In-vitro Model to Forecast the Lymphatic Uptake/Inhibition of Drugs via Chylomicrons

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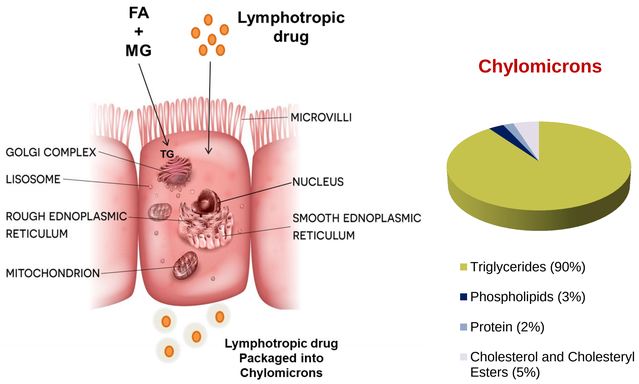
Purpose

- Lymphatic uptake of drugs through **chylomicrons** (lymph-carried species produced by intestinal cells) imparts important pharmacokinetic and pharmacodynamics implications. However, the biophysics of *in-vitro* systems and prediction of *in-vivo* lymphatic disposition has not been mechanistically examined. [1,2]
- The aim of this study was to investigate the oral lymphatic uptake of drugs and their inhibition via a novel *in-vitro* model.
- We hypothesized that by using artificial chylomicrons (Intralipid®) and Franz cells, the drug-chylomicrons association and inhibition of this process can be studied.



FA = Fatty acid, MG =Mono-glyceride, TG = Triglyceride

Figure 1. Drug-chylomicron association in the intestinal cells. Lymphotropic drugs after being absorbed into the enterocytes they get packaged into chylomicrons (formed from re-esterified absorbed fats) before being expelled to be taken up by intestinal lymphatics.

• Part of the figure was purchased from depositphotos under a standard licence.

Methods

The receiver compartment was filled with 12 ml of either Intralipid® (20%, Fresenius Kabi, Canada Ltd., Ontario, Canada) or Intralipid® containing pluronic L-81 (1%-15%), chloroquine (5%) or sesame oil (2%), maintained at 37.0 ± 0.05 °C and magnetically stirred at 600 rpm.

Synthetic 0.22 µm Polyvinylidene Fluoride (PVDF) membrane impregnated with octanol was placed between compartments.

Two ml of solution of the model drugs (rifampicin, cannabidiol and quercetin) were added to the donor compartment.

At different time intervals (0 - 4 h), 0.2 ml samples were withdrawn, extracted and analyzed for the drug content using HPLC.

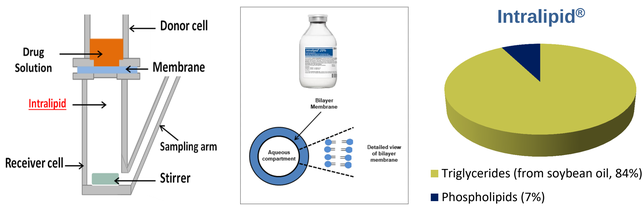


Figure 2. Drug-chylomicron association in the proposed model (left). Here synthetic chylomicrons (Intralipid®) was used and the drug release into the Intralipid® was investigated.

• Intralipid® bottle image (middle) is from the supplier's website Fresenius Kabi.com and the illustration below it is modified from [3] .

Results

1. *In-vitro* Lymphatic Uptake Profiles

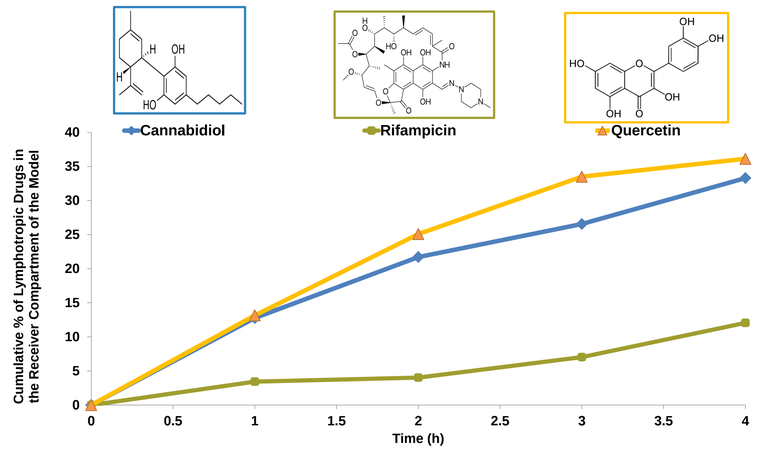


Figure 3. Graph demonstrating the cumulative % of the tested drugs in the receiver compartment of the model (% of *in-vitro* lymphatic uptake).

