Labrafac™ MC60 acts as an intestinal permeation enhancer in isolated rat colonic and jejunal mucosae in the Ussing chambers

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Introduction

Labrafac™MC60 (LMC60, glycerol monocaprylocaprate) is a lipid-based excipient that is composed of mostly mono- and diglycerides of caprylic acid (C_8) and capric acid (C_{10}) (Figure 1). It is included in the US Food and Drug Administration inactive ingredient list for oral delivery and is used primarily as a solubiliser[1]. Glycerol monocaprylocaprate is not a new excipient, but a new grade is currently being commercialised as LMC60 (Gattefossé, France). The aim of our research was to investigate whether LMC60 acts as an intestinal permeation enhancer (PE) in a manner similar to another C_8 and C_{10} containing excipient, Labrasol®ALF (LAS)[2] (Gattefossé, France) and sodium caprate (C_{10}). PEs are being researched to overcome intestinal barriers to oral macromolecule delivery.

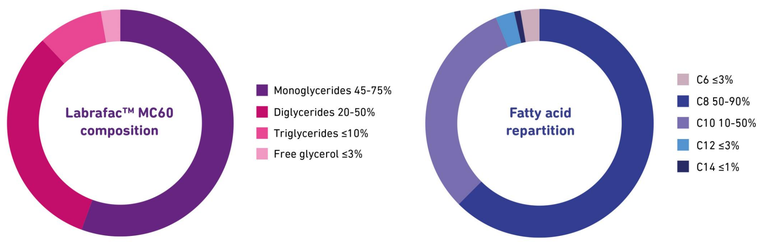
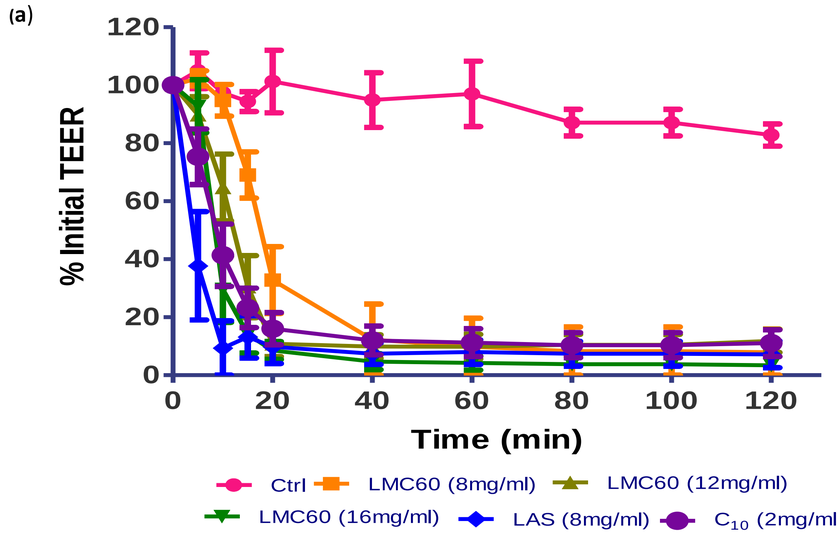


Figure 1: Components of Labrafac™ MC60

Labrafac™ MC60 reduces TEER and increases P_{app} in colon



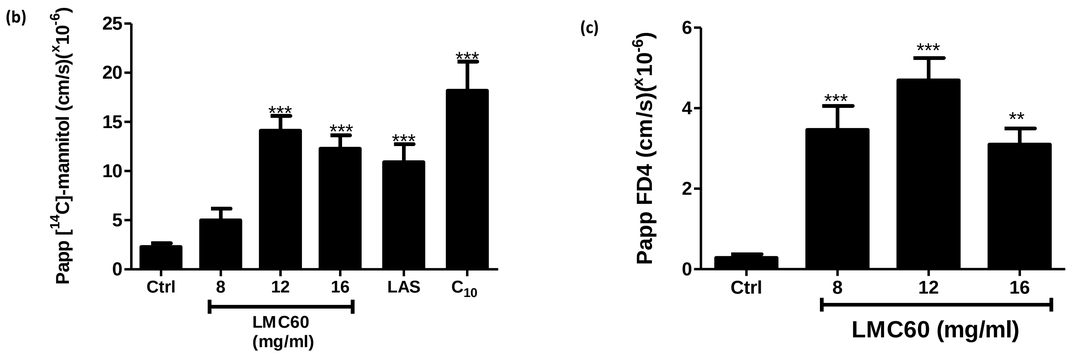


Figure 3: Labrafac™ MC60 (LMC60: 8, 12 and 16mg/ml) decreased (a) TEER and increased the P_{app} of (b) [^{14}C]-mannitol and (c) FITC-dextran (4kDa) across rat colonic (stripped) mucosae in a concentration dependent manner. Mean ± SEM, n=3-8 (**P<0.01 and ***P<0.001 compared to control (Ctrl), one-way ANOVA with Dunnett's post-test). Labrasol® ALF (LAS, 8mg/ml) and C_{10} (2mg/ml, 10mM) were used as positive controls.

