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Solubility and Thermodynamic Behavior of Naringenin in Water + Methanol Mixed Solvent Systems at Temperatures between 288.15 and 328.15K

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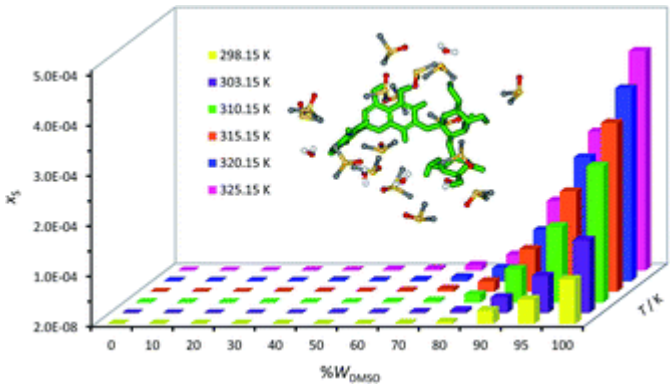
Naringin (C27H32O14) with the chemical name 4′,5,7-trihydroxyflavanone-7-rhamnoglucoside, a flavanone glycoside that is frequently found in many citrus fruits especially grapefruit and lemon, such that it is responsible for the fruit's bitter taste. It has been reported that naringin can show biological effects like antioxidant, anti-inflammatory, anti-cancer (breast cancer), anti-allergic, anti-diabetic, anti-angiogenesis and cholesterol-lowering activities. As a plant flavonoid, naringin, has attracted significant scientific and public interest in recent years due to its versatile health-promoting effects. However, due to very poor solubility of naringin in water at room temperature, its bioavailability is low and this hinders further studies on its pharmacological applications.

The experimental solubility measurement of bioactive compounds in the solution as a function of solvent composition and temperature is valuable particularly for the pharmaceutical and industrial product design, and also to obtain complete information about physicochemical characteristics of pharmaceutical dissolutions. Furthermore, the solubility data of solutes in different solvents are necessary for determining the appropriate solvents for extraction, separation, production, and purification of organic compounds there are various mathematical and empirical models to correlate and predict the solubility of drug compounds in different solvents and temperatures. These models can solve issues such as expensive cost and long time in the solubility determination process. Dependence of the solubility on the temperature allows thermodynamic analysis to give us information about the mechanisms involved in the dissolution process.

Solid-liquid phase equilibrium solubility of naringenin in (water + methanol) binary solvent mixtures was determined by using UV spectrophotometric method from 288.15 K to 328.15 K at atmospheric pressure. The solubility of naringenin increased with increasing temperature in all tested systems. The Apelblat equation, van't Hoff equation, Jouyban-Acree model and combined Jouyban-Acree models were employed to correlate the solubility data in binary solvent mixtures. The selected thermodynamic models all can give acceptable results. Furthermore, the standard Gibbs free energy, enthalpy and entropy for the dissolution of naringenin and excess enthalpy of solution HE, were calculated, which indicates that the dissolution process of naringenin is an endothermic and entropy favorable process for their trauma needs and many without any referral to address.

This study describes the thermodynamics of dissolution of flavonoid naringin in different aqueous solutions of dimethyl sulfoxide (DMSO) containing 0–100% (w/w) under atmospheric pressure and over a temperature range of 298.15 to 325.15 K. The temperature dependence of solubility of naringin was analyzed using the modified Apelblat equation model, ideal model, and the λH equation model. In a mean harmonic temperature, the dissolution thermodynamic parameters of naringin containing, and were also calculated. Furthermore, the effects of solvent composition on the solubility of this flavonoid were analyzed in terms of Hildebrand's solubility parameter (δH) and Kamlet, Abboud and Taft (KAT) solvatochromic parameters (α, β, and π*). Finally, the preferential solvation parameters of the flavonoid naringin by DMSO (δxDMSO,S) were determined from experimental solubility data using the inverse Kirkwood–Buff integrals (IKBIs). It was found that water preferentially solvates naringin in water-rich mixtures while DMSO forms local solvation shells in compositions from 50% (w/w) or xDMSO = 0.19 up to pure co-solvent. Moreover, the structure of solvation shells of naringin in the under study mixtures was obtained by molecular dynamics (MD) simulations. The computational results showed that in the compositions xDMSO > 0.20, the probability of presence of the DMSO molecules in vicinity of naringin is more than water molecules. These findings are compatible with the available IKBI data.



In addition to solubility, preferential solvation phenomenon in which the solute is surrounded preferably by the component of the solvent mixture has not been studied in many pharmaceutical compounds so far. The phenomenon can help in understanding the molecular interactions involved in the dissolution process. Therefore, the present study first focuses on measuring the equilibrium solubility of antioxidant flavonoid naringin in aqueous co-solvent systems of DMSO (0–100% by w/w) and different temperatures (298.15 to 325.15 K) using an isothermal

dissolution equilibrium method. It is noteworthy that the co-solvent DMSO is an important polar aprotic solvent with very low toxic and immense biological importance. It dissolves both polar and nonpolar compounds and is miscible in a wide range of organic solvents as well as water. In the following step, the effect of temperature on the solubility of naringin in the binary aqueous mixtures is analyzed to evaluate the thermodynamic quantities involved in the process of solubility. It is important to emphasize that the temperature range used in this work covers different room conditions as well as the normal human body temperature. We also determined the influence of co-solvent composition on the solubility of naringin by means of KAT equations. Finally, the inverse Kirkwood–Buff integrals (IKBI) approach is applied to evaluate the preferential solvation of naringin in the binary mixtures examined. On the other hand, the molecular dynamics (MD) simulations which are based on a range of complementary computational approaches provide a very powerful tool for investigating the solvation phenomenon, especially preferential solvation, directly using computed radial distribution function (RDF). We also characterized the structure of the solvation shell of the naringin molecule (preferential solvation) in the aqueous DMSO mixtures by calculating the RDFs. The results of preferential solvation are then compared with the data obtained from the inverse Kirkwood–Buff integrals (IKBI) approach.