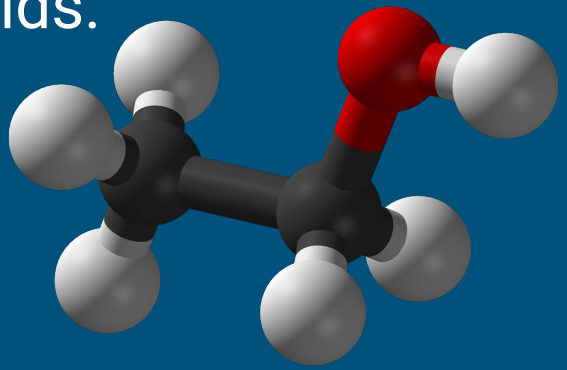
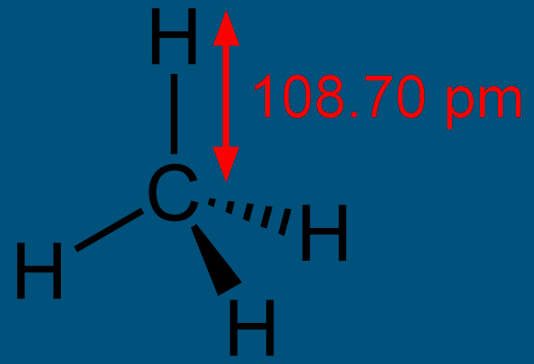
# Solubility Calculation of Active Pharmaceutical Ingredients in Alkanes, Alcohols, Water and their Mixtures Using Various Activity Coefficient Models

# Introduction

The calculation of solubility of pharmaceutical ingredients in organic groups as Alkanes, Alcohols, Water, and other mixtures has been studied by the Schroeder-van Laar equation. This equation try to explain the phase equilibrium in liquid and solids.





# Active Pharmaceutical Ingredients (API)

Substances that cause specific reactions in organisms

API’s are composed by many functional groups

Depending on the conditions and environment the API’s their composition like shape, density, state, etc.

The extraction of API’s of natural products need specific methods

For most of the API’s application, we need them in their pure form, especially when we are producing medicine.

# Active Pharmaceutical Ingredients (API)

Turnover, yield, selectivity, and thus the cost of the respective process steps are strongly influenced by the API solubility in the solvent. That means the knowledge of the API solubility is important.

BECAUSE OF COSTS ISSUES, IT'S VERY IMPORTANT TO DETERMINE THEIR SOLUBILITY IN EACH SOLVENT EXPERIMENTALLY

# Solubility Calculation

We start with star with our principle of phase equilibrium fugacity as:

$$x_i^L y_i^L (f_i)^L = x_i^S y_i^S (f_i)^S$$

And then (for this case), we assume that the solid coefficient of mole fraction and is 1 because the most liquid-phase equilibrium belong to simple eutectic where the pure solid crystallizes. This equation only depends on the melting point of the components, so we obtain:

$$x_i^L = \frac{1}{\gamma_i^L} \frac{(f_i^\circ)^s}{(f_i^\circ)^L}$$

# Schroeder-van Laar equation

An expression for the ratio of standard fugacities can be derived from a thermodynamic cycle.

