

# Development of an Assay to Study the Interaction of Poorly Water Soluble Drugs with Phospholipid-Loaded Porous Nano Matrix Carriers

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## Introduction & Objectives

The SupraVail Porous Nano Matrix<sup>®</sup> drug delivery technology of Phares Drug Delivery AG comprises the use of highly porous inorganic carriers suitable for oral administration to increase the dissolution rate of poorly water soluble drugs. The drug is dissolved in a suitable phase with surfactants (e.g. phospholipids) and added to the carriers. After removal of the liquid phase the drug/excipient mixture is adsorbed on the carrier pore-surface. Due to the large surface area the drug is adsorbed as a very thin layer on the pore surface. Upon administration the poorly water soluble drug has an increased dissolution because of the high surface area and the wetting properties of the added surfactants. In addition, due to the high adsorption properties of the carriers the resulting formulations can have a high drug load up to 50 % and powder characteristics suitable for further processing in capsules and tablets.

The technology serves as a viable alternative to nano-suspensions to increase the surface area of lipophilic drugs and avoids extensive milling procedures, which may be detrimental for the drug.

The objective of this study was to develop an assay to measure the degree and kinetics of interaction of a lipophilic drug loaded in liposomes with phospholipid containing Porous Nano Matrix carriers.

## Methods

Model Porous Nano Matrix carriers of SiO<sub>2</sub> were loaded with phospholipids by incubation with aqueous liposomal dispersions (small unilamellar vesicles, "SUVs") at several SiO<sub>2</sub>/phospholipid ratios for 5 min at 60 °C, followed by an extensive rinsing procedure with water to remove the unbound phospholipids.

The interaction kinetics of two model lipophilic drugs were studied: 1) triclobandazole (aqueous solubility approx. 1 µg/ml) and 2) cyclosporine A (aqueous solubility about 15 µg/ml) with the phospholipid loaded carriers. The SUVs were first loaded with one or both drugs and the resulting liposomal dispersions were subsequently mixed with the carriers loaded with phospholipids (at phospholipid concentrations which were the same for the liposomes as well as phospholipid on the carriers). This was followed by the separation of SUVs from the carriers by filtration at predetermined time intervals and analysis of the drug content in the filtrate (containing the SUVs) by HPLC.

The SUVs also contained the non-exchangeable Rhodamine-Lipid marker (Rh-PE). By assessment of the Rh-PE concentration in the filtrate, the interaction kinetics of the drugs can be corrected for the occurrence of aspecific adsorption onto the carrier surface.

## Results & Discussion

In the following figures, the assay characteristics of the measurement of the interaction kinetics of liposomally solubilised highly lipophilic drugs with the Porous Nano Matrix carriers are depicted. The ratio of drug to marker was used to correct for assay-related fluctuations.

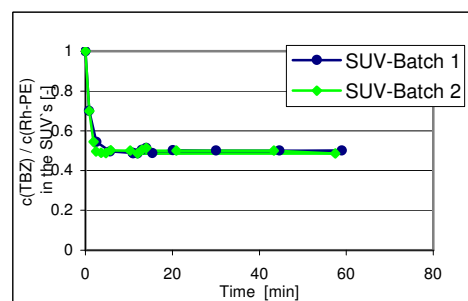


Figure 1 Reproducibility of Triclobandazole Transfer Experiments

The reproducibility of the assay is depicted in Fig. 1. Two different batches of liposomal triclobandazole were used to measure the exchange kinetics of triclobandazole at room temperature between the liposomes and the phospholipid layer on the carriers. The calculated half-life of exchange in both cases was 0.73 min. During the duration of the assay the Rh-PE concentration in the filtered liposomal dispersions did not decrease, suggesting that there was no aspecific adsorbance of the liposomal phospholipids on the carrier surface (detailed results not shown). Since the triclobandazole level reached equilibrium at 50 % of the original value and equal concentrations of lipids in the liposomes and on the carriers were used, it can be assumed that the triclobandazole was able to exchange freely between the two phospholipid pools. The temperature dependency of triclobandazole exchange is depicted in Fig. 2; the half-lives were 3.5 min at 0 °C and 0.73 min at 23 °C, respectively. However, as can be seen in Fig. 3, when the assay was performed with cyclosporine A, neither an equilibrium at 50 % nor a temperature dependence (as there was with triclobandazole) could be observed. However, a lower equilibrium level of 20 % was observed. This suggests strongly that cyclosporine A is not able to exchange freely between the two lipid pools but is also reversibly adsorbed on the surface of the Porous Nano Matrix carriers. In contrast with the interaction of triclobandazole with the carriers, there was hardly a temperature dependency of the interaction of cyclosporine A with the carriers.

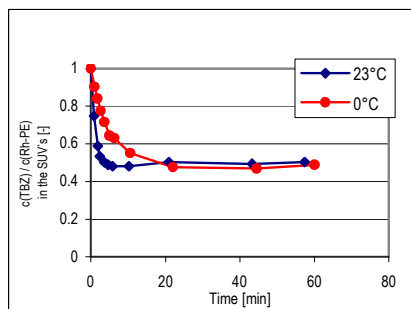


Figure 2 Temperature dependency of triclobandazole transfer

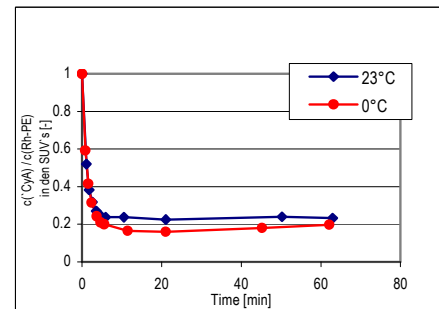


Figure 3 Temperature dependency of cyclosporine A transfer

## Conclusions

- The exchange kinetics between liposomally solubilised poorly water soluble drugs and Porous Nano Matrix carriers loaded with phospholipids could be reproducibly measured at various temperatures
- The assay shows that poorly water soluble drugs have drug specific interactions with the carriers
- The assay permits the development / optimization of Porous Nano Matrix technology-based formulations with respect to e.g. the type of carrier (chemical composition/porosity), drug load, drug crystallinity, presence of wetting agents, and drug to excipient ratio required to obtain optimal formulation characteristics

