



Simple screening methods for prediction of intestinal lymphatic transport of lipophilic drugs



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Introduction

Association of a drug with chylomicrons in the enterocyte is the main step in the intestinal lymphatic route of absorption of lipophilic molecules (Fig. 1). Since the animal models currently used to estimate the lymphatic absorption of drugs are very difficult to perform, there is a clear need for fast and efficient models to predict the intestinal lymphatic bioavailability potential of lipophilic molecules.

Aims

- > To compare the degree of uptake of lipophilic compounds by chylomicrons *ex-vivo* and by chylomicron-like artificial emulsion *in-vitro* to the corresponding intestinal lymphatic bioavailability reported in rats.
- > To evaluate the utilization of these correlations as a predictive measurement of the lymphatic bioavailability potential of lipophilic drugs.

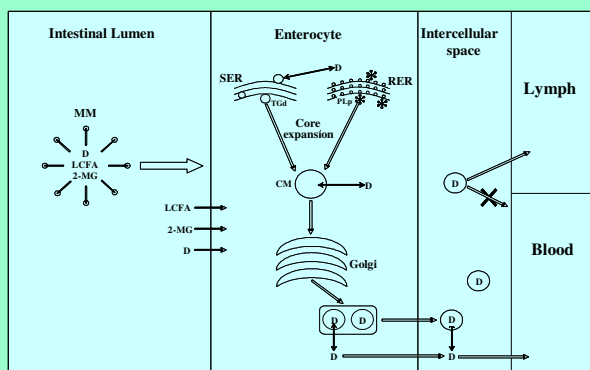


Figure 1. Schematic presentation of intestinal lymphatic absorption of lipophilic drugs. MM, mixed micelle; D, drug; LCFA, long chain fatty acids; 2-MG, 2-monoacylglyceride; SER, smooth endoplasmic reticulum; RER, rough endoplasmic reticulum; TGd, triglycerides rich droplet; PLp, primordial lipoprotein; CM, chylomicron.

Methods

- > 9 lipophilic compounds (listed in Table 1) at a concentration of 1.75×10^{-6} M were incubated for 1 hour with chylomicrons separated from rat blood or with commercially available artificial chylomicron-like emulsion at pH 7.4.
- > The lymphatic bioavailability of tested compounds reported *in-vivo* in rats was correlated with the degree of uptake by chylomicrons *ex-vivo* and by chylomicron-like emulsion *in-vitro*.

Results

- > A strong linear correlation was found between the degree of association of compounds with chylomicrons *ex-vivo* and the lymphatic transport reported in rats ($r^2 = 0.94$) (Fig 2).
- > The correlation between the degree of association of lipophilic molecules with chylomicron-like emulsion *in-vitro* and the lymphatic transport was slightly weaker ($r^2 = 0.91$) (Fig 3).
- > Physicochemical properties traditionally used to predict the intestinal lymphatic transport of lipophilic compounds have shown limited correlation with lymphatic bioavailability of tested molecules (Table 1 and Fig. 3A and 3B).

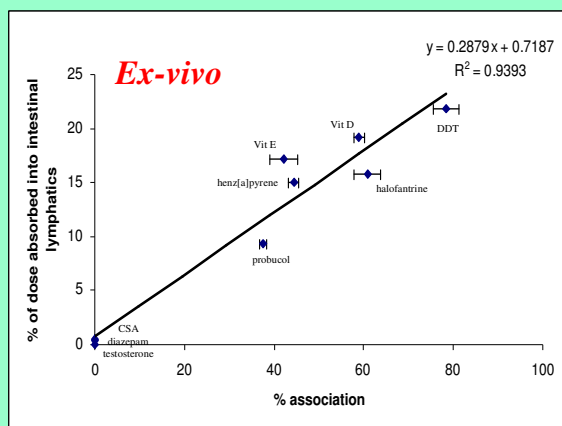


Figure 2. Lymphatic availability of tested drugs (% of dose) vs. degree of association of drugs with isolated CM in the *ex-vivo* model (% of amount).

Table 1. Summary of physicochemical properties of tested drugs

Compound	MW	LogP	Solubility in LCT (mg/g) (Mean \pm SD)
Diazepam	284.7	2.70	15.45 \pm 0.41
Testosterone	288.4	3.27	8.25 \pm 0.30
CSA	1202.6	2.92	44.9 \pm 15.1
Halofantrine	500.4	8.5	47.3 \pm 6.5
Vitamin D3	384.6	9.14	168.3 \pm 26.3
Vitamin E	430.7	12.18	miscible
Probucol	519.9	10.91	60.9 \pm 4.7
Simvastatin	418.6	5.19	8.43 \pm 0.21
Bifonazole	310.4	5.71	3.65 \pm 0.07
Paclitaxel	853.9	4	0.53 \pm 0.03
Benzo[a]pyrene	252.3	6.11	16.57 \pm 1.12
p,p'-DDT	354.5	6.79	176.57 \pm 8.45

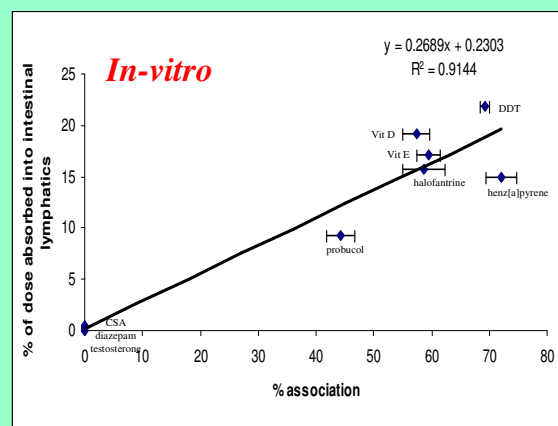


Figure 3. Lymphatic availability of tested drugs (% of dose) vs. degree of association of drugs with artificial emulsion in the *in-vitro* model (% of amount).

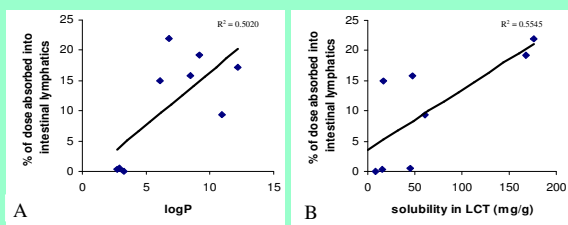


Figure 4. Lymphatic availability of tested drugs (% of dose) vs. logP (A) and TG solubility (B).

Conclusions

✓ Both *ex-vivo* and *in-vitro* methods provide a good alternative to the complicated and expensive *in-vivo* studies of intestinal lymphatic transport of lipophilic molecules.

✓ The degree of association of lipophilic compounds with chylomicrons depends mainly on the triglyceride content of lipoproteins, however surface apoproteins may play a considerable role in the process of uptake.

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