Predicting API Solubility in Lipid Excipients: A Combined PC-SAFT and Experimental Approach for Enhanced Oral Delivery

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INTRODUCTION

Oral bioavailability of active pharmaceutical ingredients (APIs) is largely driven by solubility and permeability, with **inadequate solubility now representing a major hurdle in early formulation**.

Lipid-based excipients offer a promising route to enhance dissolution and oral absorption, but **experimental solubility screening remains labor-intensive and costly** when evaluating numerous API-excipient combinations.

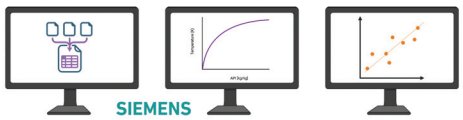
This growing challenge highlights **the need for predictive, mechanism-based tools to support rational excipient selection**. While traditional parameters such as log P, HLB, or CMC provide general guidance, they do not capture the complexity of multi-component lipid systems. Emerging predictive approaches – from empirical methods to thermodynamic models and AI-driven algorithms – therefore play an increasingly valuable role in accelerating formulation design.

The aim of this study was to **investigate the predictive ability of the PC-SAFT thermodynamic model**, implemented in the Siemens gPROMS FormulatedProducts platform, to estimate drug solubility in lipid excipients. The relevance of this approach has been previously highlighted by Brinkmann et al.[1], who applied PC-SAFT to predict the solubility of ten model APIs in lipid excipients as part of an in-silico screening strategy for lipid-based drug delivery systems.

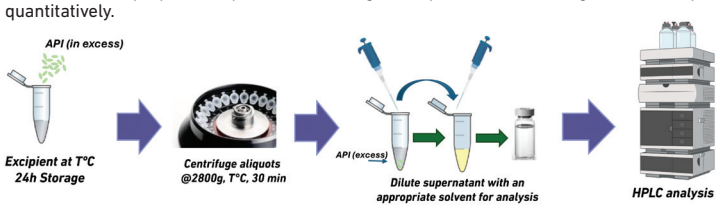
PC-SAFT (Perturbed-Chain Statistical Associating Fluid Theory) is a molecular-based thermodynamic equation of state that models fluids by explicitly accounting for molecular size, shape, dispersion, and specific interactions such as hydrogen bonding. It enables the prediction of phase equilibria and solubility - such as active compounds in lipids - by describing intermolecular interactions through physical parameters[2].

MATERIALS & METHODS

The gPROMS FormulatedProducts suite from Siemens (gProperties module) was used to simulate solubility behavior of four APIs (fenofibrate, cinnarizine, ibuprofen, indomethacin) in four excipients from Gattefossé: Transcutol® (*diethylene glycol monoethyl ether*), Capryol® 90 (*propylene glycol monocaprylate*), Labrafac™ MC60 (*glycerol monocaprylocaprate*), Lauroglycol® FCC (*propylene glycol monolaurate*).
For fenofibrate and cinnarizine, predictions were performed at three temperatures: 10, 25, and 37 °C. Predicted solubilities were then compared to experimental determinations. Statistical analysis was performed with Minitab 2024.



Experimental solubility tests were performed in selected lipid excipients by high-performance liquid chromatography coupled with UV detection (HPLC–UV). Saturated solutions were prepared, equilibrated at target temperatures, centrifuged, and analyzed quantitatively.



RESULTS

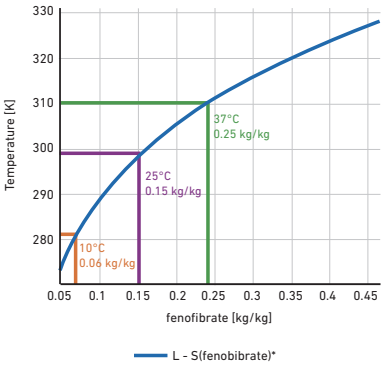


Figure 1. Phase diagram of fenofibrate in Capryol® 90 showing temperature as a function of fenobibrate mass fraction.

From the PC-SAFT phase diagrams generated in gPROMS (fenofibrate in Capryol® 90 as an example in Figure 1), the mass fraction of the drug at equilibrium (kg/kg) was extracted and converted to mg/mL for each API & excipient, yielding the predicted solubility values for the four active compounds in four lipidic excipients at three temperatures.

PC-SAFT-based predictions indicated that **solubility increased with temperature across all excipients tested**, which is also measured by experimental HPLC–UV measurements.

Statistical analysis demonstrated **a very good correlation between PC-SAFT predictions and experimental solubility data** for the whole set of data points, with a correlation coefficient r = 0.974 and $p < 0.05$ (Figure 2).

Nevertheless, certain limitations remain. Accurate PC-SAFT predictions require reliable pure-component parameters and binary interaction data, which may be **unavailable in literature or complicated to generate for complex lipidic excipients**. The model's applicability to multi-component excipient blends remains to be fully validated.

Despite these challenges, the findings highlight the robustness of the approach for binary systems and encourage further extension towards more complex formulations.

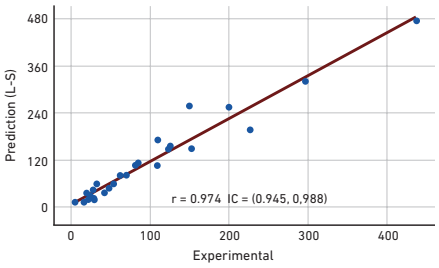


Figure 2. Regression analysis of predicted vs. experimental solubility data (Pearson correlation).

CONCLUSION

In summary, the PC-SAFT thermodynamic model provides **a predictive framework for screening drug solubility in lipid excipients**. The correlation observed between in silico predictions and in vitro measurements for fenofibrate demonstrates its utility as a reliable screening tool.

While its application requires careful parameterization and is sometimes limited by data availability, PC-SAFT significantly reduces experimental workload, API amount used and accelerates rational excipient selection in early drug development.

These results support the integration of advanced thermodynamic modelling into formulation workflows, enabling more efficient development of lipid-based drug delivery systems for poorly soluble APIs.

REFERENCES

[1] Brinkmann J, Exner L, Luebbert C, Sadowski G. In-Silico Screening of Lipid-Based Drug Delivery Systems. Pharm Res. 2020;37(12):249. doi: 10.1007/s11095-020-02955-0. PMID: 33230602; PMCID: PMC7683453.
[2] Kamil Paduszyński and Urszula Domańska. Thermodynamic Modeling of Ionic Liquid Systems: Development and Detailed Overview of Novel Methodology Based on the PC-SAFT. The Journal of Physical Chemistry B 2012 116 (16), 5002-5018. doi: 10.1021/jp3009207