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A new definition of solubilization power of a cosolvent

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The solubilization power of a cosolvent is defined based on the maximum solubility of a solute in the water-cosolvent mixtures ($X_{m,max}$) and the corresponding solvent composition ($f_{c,max}$) predicted by trained versions of the Jouyban-Acree model. The applicability of the proposed definition was checked using solubility data of three cosolvent systems where the solubilization power was ordered as: dioxane > ethanol > polyethylene glycol 400. Using this definition, one could select the most appropriate cosolvent for solubilization of a poorly water soluble drug. There are linear relationships between the solubilization power of a cosolvent and the solute's logarithm of partition coefficients.

Solubilization of a poorly water soluble drug by adding a water-miscible cosolvent is the most common method in pharmaceutical industry to enhance solubility. The main questions in designing the solvent system in the formulation process of the liquid formulation of poorly water soluble drugs are: 1) what is the best cosolvent to solubilize the desired amount of the drug? 2) Which solvent composition is the optimized cosolvent concentration to solubilize the drug? These questions are usually answered in practice by the trial/error method which requires considerable amounts of the drug and also relatively long time to get the best answers. In addition to these disadvantages, there are other restrictions such as the possible toxicity of the cosolvents (Rubino 1990) and also the cost effect of the final formulation, e.g. the more cosolvent concentration the more expensive is the formulation. Therefore it is demanded to design a liquid formulation system with the lowest cosolvent concentration providing the lowest possible toxicity and the minimum cost. Considering these points and as an alternative solution, it is possible to employ the cosolvency models to design the formulations. The aim of this communication is to provide a solubilization power scale to be used in pharmaceutical industry to speed up the design of liquid drug formulations and also dissolving media for early stage investigations of new drug discovery studies.

The most pioneering cosolvency model is the log-linear model of Yalkowsky which is expressed by:

$$\log X_m = f_c \log X_c + f_w \log X_w \quad (1)$$

where X_m is the solute's solubility in water-cosolvent mixtures, f_c and f_w the volume fractions of cosolvent and water in the absence of the solute, X_c and X_w the solubilities in neat cosolvent and water, respectively (Yalkowsy and Roseman 1981). Equation (1) could be re-written as:

$$\log X_m = \log X_w + \sigma f_c \quad (2)$$

Where σ is the cosolvency or solubilization power of a cosolvent (Li and Yalkowsky 1998) and is equal to $\log\left(\frac{X_c}{X_w}\right)$. Although the σ term provided an overall information on the solubilization of a cosolvent, the values could not be reasonably matched with the observed solubility behaviours in practice. As an example, the solubility profile of a number of drugs in water-cosolvents are not linear (see Fig. 1) and cannot be accurately represented by Eq. (1).

The Jouyban-Acree model possesses additional parameters representing the solute-solvent interactions (Acree 1992) and was used to calculate the solubility of drugs in mixed solvent systems with linear or non-linear solubility profile at a fixed and/or various temperatures (Jouyban 2006a, 2007a, 2007b, Jouyban and Acree 2006). Its basic form to calculate a solute solubility in water-cosolvent mixture is:

$$\log X_m = f_c \ln X_c + f_w \ln X_w + f_c f_w \sum_{i=0}^{2} \left(\frac{A_i (f_c - f_w)^i}{T} \right) \quad (3)$$

Where T is the absolute temperature of the solution and A_i are the model constants. The numerical values of A_i terms could be calculated employing experimental solubility data in water-cosolvent mixtures using a no intercept least square analysis (Jouyban-Gharamaleki and Hanaee 1997) for a given drug. In order to make it a practical cosolvency model, the A_i terms were computed for a number of cosolvents (Jouyban 2006b, 2007a, 2007b, Jouyban and Acree 2006) and it is possible to predict the solubility of a drug in water-cosolvent mixtures using experimental