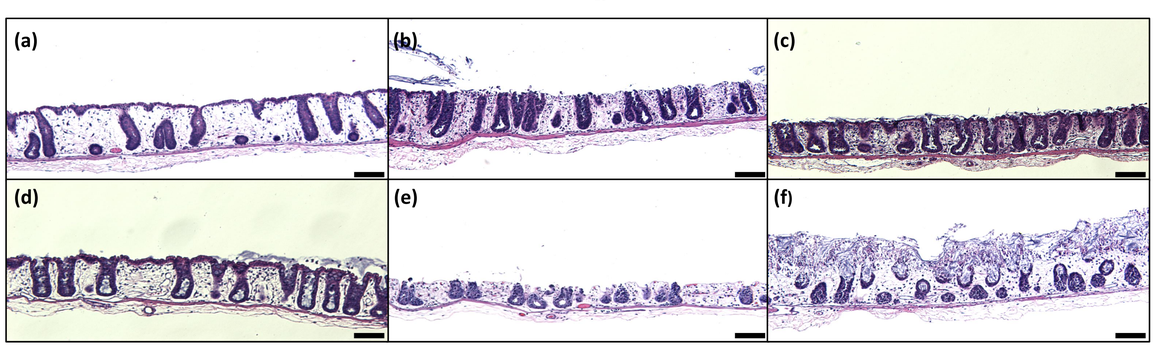


Figure 4: Effect of Labrafac™ MC60 on histology of colonic tissue (a) control (b) 8mg/ml LMC60 (c) 12mg/ml LMC60 (d) 16mg/ml LMC60 (e) 8mg/ml LAS (f) 2mg/ml C_{10}. Marker = 100 µm. Tissue is orientated with the apical side at the top of the image. Concentration dependent effects were observed with slight erosion of the epithelial layer.

Discussion and Conclusion

LMC60 acts as an intestinal PE in rat colon and jejunum in the Ussing chambers. LMC60 has potential to be included in oral formulations to improve the oral bioavailability of poorly absorbed macromolecules. *In vivo* studies are planned to further confirm this data.

Methods

Labrafac™MC60 (LMC60 8,12 and 16 mg/ml) was tested in Ussing chambers using isolated muscle stripped rat colonic and also in unstripped jejunal mucosae (20 and 40 mg/ml). Transepithelial electrical resistance (TEER, Ω.cm^2) was calculated using Ohm's law. The apparent permeability (P_{app}) coefficients of the paracellular markers [^{14}C]-mannitol (MW: 192 Da, 0.1µCi/ml) and FITC-dextran (MW: 4kDa, 2.5mg/ml) were measured over 120 min. Control (Ctrl) refers to untreated tissue. Labrasol®ALF (LAS) (8mg/ml, colon and 20 and 40mg/ml, jejunum) and sodium caprate (C_{10}, 2mg/ml, colon and 6mg/ml jejunum) were used as positive controls.

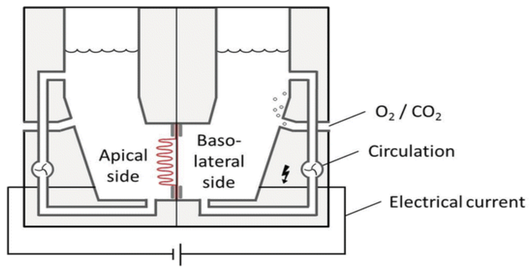
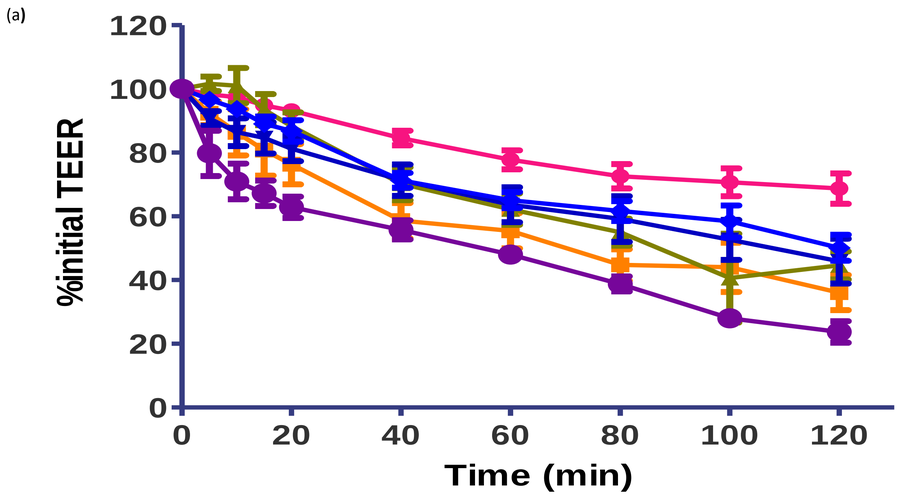


