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Bioavailability of seocalcitol II: Development and characterisation of self-microemulsifying drug delivery systems (SMEDDS) for oral administration containing medium and long chain triglycerides

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ABSTRACT

By constructing ternary phase diagrams it was possible to identify two self-microemulsifying drug delivery systems (SMEDDS) containing either medium chain triglycerides (MC-SMEDDS) or long chain triglycerides (LC-SMEDDS), with the same ratio between lipid, surfactant and co-surfactant. The SMEDDS ended up having a composition of 25% lipid, 48% surfactant and 27% co-surfactant, MC-SMEDDS: viscoleo, cremophor RH40, akoline MCM and LC-SMEDDS: sesame oil, cremophor RH40, peceol. Upon dilution with water both SMEDDS resulted in clear to bluish transparent microemulsions with a narrow droplet size of 30 nm. The industrial usefulness of the developed SMEDDS was evaluated with regard to bioavailability and chemical stability using the vitamin D analogue, seocalcitol, as model compound. The absorption and bioavailability of seocalcitol in rats were approximately 45% and 18%, respectively, from both the MC-SMEDDS and LC-SMEDDS indicating similar in vivo behavior of the two formulations, despite the difference in nature of lipid component. There was no improvement in bioavailability by the use of SMEDDS, compared to the bioavailability achieved from simple MCT and LCT solutions (22–24%) (Grove, M., Pedersen, G.P., Nielsen, J.L., Mullertz, A., 2005. Bioavailability of seocalcitol. I. Relating solubility in biorelevant media with oral bioavailability in rats-effect of medium and long chain triglycerides. J. Pharm. Sci. 94, 1830–1838.). After 3 months' storage at accelerated conditions (40 °C/75% RH), a decrease in concentration of seocalcitol of 10–11% was found in MC-SMEDDS and LC-SMEDDS compared with a degradation of less than 3% for the simple lipid solutions of MCT and LCT. In this study the simple lipid solutions seem to be a better choice compared with the developed SMEDDS due to a slightly higher bioavailability and a better chemical stability of seocalcitol.

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1. Introduction

An increasing number of potential drug substances discovered by the pharmaceutical industry are poorly soluble in water, but have a high permeability and are therefore 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, hence it will be beneficial to dose this kind of drug substances in their soluble form. For drug substances with sufficient lipophilicity, lipid-based drug delivery systems e.g. lipid solution, lipid emulsion, microemulsion, dry emulsion, Self Emulsifying Drug Delivery System (SEDDS) or Self Microemulsifying Drug Delivery System (SMEDDS) could be possible formulation approaches. Lipid-based drug delivery systems have gained considerable interest after the commercial success of Sandimmune Neoral™ (Cyclosporine A), Fortovase (Saquinavir) and Norvir (Ritonavir). Much attention has been on SMEDDS/SEDDS; an increase in bioavailability was found for L-365,260 (Lin et al., 1991), WIN 54954 (Charman et al., 1992), Ro 15-0778 (Shah et al., 1994), ontazolast (Hauss et al., 1998), halofantrine (Khoo et al., 1998) and danazol (Porter et al., 2004) when administered in self-emulsifying systems, compared to solid dosage forms.

SMEDDS are defined as isotropic mixtures of lipid, surfactant, co-surfactant and drug substance that rapidly form a microemulsion upon mixing with water. A narrow droplet size distribution is often seen with a droplet size typically less than 50 nm (Gursoy and Benita, 2004). The self-emulsification process occurs spontaneously because the free energy required to form the microemulsion is either low and positive or negative (Constantinides, 1995). The self-emulsification process was shown to be specific to the nature of the lipid/surfactant pair, the surfactant concentration, the ratio between lipid and surfactant (Pouton, 1985; Wakerly et al., 1987) and only specific pharmaceutical excipient combinations can lead to efficient self-emulsifying systems (Charman et al., 1992; Shah et al., 1994). Drug substances with adequate solubility in lipid/surfactants blends are candidates for this formulation concept (Gershanik and Benita, 2000).