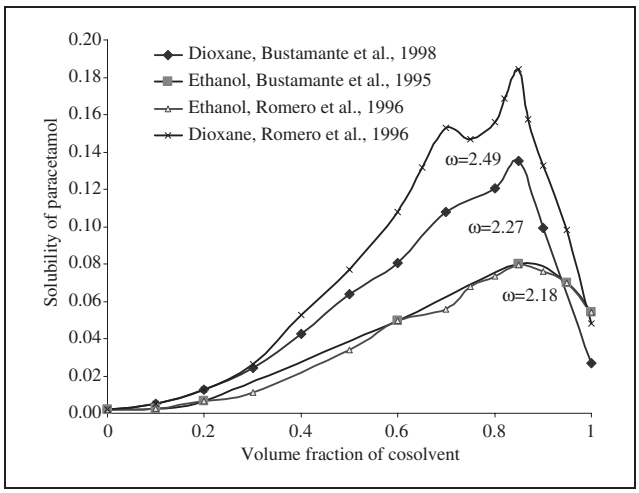

Fig. 1: Experimental solubility of paracetamol in water-ethanol and water-dioxane mixtures

values of X_c and X_w. The model was successfully predicted the maximum solubility ($X_{m,max}$) of a drug in aqueous mixtures of dioxane, ethanol and PEG 400 and the solvent composition ($f_{c,max}$) providing the $X_{m,max}$. Based on these findings, an experssion can be suggested to quantitavely determine the solubilization power of a cosolvent (ω) considering the toxicity and cost consideration of the cosolvent as:

$$\omega = \frac{\log\left(\frac{X_{m,max}}{X_w}\right)}{f_{c,max}} \quad (4)$$

The numerical values of $X_{m,max}$ and $f_{c,max}$ could be predicted using a method proposed in a previous work (Jouyban, 2007b) employing the trained versions of the Jouyban-Acree model and experimental values of X_c and X_w. The $\log\left(\frac{X_{m,max}}{X_w}\right)$ term is a similar term to the solubilization power of Yalkowsky (σ) and the difference is that the X_c was replaced with $X_{m,max}$. The $\log\left(\frac{X_{m,max}}{X_w}\right)$ term was divided by $f_{c,max}$ to normalize it based on the solvent composition of the binary solvent at the maximum solubility of the solute, the lower $f_{c,max}$ values (varying between 0–1) mean the more favored solubilization medium which is reflected in ω figures. The ω term increases with an increase in the solubility ratio of the solute at $f_{c,max}$ and $f_c = 0$ and decreases with an increase in $f_{c,max}$ value. Therefore, for a given solute, more ω terms means more solubilization power and less cosolvent concentration is required to dissolve a desired amount of the drug. As shown in Fig. 1, dioxane provided more enhancement in the solubility of paracetamol considering a given f_c value. The calculated ω values for two various experimental X_c and X_w sets were 2.27 and 2.49. The corresponding ω values for the ethanol data sets were 2.18 and 2.18. What we can justify is that the ω value of dioxane is higher than that of ethanol, and therefore, it should provide better solubilization properties using a given f_c value. The numerical values of the ω term is also linearly related to the log P of the solutes as; the corresponding relationships respectively for dioxane, ethanol and PEG 400 were:

$$\omega = 2.366 + 0.672 \log P \quad (5)$$

$$\omega = 1.781 + 0.481 \log P \quad (6)$$

$$\omega = 1.514 + 0.416 \log P. \quad (7)$$

Full details of the data sets investigated in this communication (total number of data sets is 173) including the references of the orignial solubility data in water-cosolvents, the numerical values of temperature (T (°C)), logarithm of aqueous solubility (log X_w) and the predicted logarithm of the maximum solubility in water-cosolvent mixtures (log $X_{m,max}$) and the corresponding fraction of the cosolvent ($f_{c,max}$) could be found in a previous work (Jouyban 2007b). The numerical values of the solubilization powers of this work (ω) and the Yalkowsky's definition (σ) were computed in this work using Eq. (4) and $\log\left(\frac{X_c}{X_w}\right)$, respectively. The numerical value of ω is a function of the solutes and cosolvent structures, however, it is independent from temperature and also the solubility expression units, i.e. mole/L, mole fraction, g/L etc. Any error in determining X_c and X_w values can be resulted in mis-calculated $X_{m,max}$ and $f_{c,max}$ and consequently ω values (as shown as an example in Fig. 1). As a general rule, among three cosolvents investigated in this work, dioxane is the most potent cosolvent, followed by ethanol and PEG 400. Unfortunately, dioxane is a toxic cosolvent and is not allowed to be used in pharmaceutical formulations, however, it is used as a model consolvent in many cosolvency studies.

