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Bioavailability of seocalcitol III. Administration of lipid-based formulations to minipigs in the fasted and fed state

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ABSTRACT

The bioavailability of seocalcitol from two lipid-based formulations and a propylene glycol (PG) solution was studied in minipigs in the fasted and fed state. The lipid-based formulations were a medium chain triglyceride (MCT) solution and a self-microemulsifying drug delivery system (MC-SMEDDS) having a composition of 25% MCT, 48% cremophor RH 40, 27% akoline MCM. An IV solution was administered in order to determine the absolute bioavailability. In the fasted state the absolute bioavailability of seocalcitol was 15, 21 and 28% for the PG, MCT and MC-SMEDDS, respectively. The bioavailability from the PG solution was affected by the presence of food (29%), whereas the bioavailability from the lipid-based formulations was less affected by the presence of food; MCT (22%) and MC-SMEDDS (33%). The increased bioavailability from the PG solution in the fed state is believed to be due to the presence of lipids in the food. The present study illustrates an often mentioned beneficial effect of dosing lipid-based formulations; the reduced food effect on bioavailability. Previously published solubility data in simulated intestinal media relates very well to the present *in vivo* findings as the solubility studies showed that addition of lipids to the formulation could reduce/eliminate the difference in solubility between the fasted and fed state. Previously the same formulations were dosed to rats, resulting in a lower bioavailability from the MC-SMEDDS compared to the MCT. This illustrates that the animal model used should be carefully considered when studying formulations that are dependent on the dynamic processes in the GIT.

1. Introduction

An increasing number of the discovered drug substances are poorly soluble and highly permeable and are classified as class 2 drug substances according to the Biopharmaceutical Classification System (BCS) (Amidon et al., 1995). For the class 2 drug substances the bioavailability is often low and variable due to an insufficient dissolution process in the gastrointestinal tract (GIT). Furthermore, for some of these drug substances an increased bioavailability has been seen when dosed in their solid form together with a meal, e.g. danazol (Charman et al., 1993; Porter et al., 2004; Sunesen et al., 2005), L-683,453

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(Matuszewska et al., 1996), DPC 961 (Aungst et al., 2002) and Halofantrine (Humberstone et al., 1996). The increased oral bioavailability found when applying drug substances with food may be ascribed to changes in the GIT environment such as (1) prolonged gastric emptying and decrease in intestinal motility increasing the time available for solubilisation; (2) increased dissolution rate and solubilisation of drug substance in mixed micelles due to stimulation of pancreatic secretion of bile salts and lipase; (3) protection from gastric/luminal degradation, due to protection in lipids; (4) increased lymphatic transport, thus avoiding first pass metabolism. The change in bioavailability caused by concomitant administration of food may change the pharmacokinetic parameters, e.g. C_{max} and/or t_{max} of a drug substance (Singh, 1999), which may be crucial for drug substances with a low therapeutic index (Gonzalez-Llaven et al., 1999). Consequently, guidelines for clinical trials of drug substances require investigation of pharmacokinetic parameters in the presence and absence of food intake.

When the dissolution rate is the limiting step in drug substance absorption, the bioavailability may be enhanced by administration in a formulation being a simple solution, e.g. a propylene glycol solution in order to eliminate the dissolution step. The increase in oral bioavailability observed in the presence of food, may be possible to achieve by the use of lipid-based formulations, as even small doses of lipid have been shown to facilitate the above mentioned mechanisms (Khoo et al., 2003). For poorly aqueous soluble drug substances the critical step in drug absorption is to avoid precipitation when transferred from the lipid formulation to the mixed micelles in the GIT. The capacity of the mixed micelles to keep the drug substance in solution depends on the characteristics of the drug substance, e.g. the lipophilicity, the composition and amount of the mixed micelles. For drug substances with sufficient lipophilicity self-microemulsifying drug delivery system (SMEDDS), could be a possible formulation approach in order to administer the drug substance in solution. SMEDDS consists of oil, surfactant and co-surfactant where the surfactants act by dispersing the formulation in the GIT upon dilution with the gastrointestinal fluid (Stuchlik and Zak, 2001). This results in the formation of fine droplets providing a large surface area for pancreatic lipase to hydrolyse triglycerides and thereby promoting a rapid release of the drug substance (Tarr and Yalkowsky, 1989) and/or the drug substance may be absorbed directly from the small droplets of the microemulsion (de Smidt et al., 2004).

