



Pharmaceuticals Solubility is Still Nowadays Widely Studied Everywhere

Fleming Martínez^{1*}, Abolghasem Jouyban^{2,3}, William E. Acree Jr.⁴

¹Grupo de Investigaciones Farmacéutico Físicoquímicas, Departamento de Farmacia, Facultad de Ciencias, Universidad Nacional de Colombia –Sede Bogotá, Cra. 30 No. 45-03, Bogotá D.C., Colombia.

²Pharmaceutical Analysis Research Center and Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

³Kimia Idea Pardaz Azarbayjan (KIPA) Science Based Company, Tabriz University of Medical Sciences, Tabriz, Iran.

⁴Department of Chemistry, University of North Texas, Denton, TX 76203-5070, USA.

Equilibrium solubility is a thermodynamic property of great importance in pharmaceutical area from both practical and theoretical viewpoints. It is involved in several pharmaceutical procedures like drug purification processes, drug identification, and homogenous pharmaceutical dosage forms design.¹ Although solubility is a macroscopic property it is employed to analyze the respective molecular interactions involved in dissolution processes.² Drug solubility defines the possible state of the pharmaceutical dosage form under consideration. This is of fundamental relevance if liquid solutions are solicited. Moreover, it is generally observed that the more soluble drugs also exhibit higher dissolution rates in the respective solvents.³ In this way, the experimental determination and correlation of the solubility of drugs in neat and mixed solvents has been a constantly increasing research subject. Normally, the specific references report the effect of temperature and/or mixtures composition on solubility. Temperature effect is commonly evaluated by using several empirical or semiempirical models like van't Hoff, Apelblat, Buchowski-Ksiazczak and Wilson. Mixtures composition effect is evaluated by means of Yalkowsky-Roseman log-linear and the Nearly Ideal Binary Solvent/Redlich-Kister (NIBS/R-K) models as cosolvency prediction tools. Furthermore, the combined effects of temperature and mixtures composition are analyzed by means of the Jouyban-Acree model.⁴ Observed deviations from predicted solubility values by some of these models have been attributed to specific interactions. For instance, negative deviations to Yalkowsky model in water-rich mixtures has been interpreted as the effect of hydrophobic hydration around the non-polar groups of the solute, which reduce the solubility, whereas, the positive deviations observed in cosolvent-rich mixtures has been considered as an effect of the solute solvation by the cosolvent to obtain a less polar entity.⁵ A number of attempts were made to include some

physico-chemical properties such as Abraham or Catalan parameters within the common cosolvency models for providing better predictions and extending the applicability of the models to include additional solute-solvent combinations.⁶ Moreover, from solubility values and some thermodynamic properties of the solvent mixture free of drug, the preferential solvation of several drugs has been analyzed by means of the inverse Kirkwood-Buff integrals (IKBI) method. If the solubility increases constantly with the proportion of cosolvent to reach the maximum in the neat cosolvent, the solute is preferentially solvated by water in water-rich mixtures but preferentially solvated by cosolvent in cosolvent-rich mixtures. On the other hand, when the maximum solubility is obtained in a cosolvent-water mixture instead of the neat cosolvent, the solute is preferentially solvated in water-rich and cosolvent-rich mixtures but preferentially solvated by cosolvent in those mixtures of similar proportions of water and cosolvent.⁷ Finally, it is noteworthy the increasing in the number of articles published in several journals around the world dealing with solubility and solution thermodynamics of drugs in neat and mixed solvents reveal that despite of various available solubility prediction methods reported in the literature, one needs to rely on the experimental determination of drug's solubility and further improvements in the solubility prediction methods is still required.⁸ Development of better predictive methods is greatly facilitated by accurate solubility measurements using modern instrumentation and technology.

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*Corresponding Author: Fleming Martínez, E-mail: fmartinezr@unal.edu.co

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