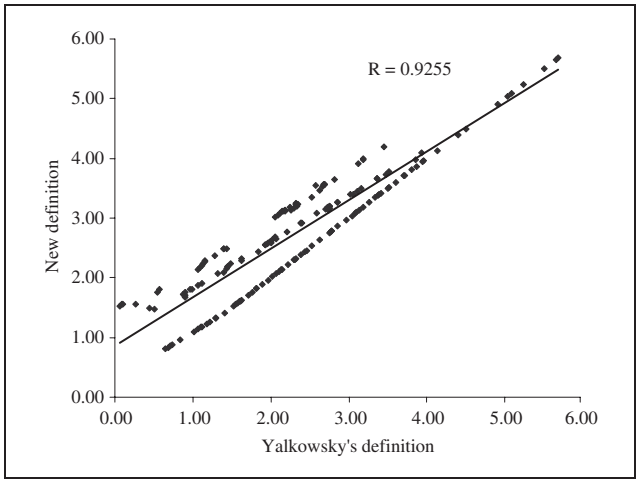

Fig. 2: The relationship between solubilization powers (ω and σ) for data sets investigated in this work

Figure 2 shows the relationship between ω and σ values. There is good correlation between ω and σ and as it is evident from the figure, there is a straight line for a number of $\omega-\sigma$ values, which belong mostly to PEG 400 and a number of ethanol data sets. When the solubility profile of a drug in aqueous-cosolvent mixtures is not linear, the σ values deviates from ω values and for these cases, the new definition is more accurate.

In conclusion, using the trained versions of the Jouyban-Acree model and employing experimental solubilities in water and cosolvent, it is possible to reproduce the solubility profile of a drug in water-cosolvent mixture and predict the $X_{m,max}$, $f_{c,max}$ and ω values. Based on the ω values for different cosolvents of interest, the formulator is able to select the most suitable cosolvent for practical applications. We have provided four trained versions of the Jouyban-Acree model and are working on the rest of pharmaceutical cosolvents to provide an accurate and easy to use predictive model to be used in pharmaceutical industry.

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In vitro and *in vivo* investigations on the binary meloxicam-mannitol system

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The objective of the study in rats was to investigate the anti-inflammatory effects of pure meloxicam (ME) with different particle sizes and of physical mixtures of the binary ME-mannitol system. The level of local inflammation was significantly decreased when the amount of mannitol was the highest and the particle size of ME was the lowest as well as the components had the interparticulate interaction. The same results were achieved in *in vitro* experiments.

Various methods are used to increase the rate of dissolution of water-insoluble drug materials (Leuner and Dressman 2000), e.g. the use of a carrier (solid dispersion), complexation (the use of cyclodextrins) or salt formation (Han and Choi 2007). In some cases, preparation of a simple physical mixture (PM) with a water-soluble carrier can improve the dissolution of the drug material. Through the establishment of an ideal ratio for the binary system and an appropriate particle size for a drug material, use of a physical mixture can be as effective as any other method, involving, for example, an eutectic mixture or complexation.

Meloxicam (ME), a nonsteroidal anti-inflammatory drug (NSAID), which selectively inhibits COX2 rather than COX1 (Altnöz et al. 2002), belongs to class II of the Biopharmaceutical Classification System (BCS) with low aqueous solubility and high permeability (Lipka and Amidon 1999).

ME1 with a bigger particle size and ME400 which was made by the milling of ME1 with a ball mill (PM200 Retsch GmbH & Co. KG. Germany) were used. Beta-D-mannitol was used as a carrier (Reisi Nassab et al. 2006) which is a highly water-soluble sugar alcohol with low hygroscopicity, suitable even for diabetic patients (Zajc et al. 2005; Arias et al. 1995).

PMs of ME1 and ME400 with mannitol were prepared with a Turbula mixer. After mixing, an appropriate amount of mixture was placed in a gelatin capsule.

The results of *in vitro* experiments are shown in the Table.

After the successful *in vitro* experiments, the anti-inflammatory effects of the pure MEs and PMs were investigated on rats. This study was approved by the Committee on Animal Research, University of Szeged, Hungary (IV/4316-7/2002).