ABSTRACT SUMMARY
Lipid based formulations have been developed containing PEGylated surfactants that modulate the extent of lipid digestion. These digestion modulating formulations can be used to control the digestion rate of co-formulated triglyceride via the formation of an anti-biofouling PEG mantle around the lipidic micellar/emulsion core. Delay or prevention of formulation digestion improved the solubilisation of a model poorly water-soluble drug (PWSD) after digestion, but reduced the degree of supersaturation when compared to non-digestion inhibited controls. A series of in vitro and in vivo studies were conducted to explore the potential application of digestion modulating formulations as a novel oral lipid-based drug delivery system. Initial in vivo studies in rats suggest that generation of some degree of supersaturation may be critical in driving drug absorption.

INTRODUCTION
Lipid-based formulations (LBFs) can improve the oral absorption of poorly water-soluble drugs by delivering the drug to the gastrointestinal (GI) tract in a pre-dissolved, molecularly dispersed form. However, on entering the intestine, LBFs (particularly those containing medium chain triglycerides (MCT)) are rapidly digested by intestinal lipases/esterases, causing the solubilisation capacity of the LBF to decrease, in turn creating the risk of drug precipitation and reduced bioavailability. Lipid digestion is an interfacial effect driven by non-specific adsorption of digestive enzymes to the oil:water interface. Surfactants containing polyethylene glycol (PEG) hydrophilic headgroups have previously been suggested to inhibit the digestion of medium-chain triglycerides (MCT).

This project has explored in detail the relationship between surfactant structure and digestion inhibition. The presence of PEGylated surfactant (of optimal PEG molecular weight (Mw)) at the interface of a dispersed LBF provides an anti-biofouling layer capable of controlling digestion by hindering lipase access to the oil-water interface. Inhibition of digestion by these digestion-modulating LBF (DM-LBF) in turn results in improved drug solubilisation capacity and the potential for increases in bioavailability.

EXPERIMENTAL METHODS
Formulation Preparation
LBFs contained 50%, medium chain (MC) lipid, and 50% hydrogenated castor oil (HCO) based PEGylated surfactants of differing PEG molecular weight. Drug loaded formulations were prepared with danazol included at 80% saturation in the formulation.

In Vitro Lipolysis and Drug Solubilisation
In Vitro lipolysis testing was conducted under simulated fasted intestinal conditions in both a standard (dog) and rat model of digestion. The rat model was employed to reflect lower pancreatic enzyme activities and slower digestion rates in the rat GI tract.

Dog model: 1 g of formulation was dispersed in 36 ml of digestion medium using an overhead stirrer. Digestion was initiated by the addition of 4 ml porcine pancreatin extract and monitored for 30 min using a pH-stat titrator at pH 6.5. The time required for 10% of the MCT to be digested ($T_{10\%}$) was estimated by linear interpolation and plotted as a function of the molecular weight of the PEG component of the surfactant.

Rat model: 0.4 g of formulation was dispersed in 4.96 ml of digestion medium using an overhead stirrer. Digestion was initiated by the addition of 0.4 ml porcine pancreatin extract and monitored for 30 min using a pH-stat titrator at pH 6.5. Lipolysis samples were collected at designated time intervals, inhibited with 4-bromophenylboronic acid and centrifuged to separate digestion phases. Danazol content was assayed using a validated HPLC method.

In Vivo absorption study in rats
Studies were conducted in accordance with the guidelines of the Monash Institute of Pharmaceutical Sciences Animal Ethics Committee. Groups of five male Sprague-Dawley rats (300 ± 20 g) were cannulated at the right carotid artery and allowed to recover overnight prior to dosing. The fasted rats were dosed with a single dose of 100mg of formulation via oral gavage. Water was available ad libitum throughout the study. Plasma samples were collected up to 5 h post dosing and analyzed for Danazol content using a validated UPLC MS/MS method.

RESULTS AND DISCUSSION
Digestion of MCT was significantly inhibited by the PEGylated surfactants and the degree of digestion inhibition was dependent on the Mw of the PEG headgroup. In all cases, maximal digestion inhibition was as observed for intermediate Mw PEG surfactants.
This inhibition led to increases in drug solubilisation. Figure 1 provides exemplar data for the HCO formulations, but the inhibition patterns were identical for all six surfactant classes tested.

Figure 1. Time taken for 10% MCT digestion in the presence of HCO surfactants of increasing PEG Mw (solid line). Dashed line, drug solubilisation in low, medium and high Mw PEG HCO formulations after 30 min digestion. (Mean ± SD (n=3))

Digestion modulation and drug solubilisation was also dependent on the digesting conditions of the model used. Thus, the decreases in danazol solubilisation observed in the low Mw HCO 7 formulation under ‘dog’ conditions were attenuated in the more slowly digesting rat model (Figure 2A). Similarly, the digestion modulating capability of the HCO 40 formulation was even more prevalent in the rat model and was essentially non-digestible, resulting in minimal losses in solubility (Figure 2B).

Figure 2. (A) Drug solubilisation profiles of low and (B) intermediate Mw PEG formulations under both standard (dog) and rat digestion conditions. (Mean ± SD, (n=3))

Interestingly, the low Mw PEG surfactant formulations (HCO 7) showed significantly higher bioavailability (p < 0.01) in rats when compared to intermediate Mw PEG formulations (Figure 3). This was surprising as the HCO 40 formulation did not lose solubilisation capacity after digestion.

Figure 3. Plasma profiles of danazol in the fasted rat model. Data normalized to a 10 mg/kg dose, (mean ± SEM (n=5)).

The superior in vivo performance of the HCO 7 formulation may be attributable to an increase in supersaturation post-digestion (Table 1). In contrast, the HCO 40 formulation does not appear to generate supersaturation. While this system is unlikely to result in drug precipitation on digestion, the lack of thermodynamic drive for absorption may impact on in vivo performance.

Table 1. DM-LBF formulation supersaturation ratios on dispersion and digestion.

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<tr>
<th>Formulation</th>
<th>S Dispersion</th>
<th>S Digestion</th>
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<tbody>
<tr>
<td>HCO7 (A)</td>
<td>1.3</td>
<td>1.9</td>
</tr>
<tr>
<td>HCO40 (B)</td>
<td>1.2</td>
<td>1.2</td>
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CONCLUSION
Digestion modulating lipid based formulations (DM-LBF) comprising PEGylated surfactants can control the rate of digestion of co-formulated MCT. The extent of digestion in turn dictates drug solubilisation and potential for supersaturation. Preliminary in vivo data suggests that the degree of supersaturation generated on in vivo processing of these formulations may be critical to optimal absorption.

REFERENCES

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