Figure 2: LMC60 and positive controls were added apically to the Ussing chambers and samples were collected every 20min for 120min to calculate P_{app}[3].

Labrafac™ MC60 decreases TEER and increases P_{app} in jejunum



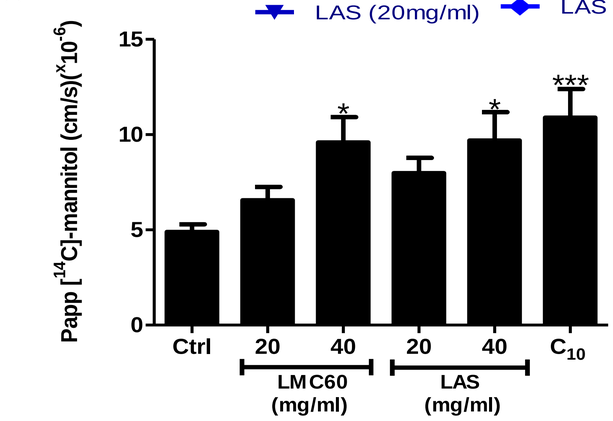


Figure 5: Labrafac™ MC60 (LMC60: 20 and 40mg/ml) decreased (a) TEER and increased the P_{app} of (b) [^{14}C]-mannitol across rat jejunal (unstripped) mucosae. Mean ±SEM, n=4-9 (*P<0.05 and ***P<0.001 compared to control (Ctrl), one-way ANOVA with Dunnett's post-test). Labrasol® ALF (LAS, 20 and 40mg/ml) and C_{10} (6mg/ml, 30mM) were used as positive controls.

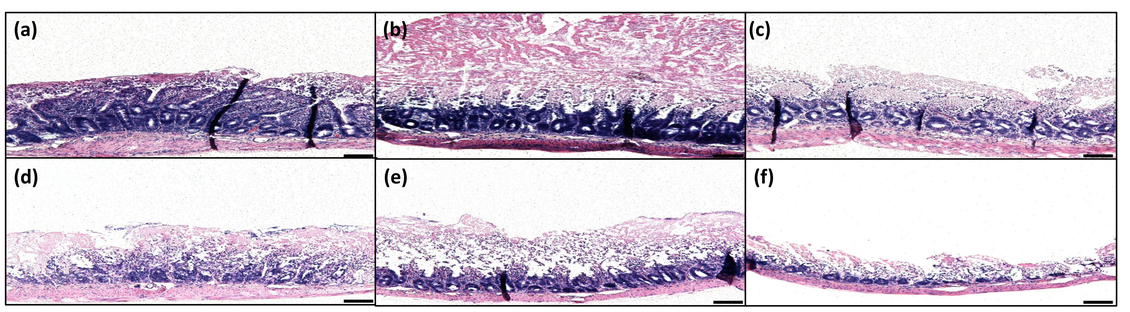


Figure 6: Effect of Labrafac™ MC60 on histology of rat jejunal tissue (a) control (b) 20mg/ml LMC60 (c) 40mg/ml LMC60 (d) 20mg/ml LAS (e) 40mg/ml LAS (f) 6mg/ml C_{10}. Marker = 100 µm. Tissue is orientated with the apical side at the top of the image. Erosion at the tops of the villi was observed with C_{10} showing the most effects.

References

1. US FDA inactive ingredients list., https://www.accessdata.fda.gov/scripts/cder/iig/index.cfm
2..McCartney et al., J Control Release. 2019 Sep 28;310:115-126. doi: 10.1016/j.jconrel.2019.08.008
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