The SMEDDS are believed to be superior compared with lipid solutions due to the presence of surfactants in the formulations leading to a more uniform and reproducible bioavailability as seen for cyclosporine (Mueller et al., 1994). The surfactants act by dispersing the lipid formulation in the gastrointestinal tract (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 and/or the formation of mixed micelles containing the drug substance (Tarr and Yalkowsky, 1989). The small droplets formed in contact with the gastrointestinal fluid may also be responsible for transporting the drug substance through the unstirred water layer to the gastrointestinal membrane for absorption (de Smidt et al., 2004).

In the literature, medium chain triglycerides (MCT) have been preferred in SMEDDS due to the higher fluidity, better solubility properties and self-emulsification ability compared with long chain triglycerides (LCT) (Charman et al., 1992; Shah et al., 1994), as well as a better chemical stability of drug substance in MCT due to the purity of the lipid and the lack of double bonds, that can catalyse oxidation. The two lipids are differently transported in the body: MCT is directly transported by the portal blood to the systemic circulation (Porter and Charman, 1997), whereas LCT is transported in the intestinal lymphatics. Lipid-based drug delivery systems containing LCT are likely to enhance the lymphatic transport of a lipophilic drug substance (Palin and Winson, 1984; Caliph et al., 2000) and as the lymphatic transport circumvents the liver, the first-pass metabolism of a drug substance may be reduced (Porter and Charman, 1997). SMEDDS containing either MCT or LCT have been studied with halofantrine (Khoo et al., 1998) and danazol (Porter et al., 2004) and in both cases LC-SMEDDS were found to give the highest bioavailability.

Studies comparing the bioavailability of drug substance from SMEDDS and other lipid-based drug delivery systems e.g. pure lipid solutions are still limited in number and until now most studies have been comparing self-emulsifying systems with solid dosage forms (Lin et al., 1991; Charman et al., 1992; Shah et al., 1994). MC-SMEDDS and LC-SMEDDS have been compared in two studies with halofantrine (Khoo et al., 1998) and danazol (Porter et al., 2004). However, in these studies the SMEDDS contain different amounts of lipid and surfactant, which makes the comparison complicated, since more than one variable exists. In a study with vitamin E a SMEDDS was found to give rise to a higher bioavailability compared with a lipid solution, but more lipid was dosed in the SMEDDS, which makes the comparison difficult (Julianto et al., 2000).

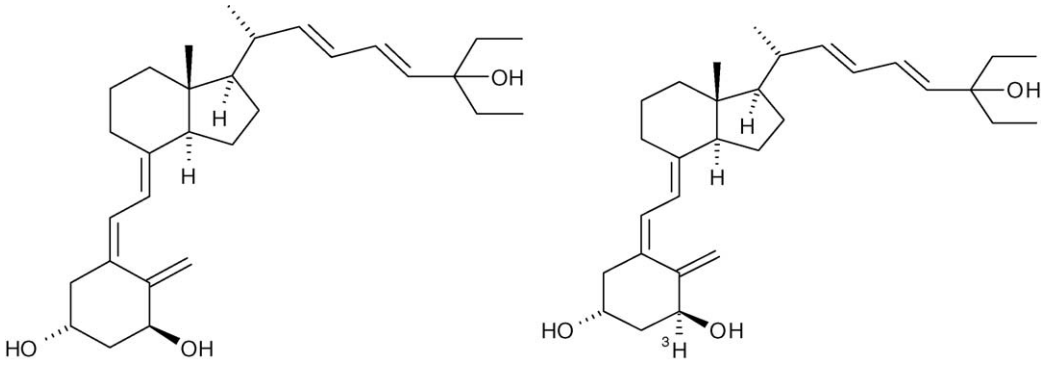

Fig. 1 – Chemical structure of seocalcitol and tritium labeled seocalcitol, ^{3}H-seocalcitol.