

In vivo confirmation of the permeation enhancement capacity of Labrafac™ MC60

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PURPOSE

Intestinal permeation enhancers (PEs) are included in oral dosage forms to improve the permeability of peptides by facilitating transport across the intestinal epithelium. Our aim was to investigate whether Labrafac™ MC60 (LMC60, glyceryl mono and dicaprylocaprate) acts in vivo as an intestinal permeation enhancer similar to another established excipient, Labrasol® ALF (LAS, caprylocaproyl polyoxyl-8 glycerides), using insulin as a model peptide (1). We have previously demonstrated ex vivo that LMC60 acts as a PE by reversibly opening tight junctions in isolated rat colonic and jejunal mucosae in Ussing chambers (2). LMC60 is a lipid-based excipient composed of mono- and diglycerides of caprylic acid (C8) and capric acid (C10). It is used as a solubiliser in oral formulations such as self-emulsifying (or self microemulsifying) drug delivery systems (SEDDS or SMEDDS). As part of this study, we also investigated whether bile salts in intestinal fluid could interact with the fatty acids in LMC60 and potentially reduce its effectiveness as a PE.

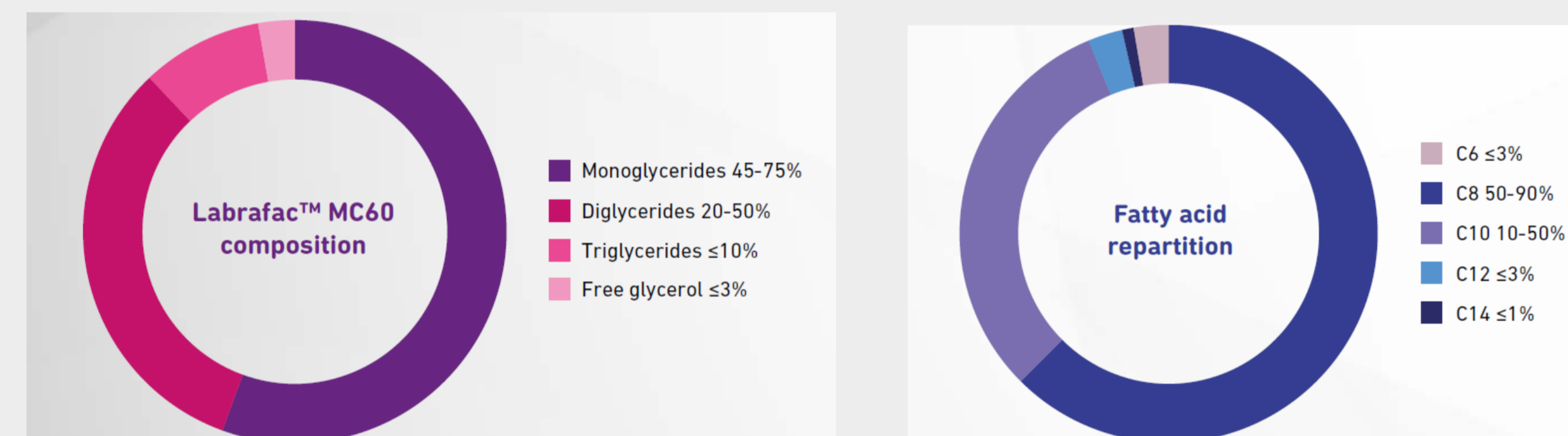


Figure 1: Components of Labrafac™ M60

OBJECTIVE

To investigate the ability of Labrafac™ MC60 to increase the relative bioavailability of insulin using an in-situ rat instillation model using PBS and simulated intestinal fluid as buffers.

METHODS

The effects of excipients on improving the relative bioavailability of insulin were tested using the in-situ rat jejunal instillation technique. LMC60 and LAS (40mg/ml) in either PBS or fasted state simulated intestinal fluid (FaSSIF, pH 6.5 with 3mM taurocholate) were instilled with 50IU/kg insulin. In brief, Wistar-CRL rats were anaesthetised, and a midline laparotomy was performed to expose the intestine. A small pouch was created by tying the intestine 5-7cm apart. Insulin and the excipient were injected into the pouch with a 30G needle. The animals remained under anaesthesia for the duration of the experiment. Blood glucose was measured using a glucometer and blood was taken retro-orbitally to measure plasma insulin levels using an ELISA. Insulin (1IU/kg) was also administered by the subcutaneous (s.c.) route in order to calculate relative bioavailability (%F).

