A PERMITTIVITY-GUIDED APPROACH TO DRUG SOLUBILITY SCREENING FOR LIPID-BASED FORMULATIONS

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INTRODUCTION

One of the fundamental aims in formulating lipid based drug delivery systems (LBDDS) is to find suitable candidate formulations with high stability and drug load that can be for example filled into capsules. Therefore, an extensive screening for mixing and solubilization behavior is required. Interesting is an empirical relationship between the solubility parameters and the experimental relative permittivity [1;2] so the usage of permittivity values may provide formulation guidance. Especially at an early stage of the development, when drug quantities and resources are limited, a fast ranking of excipients and mixtures would be much desirable. A substantial advantage would be the easy and fast determination of the relative permittivity, which includes measurement of complex mixtures of oils, solvents and cosolvents. For an efficient drug solubility screening, we propose to combine evaluation of pharmaceutical additives with solvents that are rather used for a technical or analytical purpose. There are several theoretical models to estimate drug solubility in a solvent [3-6]. Based on the empirical relationship between the solubility parameter and experimental relative permittivity, we introduce the idea to predict a permittivity range of optimal drug solubilization (PROS) in pharmaceutics. The aim of this study is to present such permittivity-guided drug solubility screening, which should provide guidance to formulate a model drug (fenofibrate) as a LBDDS.

EXPERIMENTAL METHODS

Permittivity measurements

For the permittivity measurements (quintuplicates at RT) we employed the dielectric constant meter BI-870 from Brookhaven Instruments Corp. (NY,USA).

Permittivity Range of Optimal Solubility (PROS)

Paruta and coworkers [1] correlated the relative permittivity with the solubility parameter and obtained a linear relationship for 25 solvents at 25 °C (Equation 1: $\delta = 0.45\epsilon + 15.3$) [1;2] where δ is the solubility parameter and ϵ stands for the relative permittivity. The present work uses the inverse function based on in *silico* predicted solubility parameters. We calculated the total solubility parameter for the model drug fenofibrate by means of classical group contribution methods (Hansen: 18.97 $MPa^{1/2}$; van Krevelen and Hoftyzer: 22.67 $MPa^{1/2;}$ and Hoy's approach: 20.47 $MPa^{1/2}$) using the software Molecular Modeling Pro® V.6.2.6 (Norgwyn Montgomery Software, North Wales, USA) and Equation 1 to obtain the Permittivity Range of Optimal Solubilization (PROS).

API concentration determination

Fenofibrate concentrations were measured in triplicates at RT by a HPLC 1200 series instrument from Agilent Technologies (Santa Clara, USA) using an UV detector at 286nm, 1ml/min flowrate and 2 µL injection volume. As mobile phase, the Pharm Eur. medium for fenofibrate was used (30% (v/v) deionized water pH adjusted to 2.5 with phosphoric acid (85%) and 70% (v/v) acetonitrile).

Sample preparation

Monoacyl PC (S LPC 80) was added to the premixed liquid components and stirred at 500 rpm (magnetic stirrer) at 40°C until everything was dissolved. For the HPLC analysis of solubility, saturated solutions with excess of fenofibrate were prepared. These solution were stirred for 24 hours, filtered and diluted prior to analysis.

