Nanostructured Microparticles that Mimic the Food Effect for Enhancing Oral Drug Absorption

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ABSTRACT SUMMARY
Silica-lipid hybrid (SLH) microparticles with specific internal nanostructured networks were generated employing submicron emulsions and silica nanoparticles as building blocks. These nanostructured hybrid microparticles can be used to mimic and control the pharmaceutical food effect for optimizing the pharmacokinetic properties of poorly water-soluble bioactives. A series of in vitro and in vivo studies illustrating the promising application of the SLH microparticles as a self-responsive oral lipid-based drug delivery system are presented.

INTRODUCTION
Lipid-based colloidal systems (e.g. micelles, emulsions, liquid crystalline lipids) are effective solubilizing carriers for poorly water-soluble, lipophilic compounds due to the mimicking of positive food effect (i.e. enhanced oral bioavailability in the presence of lipids). However, successful therapeutic translations of many oral lipid-based formulations have been limited by incomplete understanding on the mechanisms of action and inadequate in vitro-in vivo correlations of these formulations. The extent of the food effect contributed by various lipid dosage forms has remained ambiguously drug-specific and mostly unpredictable.

In this investigation, we demonstrate the use of silica-based nanostructured microparticles in controlling the enzymatic digestion of lipid colloids for optimizing the release kinetics and absorption of a model poorly water-soluble drug, celecoxib (CEL). The biopharmaceutical advantages of the nanostructured silica-lipid hybrid (SLH) microparticles in comparison with the pure drug and conventional lipid formulations (i.e. lipid solution and submicron emulsions) were explored.

EXPERIMENTAL METHODS
Preparation of SLH microparticles
SLH microparticles were prepared in a two-step process: (a) high pressure homogenization (Avestin® EmulsiFlex-C5 homogenizer) of the precursor lipid emulsions, using lecithin as an emulsifier and silica nanoparticles as stabilizers and solid carriers; followed by (b) spray-drying of the silica-stabilized emulsions (Mini Spray Dryer B-290, BUCHI Labortechnik AG) to form dry powdery microparticles composed of internal nanoporous matrices.

In vitro lipolysis and drug phase distribution
Lipolysis test was conducted under simulated fasted intestinal condition (1.25 mM phosphatidylcholine/5 mM sodium taurodeoxycholate, pH 7.2, 20 ml), using a previously established pH-stat titration method. Formulation samples equivalent to 200 mg of lipid was digested by porcine pancreatic enzyme (1000 TBU/ml) for 60 min. The magnitude of lipid hydrolysis was quantified based on the consumption of NaOH in the titration of free fatty acids produced. Lipolysis samples (1 ml) were collected at designated time intervals and ultracentrifuged for examining the phase distribution of CEL using HPLC. Lipolysis of the collected samples was inhibited by 4-bromophenylboronic acid.

In vivo absorption study in rats
The rat experiment was approved by the Animal Ethics Committee, Institute of Medical and Veterinary Science (Australia). Groups of five male Sprague-Dawley rats (330±30 g) were cannulated at the right jugular vein and dosed with various CEL formulations (suspended in 0.25% sodium carboxymethylcellulose) at a single dose of 5–50 mg/kg by oral gavage under fasting condition, while water was accessible at all time. Plasma samples were collected up to 10 h and analyzed for CEL content using HPLC. Pharmacokinetic parameters were determined based on a non-compartmental model (WinNonlin® Standard Edition Version 4.1).

In vivo absorption study in dogs
The dog absorption study was conducted according to the guidelines of the Institutional Ethics Committee (Melbourne). Four male beagle dogs weighing between 12–16 kg were used in the four-treatment, four-way, cross-over study with a 7-day washout period. The dosing was fixed at 3 mg/kg of celecoxib (filled into gelatin capsules). The fed treatment group was given 700 g of commercial dog food (containing ≤5% w/w crude fat) 1 h prior to dosing, whereas the fasted treatment groups were fasted for 24 h pre-dose and 10 h post-dose. Blood samples were collected from the cephalic vein via an indwelling catheter at the designated time intervals and analyzed for drug content in the plasma by using HPLC. Pharmacokinetic parameters were determined based on a non-compartmental model.

RESULTS AND DISCUSSION
Crystallinity analysis using X-ray powder diffraction (XRD) confirmed that CEL (log P = 3.5, pK_a = 11.1) was encapsulated in a molecular state in the lipid-embedded nanopores for at least 12 months when stored at ambient conditions (Figure 1).
The specific internal nanostructure of the microparticles (i.e. lipids and drugs adsorbed in the silica nanoporous network) has been shown to facilitate:
(a) a more predictable and enhanced lipid digestibility in comparison with the coarse lipid solution and submicron emulsions (Figure 2);
(b) enhanced drug solubilization (i.e. 2- to 7-fold higher) under both digesting and non-digesting conditions; and
(c) significantly improved bioavailability and other pharmacokinetic properties of CEL in rats and dogs ($p > 0.05$): nanostructured SLH microparticles (fasted) > conventional lipid solution and emulsions (fasted) > pure CEL (fasted/ fed) (Figure 3).

**REFERENCES**

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