Precipitation of a Poorly Soluble Model Drug during *In Vitro* Lipolysis: Characterization and Dissolution of the Precipitate

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ABSTRACT: Precipitation of cinnarizine during *in vitro* lipolysis of a self-microemulsifying drug delivery system (SMEDDS) was characterized to gain a better understanding of the mechanisms behind the precipitation. During *in vitro* lipolysis of the SMEDDS with or without cinnarizine, samples were taken at several timepoints and ultracentrifuged. Cinnarizine content in the pellet increased from 4% to 59% during lipolysis. The precipitation of cinnarizine during *in vitro* lipolysis correlated well with the degree of lipid digestion, determined by sodium hydroxide addition. The pellet from the endpoint of lipolysis was isolated and subjected to dissolution in biorelevant media. Dissolution rate of cinnarizine from pellets containing precipitated cinnarizine was initially 10-fold higher than dissolution from blank pellet spiked with crystalline cinnarizine, reaching more than 50% drug dissolved in the first minute. Pellets were further characterized by X-ray powder diffraction (XRPD) and polarized light microscopy (PLM). Both methods indicated the presence of liquid crystalline phases of calcium fatty acid soaps, but no presence of crystalline cinnarizine in the pellet. Overall, dissolution studies along with XRPD and PLM analysis indicate that cinnarizine precipitating during *in vitro* lipolysis of this SMEDDS is not crystalline, suggesting an either amorphous form or a molecular dispersion.
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INTRODUCTION

An increasing number of active pharmaceutical ingredients (APIs) are poorly water soluble, but have a high permeability and are therefore classified as class 2 drugs according to the Biopharmaceutics Classification System (BCS).[1] For these BCS class 2 drugs the bioavailability from traditional dosage forms, for example, tablets are often low and variable due to either low solubility and/or slow dissolution in the gastrointestinal (GI) tract. One way to overcome solubility or dissolution issues in the GI tract is to administer the poorly soluble API in solution in a lipid-based drug delivery system. Especially for APIs with sufficient lipophilicity, lipid-based drug delivery systems such as self-microemulsifying drug delivery systems (SMEDDSs) have shown better performance than solid dosage forms.[2–5] A SMEDDS is composed of lipids, hydrophilic and/or lipophilic surfactants and co-solvents and will disperse rapidly upon ingestion to form a microemulsion in the GI tract. Rational development of a SMEDDSs is dependent on an understanding of the properties of each component, their interactions and their ability to solubilize the API.[6]

However, a major concern with regard to lipid-based drug delivery systems, in particular SMEDDSs, is the possible precipitation of the API in the GI tract prior to absorption.[3,7–9] Precipitated API will need to be redissolved prior to absorption and thereby precipitation might hamper its absorption. The liability of an API to precipitate during transit of the GI tract is not very well elucidated, but is believed to be dependent on many different factors such as the degree of API saturation in the formulation and the loss of solubilizing capacity of the delivery system due to partitioning

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of excipients into the aqueous phase of the GI fluids. Further hydrolysis of digestible lipids and surfactants in the SMEDDS by gastric and intestinal lipases during the passage in the GI tract can lead to a reduction in the solubilization capacity also causing the API to precipitate.[9] Thus elucidation of the kinetic profile of API precipitation, and also the nature of the precipitated API, is needed, in order to achieve an understanding of the mechanism behind the precipitation and the impact it might have on drug absorption.

The applied model drug cinnarizine is a BCS class II drug and therefore a suitable candidate for a SMEDDS.[10] It is a selective calcium antagonist that inhibits the calcium dependent contraction of the arterial smooth muscles[11] and it is thus used for treatment of different cerebral and cardiac diseases.[12] Cinnarizine is furthermore used as an agent to reduce motion sickness.[13] It is a weak base with a $pK_{a1} = 2.0$ and $pK_{a2} = 7.5$[14] having higher solubility at lower pH (0.29 mg/mL in 0.1 N HCl) and lower solubility at higher pH (0.002 mg/mL in phosphate buffer pH 7.2).[15] Finally cinnarizine has a $\log P$ of 5.8 and is a lipophilic compound having a solubility in oleic acid of 237 mg/g.[16]

