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# *In silico* prediction of liquid-liquid phase separation concentration using abraham solute descriptors

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## Introduction

Recently, the liquid-liquid phase separation concentration ($S_{LLPS}$) of a drug has attracted a lot of attention in drug development. $S_{LLPS}$ is the maximum drug concentration that drug dissolved in water. Therefore, the $S_{LLPS}$ is important for estimating the dissolution behavior of supersaturable active pharmaceutical ingredients. However, few studies have focused on *in silico* $S_{LLPS}$ prediction. In this study, an *in silico* $S_{LLPS}$ prediction model was established using the Abraham solute descriptors.

## Methods

From our previous research, the crystalline solubility ($S_c$) LLPS concentration ($S_{LLPS}$) melting point ($T_m$) equation (CLME) was derived based on thermodynamic principles.

$$\log S_{LLPS} = \log S_c + 0.0099 (T_m - 298) \text{ for } 25\ ^\circ\text{C} \quad (1)$$

The $S_{LLPS}$ of 293 drug compounds was calculated using $S_c$ and $T_m$ (Eq. 1). The calculated Abraham solute descriptors were collected from the literature. The 293 drug compounds were divided into a training (205) and a test set (88). The coefficients of Abraham solute descriptors were determined by multiple regression analysis using the training set.

## Results

Eq. 2 was obtained using the 205 model drugs.

$$\log S_{LLPS} = 0.316 A + 2.121 B + 0.298 S_\pi - 1.095 E - 1.716 V - 0.181 \quad (2)$$

where $A$ is the overall or summation hydrogen-bond acidity, $B$ is the overall or summation hydrogen-bond basicity, $S_\pi$ is dipolarity/polarizability, $E$ is the excess molar refraction, and $V$ is the McGowan characteristic volume.

The $S_{LLPS}$ of 88 compounds was predicted using Eq. 2. The root mean square error (RMSE) and coefficient of determination ($r^2$) were 0.96 and 0.65, respectively.

## Discussion

The Abraham solute descriptors would be an essential parameter for estimating the $S_{LLPS}$ of a drug compound. The present model could be applicable to drug development.