based drug delivery systems, compared to the pure drug powder.

In the present study, the BCS Class II compound cinnarizine in the form of a commercially available tablet (Sepan®) was selected as the test compound. Cinnarizine is a calcium antagonist that inhibits smooth muscle contraction. It is used mainly for the treatment of motion sickness due to its anti-histaminic effect (Godfraind et al., 1986; Singh, 1986; Towse, 1980). Cinnarizine is a weak base with pKa values of 2.0 and 7.5 and a log P of 5.8 (Gu et al., 2005). A previous study in dogs by Christiansen et al. (2014), where fed state was induced by administration of a nutritional drink, Fresubin Energy®, showed food effect on the commercial tablet, while a SNEDDS lowered the difference in area under the plasma concentration curve (AUC) between fasted and fed state. Energy drinks have in fact been used to mimic intestinal content *in vitro* (e.g. Franek et al., 2014; Klein et al., 2004) as well as in human studies, where the intestinal content has been analysed in both the fasted and fed state, where the fed state was actually induced after administration of an energy drink instead of an FDA meal (e.g. Kalantzi et al., 2006a, 2006b; Bevernage et al., 2010; Diakidou et al., 2009). Investigating the potential of energy drinks to induce food effect for low soluble compounds in humans as a controlled standardised food source is therefore of general interest.

The chemical stability in lipid based formulations may be suboptimal for some compounds, however, co-administration of a solid dosage form with a placebo lipid based formulation system may allow in situ solubilisation and thereby provide the positive effects from the lipid based formulation system on the bioavailability. The purpose of this study was therefore to investigate i) if a nutritional drink, Fresubin Energy®, containing less kcal, but the same energy distribution as the FDA breakfast, could induce a significant food effect in humans for the poorly soluble compound cinnarizine; and ii) if a placebo SNEDDS co-administered with the commercial tablet could reduce the food effect.

2. Materials and Methods

2.1. Materials

Sepan® (Cinnarizine, 25 mg) tablets were obtained from Janssen-Cilag (Neuss, Germany). Panodil® (Film coated 500 mg Paracetamol) were purchased from Glaxo Smithkline A/S (Brentford, UK). European Pharmacopeial grade of sesame oil, oleic acid, and ethanol were all obtained from Sigma Aldrich chemie Gmbh (St. Louis, MO, United States of America). Brij® 97 was obtained from Croda (Rawcliffe Bridge, United Kingdom). Cremophor RH 40 from BASF (Ludwigshafen, Germany), and Hard Gelatine capsules were purchased from Apodan Nordic (Copenhagen S, Denmark). The nutritional Fresubin Energy® drink (Vanilla flavour), was a gift from Fresenius Kabi (Copenhagen, Denmark).

2.2. Formulations for in Vivo Investigations

A commercial immediate release tablet (25 mg Sepan®, JANSSEN-CILAG, Denmark) and a placebo SNEDDS filled into hard gelatine capsules were used in this study.

The employed SNEDDS (Table 1) was previously developed by Larsen *et al.* and was designed with sesame oil as the only component undergoing lipolysis (Larsen et al., 2012). For the preparation, the components were weighed and mixed using a magnetic stirrer. Ethanol was added last, to minimize the evaporation and the mixture was stirred in a sealed flask until a clear solution was obtained.

On the morning of dosing 0.5 g SNEDDS was weighed into hard gelatine capsules.

2.3. In Vivo Study

Ten healthy male volunteers gave written informed consent to participate in this study, which had been accepted by the regional ethical committee and followed the tenets of the Declaration of Helsinki promulgated from 1964.

The healthy volunteers were all of Caucasian origin and between 18 and 40 years old with a BMI between 18 kg/m^2 and 30 kg/m^2. Of these seven had a BMI under 25 kg/m^2, three between 25 and 30 kg/m^2, two of these three had a BMI of 30 kg/m^2. The volunteers were ascertained to be healthy by a clinical examination.

The 10 volunteers were treated in a crossover design, dosed half-sitting after an overnight fast with a wash-out period of at least one week. Each week the volunteers were administered with either one Sepan® tablet (25 mg cinnarizine) with and without food, or one Sepan® tablet in combination with a hard gelatine capsule containing 0.5 g placebo SNEDDS also with and without food. Further, 500 mg paracetamol was co-administered as a commercial tablet to evaluate the gastric emptying. The meal was 200 mL Fresubin Energy® drink, which was ingested 20 min prior to dosing. The tablets and capsules were ingested with 200 mL of tap water. The volunteers were provided a lunch 4 h after dosing. The lunch consisted of dark rye bread with different kinds of meat toppings and water. After dosing, the volunteers were allowed to drink water ad libitum.

Blood samples of 3 mL were collected into EDTA-coated tubes via a vein catheter at pre-dose and 0.5, 1, 1.33, 1.67, 2, 2.33, 2.67, 3, 4, 5, 7 and 24 h post dosing. Plasma was obtained by centrifugation and stored until analysis at −80 °C.

2.4. Analysis of Plasma Samples

Plasma samples were analysed for the content of cinnarizine and paracetamol by the use of a LC–MS method using an Agilent 1200 HPLC system connected to an Agilent quadropole 6140 MS detector. The chromatographic separation was achieved using a Kinetex 5 μ XB-C18 (100 × 4.6 mm) column at a column temperature of 40 °C. The chromatography was obtained by a gradient method over the course of 12 min and mobile phases of 0.1% glacial acetic acid in MilliQ water and methanol. The gradient was performed as described in Table 2.

Electrospray settings were; capillary voltage 2.0 kV, drying N_2 flow 12–13 L/min and drying gas temperature at 250 °C and SIM dwell time at 100 ms. The detector was operated in the positive ionization

Table 1
SNEDDS composition filled into hard gelatine capsules.

Component	Ratio (*w*/w) %
Sesame oil	20.6
Cremophor RH 40	45
Oleic acid	15.4
Brij 97	9
Ethanol	10