RESULTS

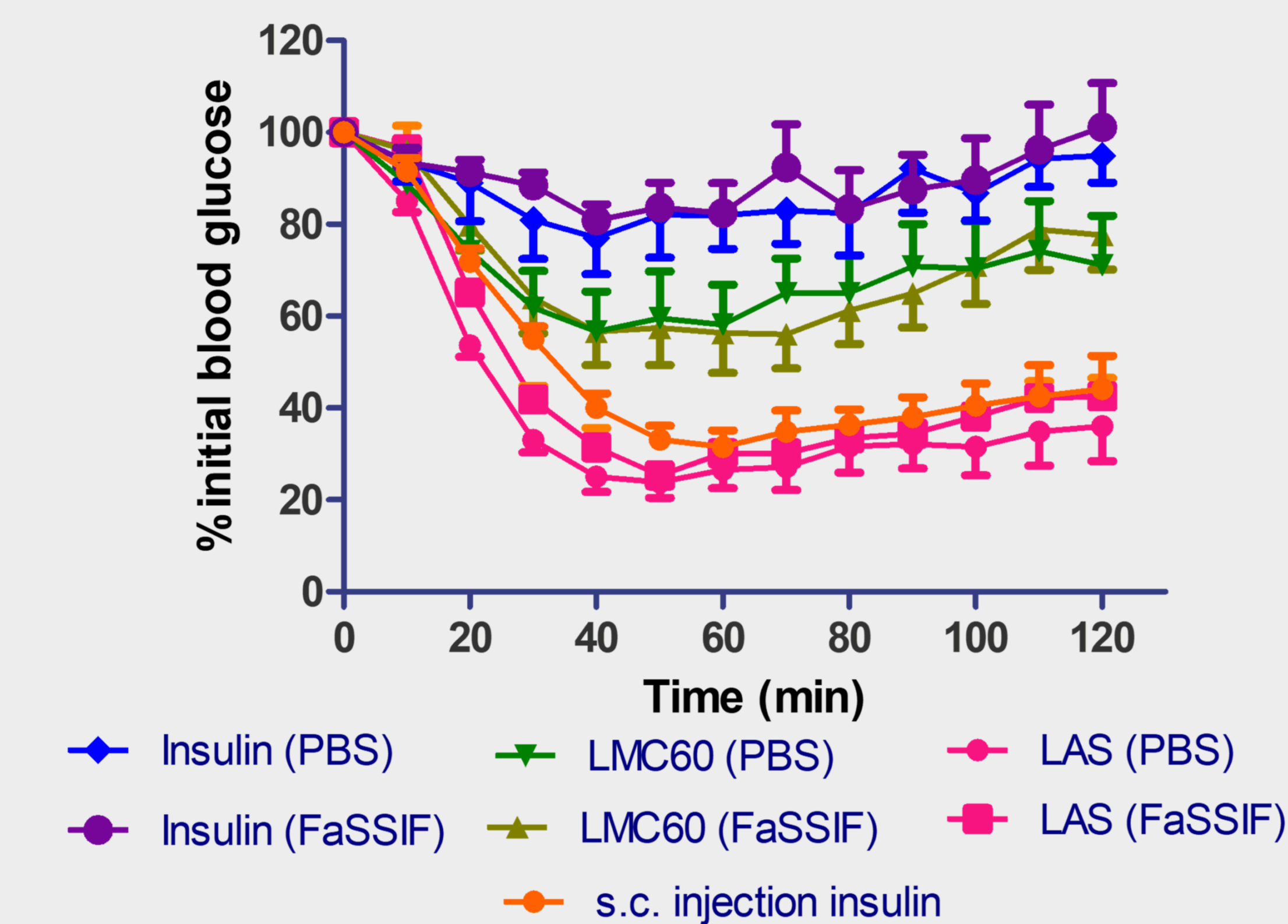


Figure 2: Blood glucose levels following intra-jejunal instillation of insulin (50IU/kg) alone or ad-mixed with Labrafac™ (LMC60) or Labrasol® (LAS, both 40 mg/ml). Insulin (1 IU/kg) was administered by the s.c. route. Mean ± SEM of n=6 per group.

