Gastric Processing is a Critical Determinant of the Ability of Lipid-Based Formulations to Enhance the Oral Bioavailability of a Model Poorly Water-Soluble Drug

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ABSTRACT SUMMARY

The bioavailability cinnarizine, a model poorly water soluble drug was more dependent on gastric digestion than emulsification when administered in medium chain triglyceride, but when administered in long chain triglyceride, emulsification was more important than gastric digestion.

INTRODUCTION

The contribution of gastric processing of lipid based drug formulations to drug bioavailability is not yet well understood. Although it is well known that medium chain lipids are digested to a greater degree than long chain lipids, the relative contributions of gastric lipolysis and gastric emulsification for different types of formulation lipids has not been elucidated, despite being critical to determining the utility of lipid based formulations. In order to elucidate the relative importance of emulsification and digestion, lipid formulations were administered orally or intraduodenally (ID), as either bolus or in pre-emulsified form, using medium chain (MCT) or long chain triglyceride (LCT). Cinnarizine was used as the model poorly water soluble drug.

EXPERIMENTAL METHODS

Formulations were prepared by dissolving drug in 250 mg lipid directly at 50% of its saturated solubility in the lipid. For pre-emulsified samples the drug + lipid mixture was sonicated in 10 mL, 5 mM taurodeoxycholate solution. Oral formulations were administered to Sprague Dawley rats (250-300g) by oral gavage. For intraduodenal administration, a cannula was inserted into the duodenum and exteriorized to enable administration either as a bolus for the lipid solution, or as an infusion for the dispersion. Plasma samples were obtained via an indwelling cannula inserted into the carotid artery. Rats were fasted for 12 hrs prior to and 8 hrs after administration. Samples were extracted using tert-butyl methyl ether and analyzed using HPLC with fluorescence detection as previously described1.

RESULTS AND DISCUSSION

Overall exposure was greater for oral than for ID administration. As previously reported, LCT provided increased exposure of drug compared to MCT2,3. The oral bioavailability after oral administration of the two dispersed equivalent formulations was the same. The bioavailability for the MCT dispersion had increased to be similar to the LCT formulations (bolus or dispersed). Assuming that emulsification efficiency is similar for the oily formulations, this would indicate that access of the enzyme to the MCT substrate, and hence gastric digestion is more critical for MCT than LCT in determining bioavailability.

![Figure 1](image1.png)

**Figure 1:** Dose normalised plasma profiles for CZ after bolus oral and intraduodenal administration of MCT and LCT lipid solution formulations. Lipid solutions contained CZ at 50% saturated solubility in the respective lipids, n = 4 – 6 ± SEM.

![Figure 2](image2.png)

**Figure 2:** Dose normalised plasma profiles for CZ after oral administration of lipid dispersion MCT and LCT formulations. Lipid dispersions (3 mL) contained 250 mg of lipid with CZ at 50% saturated solubility in the respective lipids in a bile salt micellar formulation, n = 4 ± SEM.
Intraduodenal infusion of the LCT dispersion reduced the bioavailability of cinnarizine compared to ID administration of equivalent bolus formulation (Figure 4). This indicates that incomplete digestion of the formulation may have occurred by the infusion forcing formulation past the site of absorption. In contrast the bolus was administered to the duodenum and left to be processed at normal physiological rate. The slower infusion rate provided greater bioavailability, further supporting the hypothesis of incomplete digestion.

The fact that infusion of the MCT dispersion provided greater bioavailability than the ID bolus, but not as great as the oral dispersion (Figure 4) then indicates that gastric digestion is an important aspect of determining the oral bioavailability over and above emulsification. Digestion of MCT to produce relatively short chain fatty acids with moderate aqueous solubility may trigger an increase in drug activity in the residual oil droplets as one possible explanation for this observation. This mechanism for enhanced drug activity would not be present in the intraduodenal infusion, where the gastric digestion step is bypassed.

The form of oral LCT formulation (bolus vs dispersed) did not influence the bioavailability of CZ. This is consistent with previous findings comparing bolus lipid formulation to ‘self-emulsifying’ formulations. The orally administered bolus formulation provided lower bioavailability than the two oral formulations. This indicates that the form of presentation to the duodenum is important for LCT formulations, and specifically that emulsification in the stomach of the bolus oral formulation such that it ‘resembles’ the oral dispersion on gastric emptying is also a governing factor over bioavailability.

CONCLUSION

The set of in vivo studies shows that for MCT formulations, gastric digestion is a more important factor in dictating the oral bioavailability of a co-administered poorly water-soluble drug than is emulsification. In contrast, for LCT formulations, it is apparent that gastric emulsification is an important step in the process, and gastric digestion is unlikely to be a significant contributor to bioavailability. The pattern of LCT outperforming MCT in oral bioavailability studies is continued in this work, although intraduodenal administration of the MCT and LCT dispersed formulations did provide equivalent bioavailability but was likely due to incomplete digestion for the LCT formulation. Overall, bypassing gastric digestion of MCT formulations be eg. coating technologies or use of inhibitors may lead to reduced performance from a bioavailability perspective.

REFERENCES