RESULTS

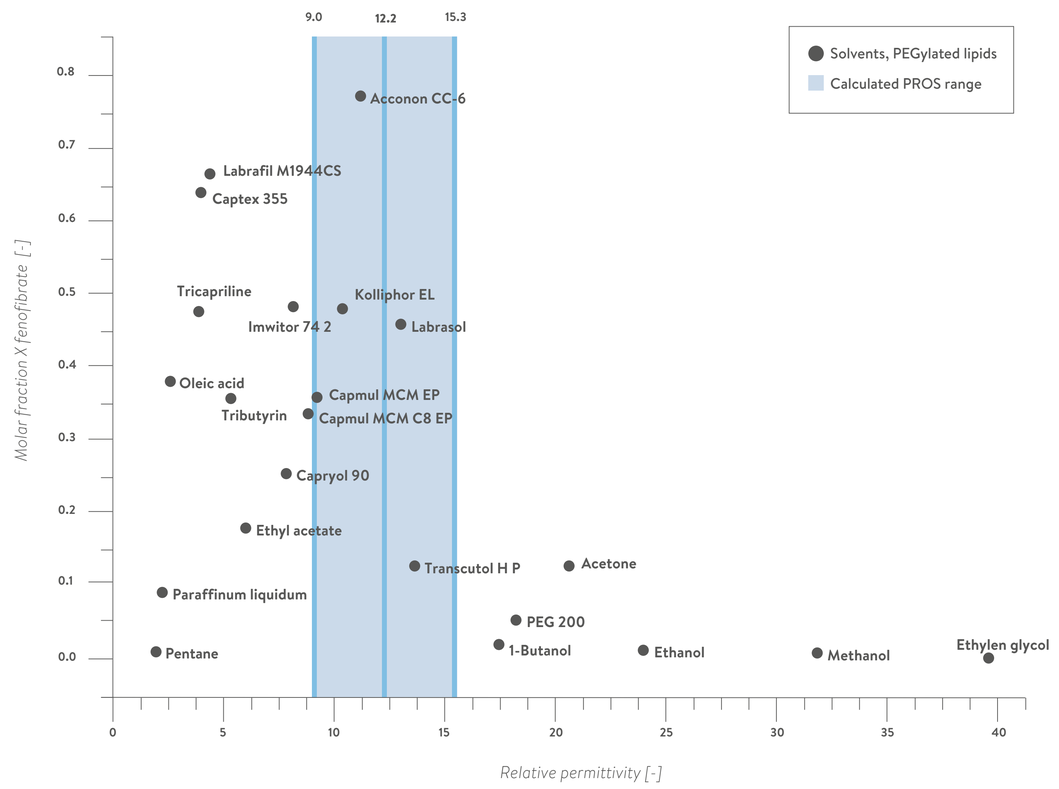
For each of the 22 excipients and solvents (lipids, PEGylated lipids, surfactants, co-surfactants), we measured the relative permittivity and the saturation solubility of the model compound fenofibrate. **Figure 1** shows the solubilized molar fraction of fenofibrate in dependence of the relative permittivity. The results suggest an optimum range of the relative permittivity regarding the solubility of fenofibrate (of about 9 – 15 [-]).

Moreover, the calculated PROS regimen for fenofibrate by using the mean value of the three calculated total solubility parameter and Equation 1 (see **Figure 1**, green shaded area, 12.2 ± 3.16 [-]) is in agreement with our measured saturation solubility results. Since the optimal LBDDS should have a dielectric constant analogous to the solute being dissolved. Formulators can use the PROS approach as guidance for selecting individual formulation ingredients to obtain high drug loadings.

A new step is about analysis of lipid-based mixtures for which solubility predictions are particularly challenging so that a PROS approach may provide a substantial advancement.

A simple calculation of the relative permittivity for mixtures is further attempted by using the sum of the products between the individual volume fractions and relative permittivities (Onsager–Kirkwood equation). This theoretical approach is primarily valid when the mixture behaves like an ideal solution, so that the use of the Onsager–Kirkwood's equation is a simplified approach [7] but is promising from a formulators' perspective.

Figure 1 SLUBILIZED MOLAR FRACTION OF FENOFIBRATE VERSUS RELATIVE PERMITTIVITY PLOT



Solubilized molar fraction of fenofibrate versus relative permittivity plot.

CONCLUSIONS

The permittivity-guided approach is a tool for drug solubility screening in solvents and lipid-based excipients. Together with information about excipient mixing behavior, an optimum range for the relative permittivity is targeted to achieve maximum dzrug solubilization in lipid-based delivery systems that are typically filled in capsules.

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