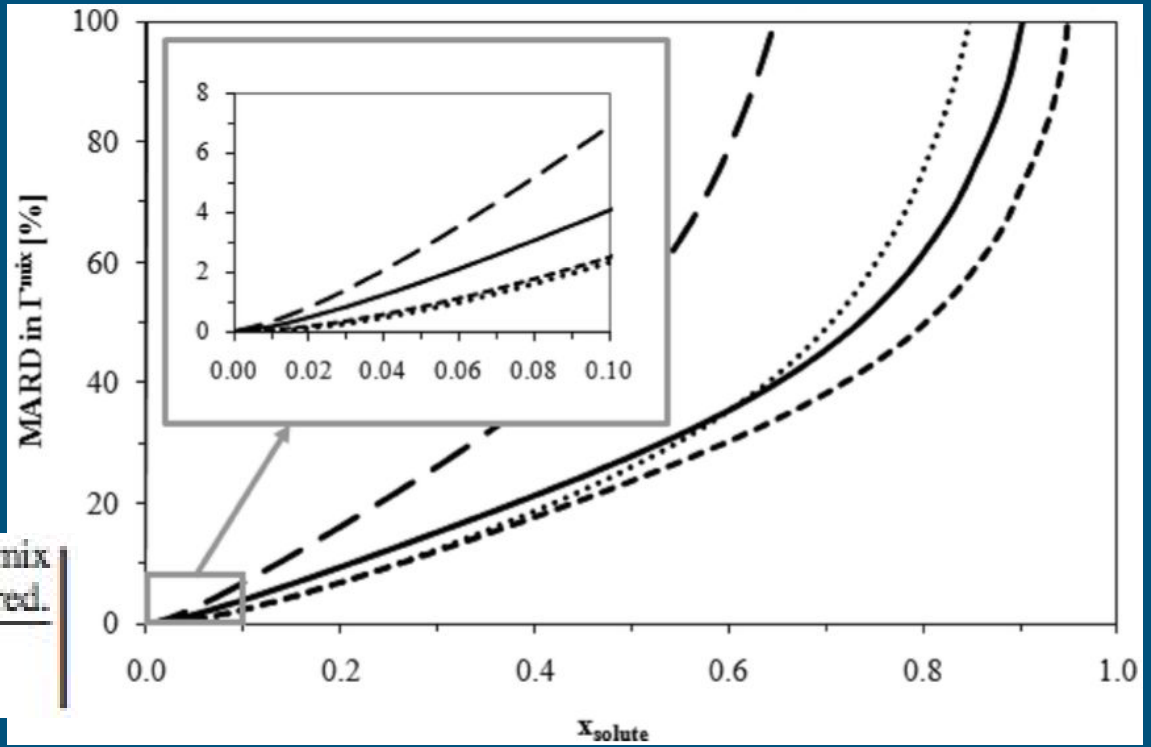
We could express the equation with the following way:

$$x_i^L = \frac{1}{\gamma_i^L} \exp\left[-\frac{\Delta h_{m,i}}{RT}\left(1 - \frac{T}{T_{m,i}}\right)\right]$$

# Pharma Mod. UNIFAC

- Just applied to a maximum to API X= 0.1
- Interaction parameters defined by structural groups of the solvent.

$$\mathrm{MARD}[\%] = \frac{1}{N}\sum_{i=1}^{N}\left|\frac{\Gamma^{\mathrm{mix}}_{\mathrm{full}} - \Gamma^{\mathrm{mix}}_{\mathrm{red.}}}{\Gamma^{\mathrm{mix}}_{\mathrm{full}}}\right|$$



# Comparison of Activity Coefficient Models around Room Temperature.

- Solubility calculation in three solvent classes (alkanes, alcohols and water)
- Using seven activity coefficient models: ideal, Hansen, UNIFAC, Mod UNIFAC (Do), COSMO-RS(Ol), NRTL-SAC and Pharma Mod. UNIFAC.
- API considered as any substance that is part of a Drug Bank or belong to a pharmaceutical list published by DDBST GmbH.
- Substance had to be solid at room temperature, to be no salt and no hydrate and to contain at least one carbon atom.

# Ranking of the models

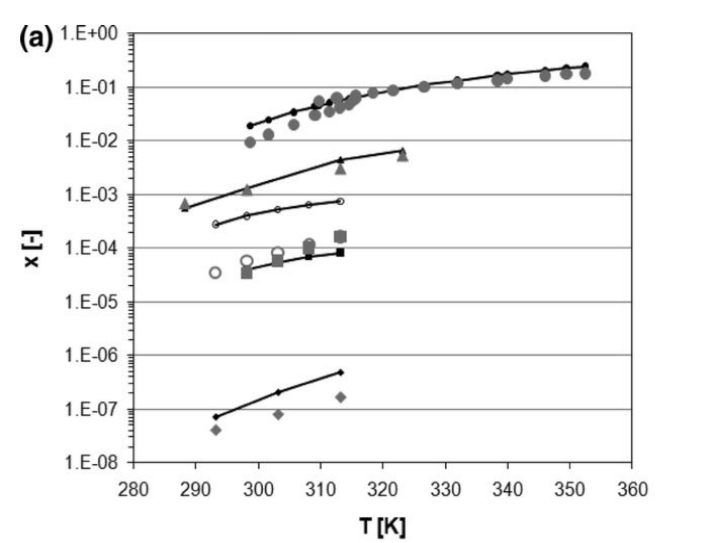
1. NRTL-SAC Uses information of experimental solubility data of the considered API
2. Pharma Mod. UNIFAC → prove that the concept of parameter reduction is valid in the concentration range applied.
3. COSMO-RS(Ol) → The lower the experimental composition is, the higher the deviation between the calculated and experimental composition becomes.
4. Ideal → The assumption of an ideal mixture provide the worst results

# Temperature Dependency of Pharma Mod. UNIFAC for Binary Systems.

- Experimental solubility data only at room temperature are available for most substances.