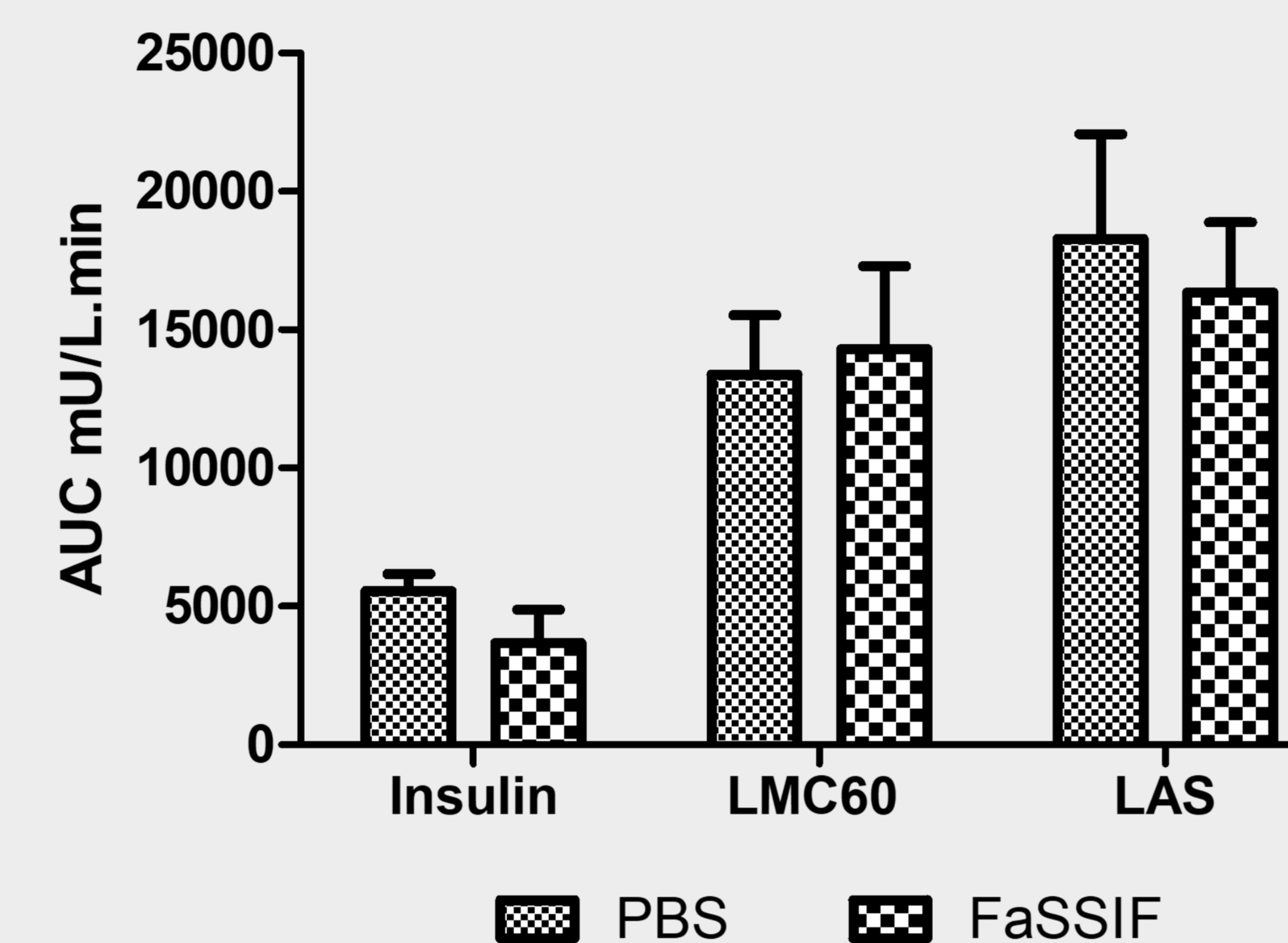


Figure 3: Comparison of the area under the curve from the plasma insulin concentration v time following intra-jejunal instillation of insulin (50IU/kg) alone or ad-mixed with Labrafac™ (LMC60) or Labrasol® (LAS, both 40 mg/ml). Mean ± SEM of n=6 per group.

