Solid state characterization of drug precipitation during digestion of super-SNEDDS lipid based drug delivery system using synchrotron SAXS/WAXS

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ABSTRACT

The nature of precipitated drug formed under dynamic lipolysis conditions in simulated gastrointestinal fluids was studied by coupling the in vitro lipolysis model and synchrotron small angle X-ray scattering (SAXS).

INTRODUCTION

There is increasing interest in the solid state form of drug precipitation in the gastrointestinal tract following oral administration of lipid based formulations (LBF). During the digestion of lipids, glycerides and fatty acids are produced and combine with endogenous amphiphilic molecules (bile salts and phospholipids) to form colloidal structures. Co-administered drugs can be solubilized in these colloidal phases, thus improving bioavailability of poorly water soluble drugs.

In the past, precipitation has been previously assumed to lead to reduced absorption. However a recent study showed that during digestion of a self-microemulsifying drug delivery system, cinnarizine precipitated in a non-crystalline form, which exhibited a higher dissolution rate [1]. Thus precipitation isn’t necessarily detrimental to drug performance, and the polymorphic structure of the precipitate and the in vivo implications are of interest.

In the present work, we aim to characterize the nature of the precipitated drug during digestion of so-called ‘super-SNEDDS’, containing a high load of drug in a self-dispersing lipid formulation, using the in vitro lipolysis model and small angle X-ray scattering.

EXPERIMENTAL METHODS

Supersaturated self-nanoemulsifying drug delivery systems (super-SNEDDS) [2] were prepared using lipid (long or medium chain), surfactant (Cremophor RH40) and cosolvent (ethanol) in a 60:30:10 w/w % ratio. Long chain (LC) (soybean oil/Maisine) and medium chain (MC) (Captex 355/Capmul MCM) lipids were utilized for LC and MC super-SNEDDS respectively.

Super-SNEDDS have a higher capacity for drug loading, and formulations were loaded above equilibrium solubility with model drugs fenofibrate, danazol and halofantrine.

In vitro lipolysis studies were performed using a pH-stat auto titrator. 250 mg of LC or MC super-SNEDDS formulation containing model drug was added to fasted simulated intestinal fluid pH 6.5 in the thermostatted digestion vessel at 37 °C. Pancreatin was added to initiate digestion and titrated with NaOH to maintain the system at pH 6.5. At predetermined time intervals, samples were placed into capillaries containing a lipase inhibitor, and centrifuged for 1 min at 10000 rpm to pellet precipitated drug. Capillaries were then immediately placed in the SAXS/WAXS X-ray beam at the Australian Synchrotron to determine the solid state characteristics of any precipitated drug during digestion.

RESULTS AND DISCUSSION

At 0 min in vitro lipolysis in the fasted state, no drug precipitation was evident in the pellet for LC and MC super-SNEDDS for any of the three drugs, as shown by the lack of peaks in the scattering patterns (Figure 1), indicating that dispersion alone did not induce precipitation.

After 60 min in vitro lipolysis, scattering profiles for LC and MC super-SNEDDS systems containing fenofibrate (Figure 1.A) and danazol (Figure 1.B) exhibited peaks. This indicates the formation of crystalline precipitate during lipolysis.

The fenofibrate MC super-SNEDDS system, and the danazol systems were all crystalline at the first 5 min time point, however in the fenofibrate LC system, no peaks were present for the precipitate within the first 10 min of lipolysis, indicating an amorphous to crystalline transition had occurred. At 15 min, crystalline precipitate was detected, which increased in intensity over the 60 min lipolysis period (Figure 1.A).

There were no peaks in the diffractograms from pellets from the LC and MC super-SNEDDS systems containing halofantrine (Figure 1.C), and
thus the absence of crystalline precipitate. This finding is in agreement with previous work, where it was reported that halofantrine precipitates in an amorphous form with enhanced dissolution [2].

Halofantrine is a basic drug, whereas fenofibrate and danazol are not (Figure 2), and there is the potential for formation of an ion pair with the fatty acid [3] produced during digestion. Thus fatty acid produced during lipid digestion may influence the crystallization of precipitated drug.

Figure 1. Scattering profiles of crystalline fenofibrate (Panel A), danazol (Panel B) and halofantrine (Panel C) and profiles obtained after 0 and 60 min lipolysis of drug loaded LC and MC super-SNEDDS systems in the fasted state.

Scattering from crystalline drug was also measured for comparison. (The broad baseline hump underlying the scattering profiles is due to background scattering from the wide angle detector).

Figure 2. Molecular structure of fenofibrate (Panel A), danazol (Panel B) and halofantrine (Panel C).

CONCLUSION
Precipitation of drug on digestion of super-SNEDDS formulations does not necessarily induce crystallization. Early data suggest that basic drugs may not precipitate crystalline. Determination of the solid state of precipitated drug is important to understand how and why precipitation occurs, and how it may influence drug absorption.

REFERENCES

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