The published number of food effect studies with lipid-based formulations is limited. However, a limited food effect has often been postulated due to the fact that the drug substance is dosed in solution and that the lipid keeps the drug substance in solution in the GIT. A limited food effect was observed for danazol formulated in an emulsion (Charman et al., 1993) and L-683,453 formulated in a self-emulsifying system (Matuszewska et al., 1996). Moreover, studies containing cyclosporine have been conducted with lipid-based formulations in the fasted and fed state (Mueller et al., 1994a; Gonzalez-Llaven et al., 1999). The SMEDDS (Neoral®) has been found to be superior compared with Sandimmune®, in terms of a more uniform and reproducible bioavailability in the fasted as well as in the fed state (Mueller et al., 1994a). Furthermore, dose linearity and less inter- and intra-variability have been reported for Neoral® (Mueller et al., 1994b).

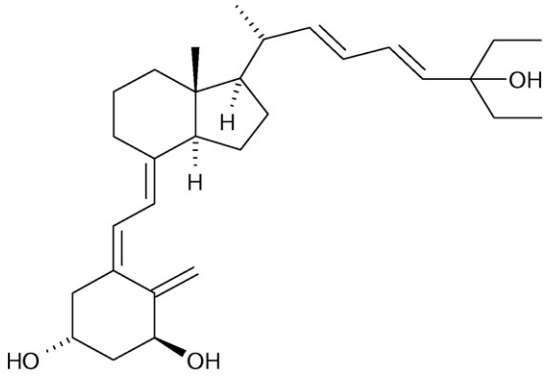

Fig. 1 – Chemical structure of seocalcitol.

The bioavailability of the vitamin D-analog seocalcitol has been studied in rats after oral dosing of oil solutions or SMEDDS containing either MCT or LCT (Grove et al., 2005, 2006). However, formulating seocalcitol in SMEDDS did not increase the bioavailability of seocalcitol. One possible explanation could be that the liquid volume in the GIT of the rat is too small to emulsify the SMEDDS. This hypothesis is studied further in the present study in the minipig a larger ranking animal. The pig has an interesting potential as a model for studying GI function, as the pigs resemble humans more than rats, with regard to gastrointestinal function and bile acid concentrations (Flores et al., 1992). Rats secrete bile continuously whereas the gallbladder in pigs releases bile only in the presence of food (Kararli, 1995). When conducting food effect studies and studies in the fasted state, pigs are therefore more likely to mimic the situation in humans to give a true picture about the fate of poorly aqueous soluble drug substances in the GIT.

The objectives of the present explorative work were to study the usefulness of lipid-based formulations by (a) investigating the oral bioavailability of seocalcitol in minipigs from two lipid-based formulations (MCT solution and MC-SMEDDS) and one reference formulation without lipid containing propylene glycol (PG) in the fasted and fed state, (b) compare the obtained *in vivo* data with *in vitro* solubilisation data of seocalcitol in simulated intestinal media previously published and finally (c) compare the oral bioavailability achieved in the fasted state in the minipig with the bioavailability obtained in rats and discuss the value/applicability of using the rat for studying the bioavailability from SMEDDS. The chemical structure of seocalcitol is shown in Fig. 1. Log *P* for seocalcitol is 4.8 and the solubility in MCT is 5.3 mg/g.

2. Materials and methods

2.1. Chemicals

Seocalcitol was synthesized at LEO Pharma A/S. Viscoleo (MCT) was purchased from ICI Espana, Spain. The fatty acid composition of the triglycerides in MCT is as specified in Ph.Eur. Cremophor RH40 (macrogol-40-glycerol hydroxys-