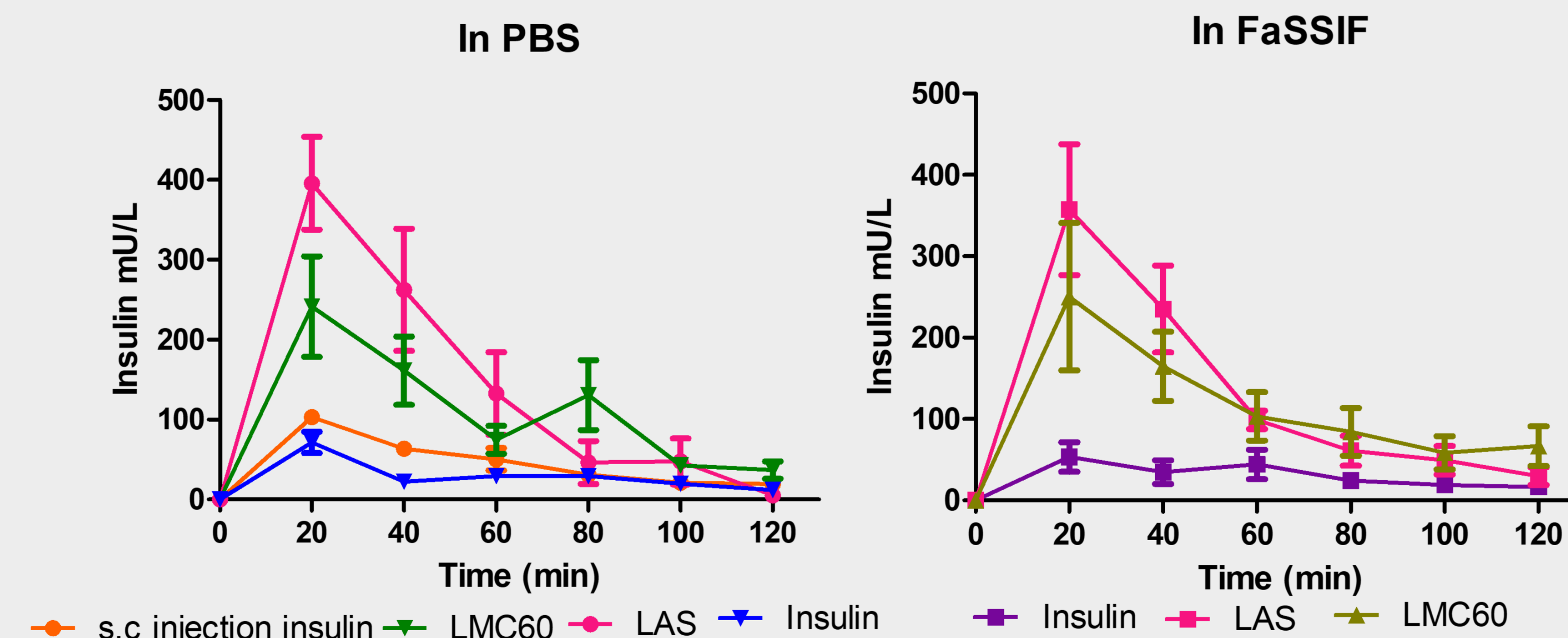


Figure 4: Plasma insulin (mU/L) levels in response to administration of insulin (50 IU/kg) alone or ad-mixed with Labrafac™ (LMC60) or Labrasol® (LAS, both 40 mg/ml). Insulin (1 IU/kg) was administered by the s.c. route. Mean ± SEM of n=6 per group.