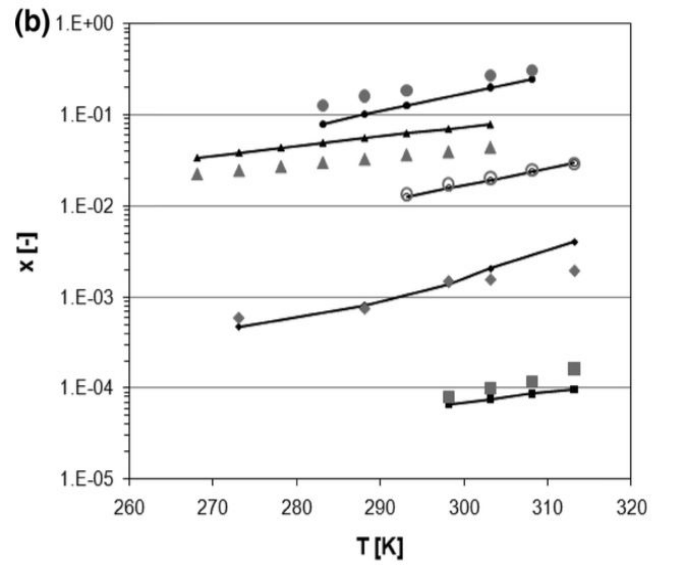
- To demonstrate the capability of the new model Pharma Mod. UNIFAC in capturing temperature dependence of the solubility, the solubilities of some APIs in different solvents were calculated.

# Solubilities in different solvents.



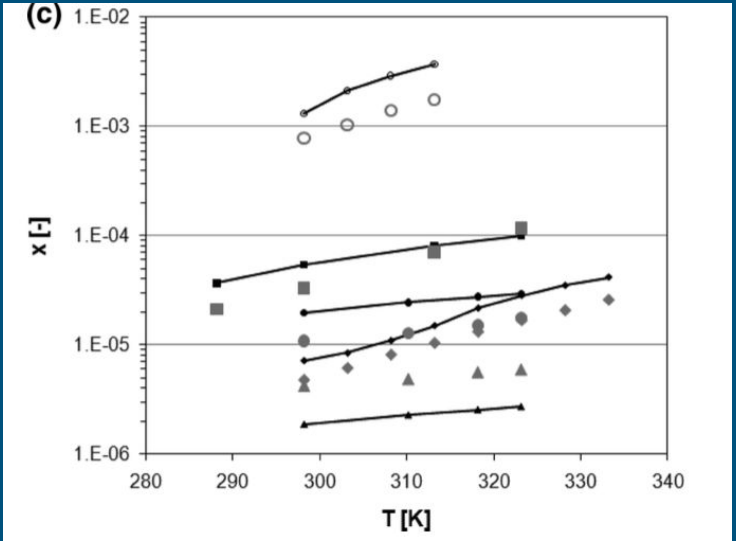

- Solubilities of various APIs in cyclohexane (gray symbols are experimental data; black scatter lines are calculation results using Pharma Mod. UNIFAC)

# Solubilities in alcohols.




- Solubility of various APIs in different alcohols (gray symbols are experimental data, black lines are calculations).

# Solubility of APIs




- Solubility of various APIs in water as solvent (gray symbols are experimental data; black scatter lines are calculations).

# Conclusions

- The number of calculable solubility data depends on the activity coefficient model because of the required model-specific parameters.
- The correlative model NRTL-SAC provides the best results of all activity coefficient models because this model already uses information of experimental solubility data of the considered API.
- Solubility temperature dependency and the solubility in solvent mixtures can be qualitatively captured with Pharma Mod. UNIFAC model.