2. *In-vitro* Lymphatic Uptake Inhibition via Pluronic L-81 (surfactant)

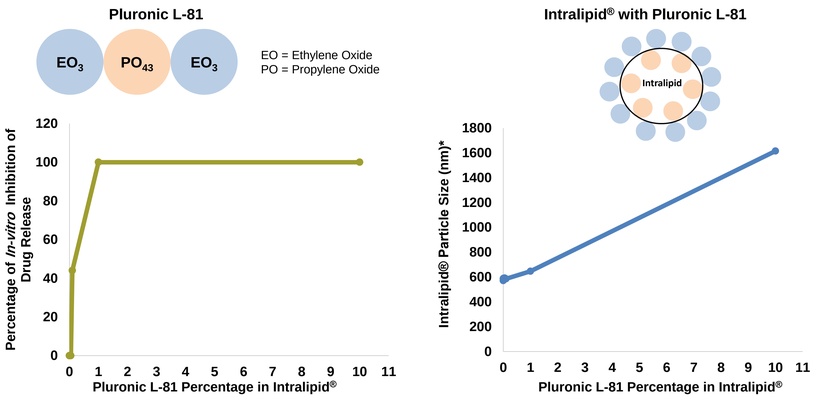


Figure 4. Effect of adding Pluronic L-81 to Intralipid®. The effect of percentages used in the inhibition of the drug release (left) and change in the Intralipid® particle size with the different percentages used (right). Pluronic L-81 being a surfactant is proposed to coat the Intralipid®.

*** Particle size was measured via dynamic light scattering using Malvern Utlra Zeta Sizer (25 °C and an angle of 173°).**

3. *In-vitro* Lymphatic Uptake Inhibition via Chloroquine (as Cholesterol Lowering Agent)

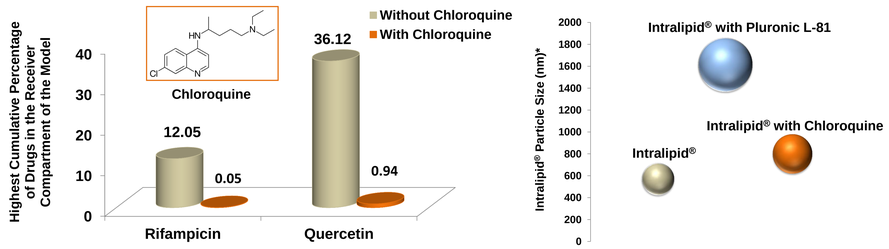


Figure 5. Ilustration of the differences in extent of the *in-vitro* lymphatic uptake of the model drugs; rifampicin and quercetin via the developed model when 5% chloroquine was added to the Intralipid® (left). Comparison of particle size of Intralipid® alone and with chloroquine (5%), and pluronic L-81 (10%) is also shown (right).

*** Particle size was measured using via dynamic light scattering using Malvern Utlra Zeta Sizer (25 °C and an angle of 173°).**

Results

4. *In-vitro* Lymphatic Uptake Enhancement by Sesame oil

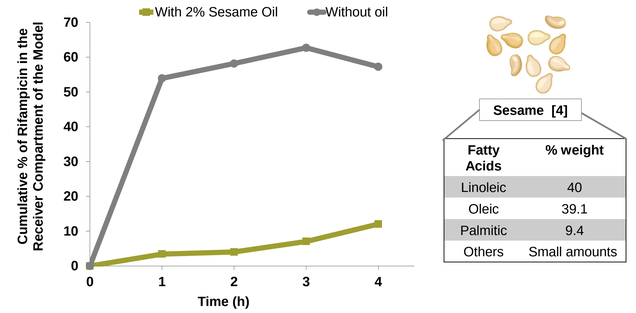


Figure 6. Demonstration of the increased *in-vitro* lymphatic uptake of rifampicin via the developed model when sesame oil (2%) was added to Intralipid®.

• Sesame seeds image was purchased from depositphotos under a standard licence.

Conclusions

- The presented *in-vitro* model demonstrated its ability to mimic drug uptake into chylomicrons, enhancement and inhibition of this process.
- Both Pluronic L-81 and chloroquine used for studying the inhibition affected the particle size of the synthetic chylomicrons (Intralipid®).
- The new model showed promising results that can potentially be used to study and mechanistically predict the lymphatic drug uptake and xenobiotics effects to inhibit or enhance this process.

Future Work

- Analyzing other lymphotropic drugs to confirm the utility of the model for a wider range of drugs.
- Correlating the collected data with the *in-vivo* lymphatic uptake of the tested drugs.
- Test other xenobiotics to investigate the lymphatic uptake enhancement through food or formulation effects.

References

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Acknowledgements

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