| Treatment | T _{max} (min) | C _{max} (mU/L) | AUC (0-120) (mU/L.min) | % F |
|--------------------------------|------------------------|-------------------------|------------------------|-----|
| Insulin, s.c. | 27±7 | 104±3 | 5544±642 | - |
| Insulin, i.j. in PBS | 30±10 | 74±12 | 3568±691 | 1.3 |
| Insulin (i.j.) in FaSSIF | 40±13 | 58±18 | 3683±1197 | 1.3 |
| Insulin in PBS with: | | | | |
| Labrafac™ MC60 (40mg/ml) | 43±12 | 267±60 | 13377±2144 | 4.8 |
| Labrasol® ALF (40mg/ml) | 23±3 | 420±58 | 18272±3800 | 6.6 |
| Insulin in FaSSIF with: | | | | |
| Labrafac™ MC60 (40mg/ml) | 30±7 | 316±75 | 14297±3007 | 5.2 |
| Labrasol® ALF (40mg/ml) | 23±3 | 380±69 | 16340±2537 | 5.9 |

Table 1. Pharmacokinetic results after intra-jejunal instillation of insulin (50IU/kg) alone or ad-mixed with Labrafac™ (LMC60) or Labrasol® (LAS, both 40 mg/ml). S.c.-administered insulin dose was 1 IU/kg.

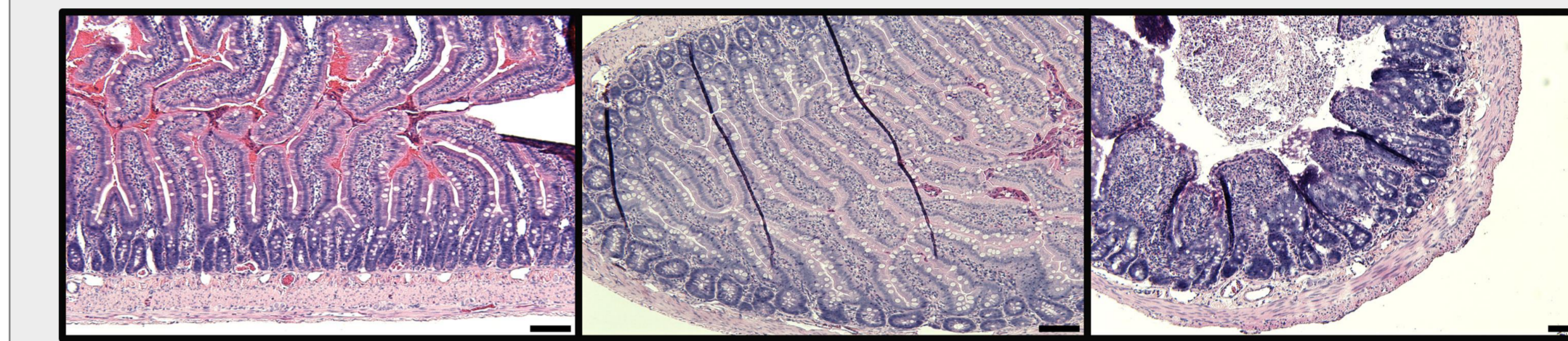


Figure 5: Haematoxylin & eosin-stained rat jejunal tissue after 120min jejunal instillation. Marker bar=100 microns.

DISCUSSION

Jejunal-instilled LMC60 with insulin in PBS decreased blood glucose levels and increased the relative bioavailability (%F) of insulin compared to insulin alone (Fig. 2 & 4, Table 1). Insulin when ad-mixed with LMC60 reduced blood glucose by 43% compared to LAS 76% (Fig. 2). Both excipients increased the %F of insulin: LMC60 increased it to 4.8% and LAS to 6.6% (Table 1). This data also showed the reproducibility of LAS as previously when tested in a separate study a %F of 6.7 was achieved for insulin (1). In order to make the studies more physiologically relevant they were repeated using FaSSIF. The presence of bile salts in the buffer did not interfere with the capacity of these excipients to act as PEs in vivo. LMC60 and LAS reduced blood glucose and increased plasma insulin levels similarly in FaSSIF and PBS. (Table 1). A comparison of the AUC of plasma insulin levels for both PE groups showed no differences using PBS or FaSSIF as the buffer in instillations (Fig. 3). Histological examination of the tissue after the two hours showed treated tissue was similar to the insulin control with minor cell debris observed in the lumen. For both LMC60 and LAS tissue villi were intact.

CONCLUSION

Labrafac™ MC60 has the potential to be used in oral dosage forms as an intestinal permeation enhancer for poorly permeable drugs, such as peptides as an additional option to Labrasol® ALF.

REFERENCES

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