In the present study a dynamic *in vitro* lipolysis model[17,18] was applied to a SMEDDS containing cinnarizine. The SMEDDS used in this study was developed as a tool for the elucidation of the mechanisms involved in SMEDDS formation, digestion, and drug solubilization.[19] It contains sesame oil as lipid phase, Cremophor RH40 and Brij 97 as hydrophilic surfactants, oleic acid as co-surfactant and ethanol as co-solvent. Thus sesame oil is the only excipient that is substrate for lipolysis.[19] Often SMEDDS contains various components susceptible to digestion, which complicates the interpretation of data, due to the complex mixture of digestion products that will be formed. Therefore the simplified SMEDDS used in this study, enable a better understanding of the events occurring during *in vitro* lipolysis.

The aim of this study was to characterize the precipitation of cinnarizine during *in vitro* lipolysis of SMEDDS in order to gain an increased understanding of the mechanisms behind API precipitation during digestion of SMEDDS. The distribution of cinnarizine between pellet and supernatants was determined during *in vitro* lipolysis and the formed pellet was characterized by X-ray powder diffraction (XRPD) and polarized light microscopy (PLM). The dissolution rates of the cinnarizine pellet and of the blank pellet spiked with crystalline cinnarizine were determined.

MATERIALS AND METHODS

Materials

Cinnarizine (C-5270), sesame oil (S-3547), oleic acid (Fluka, Buchs, Switzerland), Brij® 97 (431281), bile extract (porcine) (B-8631), 4-bromobenzene boronic acid (4-BBBA) (Fluka), and porcine pancreatic lipase (P-1625) were purchased from Sigma–Aldrich (St. Louis, Missouri). Cremophor® RH 40 was donated by BASF (Ludwigshafen, Germany) and phospholipid (S-PC) was purchased from Lipoid (Ludwigshafen, Germany). All other chemicals were of analytical grade and supplied by Sigma–Aldrich.

Table 1. Composition of the SMEDDS

Component	Ratio (w/w) %
Sesame oil	20.6
Cremophor RH 40	45
Oleic acid	15.4
Brij 97	9
Ethanol	10
Cinnarizine	50 mg/g SMEDDS

Preparation of SMEDDS

The SMEDDS was prepared 24 h prior to use. The components were mixed at the ratios indicated in Table 1 in an Erlenmeyer flask using a magnetic stirrer. The SMEDDS was visually examined before use to inspect homogeneity and to control that the cinnarizine was fully dissolved.

Dynamic *In Vitro* Lipolysis

The *in vitro* lipolysis was carried out as described by Zangenberg et al.,[18] with minor adjustments; a total of 195 mL media was placed in a thermostated glass vessel. SMEDDS (1.5 mL, 1.3 g) with or without 66 mg cinnarizine and 3.5 mL of Milli-Q water was added to the media followed by an equilibration for 2 min prior to the initiation of the lipolysis in order to obtain 37°C and pH 6.5. The lipolysis was initiated by addition of 100 mL pancreatic extract (800 USP units/mL) within a 10 s period followed by the start of addition of 0.045 mmol/min calcium chloride. The initial composition of the lipolysis media after the addition of 100 mL of lipase, making the total volume 300 mL, is as shown in Table 2. During lipolysis pH was maintained at 6.5 by addition of a 1.00 M NaOH solution. This pH was chosen as a compromise between the optimal activity of pancreatic lipase (pH 6–10)[20] and duodenal pH (5–5.5).[21–23]

Table 2. Composition of the Lipolysis Media

Component	Initial Concentration
Bile salts	5 mM
Phosphatidyl choline	1.25 mM
Trizma maleate	2 mM
Sodium	150 mM
Cinnarizine	66 mg/300 mL
Added during the lipolysis	Concentration
Pancreatic lipase	800 UPS units/mL
Ca^{2+}	0.5 mM

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