Application of an In Vitro Lipolysis Model to Predict and Elucidate the Mechanism of Positive Food Effect
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Purpose
A number of BCS class II drugs have shown increased bioavailability when administered with food. Food effect bioavailability and bioequivalence clinical studies are performed for a large majority of New Drug Applications. The mechanism(s) underpinning positive food effect, which we hypothesize to involve drug solubilisation by mid-digestion colloids, is poorly understood. The objective was to develop an in vitro tool to predict positive in vivo food effect for BCS class II drugs and to elucidate the mechanism using atomic force microscopy (AFM).

Methods
A preliminary in vitro lipolysis model to predict positive food effect of weakly basic and neutral drugs was constructed. Dissolution studies of five BCS Class II drugs with known positive food effect were conducted in an in vitro lipolysis model. The bioavailability enhancement for each drug was evaluated by comparing its dissolution profile in a fed state media versus a fasted state media. Samples were collected at predetermined time points and the aqueous fractions were analyzed for drug content using HPLC (Waters, Model 5225). Aqueous fractions were subject to imaging studies carried out using AFM (Asylum Research, Model MFP3D) to observe temporal changes occurring during lipolysis.

Results
The in vitro lipolysis model correctly predicted in vivo food effect of Danazol, Amiodarone, Itraconazole, Griseofulvin and Ivermectin. The fold enhancements in bioavailability were: Danazol - 2.46±0.1, Amiodarone - 10.78±0.2, Itraconazole - 1.48±0.03, Griseofulvin - 2.41±0.04 and Ivermectin - 1.46±0.15. The lipolysis model was able to accurately predict in vivo food effect. AFM images showed mid-digestion colloidal particles and quantified temporal size changes (Range: 50nm to 5µm). Over the course of the lipolysis experiment the number of colloidal particles decreased with the samples becoming more monodisperse. Overall, imaging studies showed that the use of AFM to characterize temporal colloidal changes during the in vitro lipolysis process provides a strong basis to elucidate the mechanism of positive food effect.

Conclusion
An in vitro lipolysis model was developed and tested. The lipolysis model showed the ability to correctly predict in vivo food effect. AFM characterized the dynamic nature of colloid size and number during the lipolysis process.