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Solubility and thermodynamic functions measurement of morin hydrate in different alcohols

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ABSTRACT

Solubility of morin hydrate was measured in five pure alcohols (methanol, ethanol, propan-1-ol, propan-2-ol, and butan-1-ol) at 298.15 K as well as in different aqueous solutions of ethanol in a temperature range from 298.15 to 313.15 K and constant ionic strength (0.1 mol·dm^{-3} NaCl) using spectrophotometric method. The obtained results have shown that by increasing both temperature and ethanol percent as well as decreasing the dielectric constant of the medium causes an increase in solubility of the flavonoid. The solubility of morin hydrate was analyzed in different aqueous solutions of ethanol using normalized polarity and its blend with the Kamlet, Abboud, and Taft parameters. The experimental data in the binary systems were fitted using the Apelblat equation. The model was proven to give good representation of the experimental data. The thermodynamic functions of dissolution were calculated at different percent of ethanol using the modified van't Hoff equation. The dissolution process was endothermic and entropy-driving. Finally, the thermodynamic functions of morin hydrate were determined at 0% ethanol which are: $\Delta H^\circ = 54.53$, $\Delta G^\circ = 24.87$ kJ·mol^{-1} and $\Delta S^\circ = 97.04$ J·mol^{-1}·K^{-1} at the mean harmonic temperature.

1. Introduction

Flavonoids are naturally-occurring compounds, containing a number of phenolic hydroxyl groups attached to ring structures, designated A, B, and C. The structure of flavonoids is usually considered by two aromatic rings (A and B), joined by a three-carbon linked C-pyrone ring (C), forming a C6—C3—C6 skeleton unity where polar groups, usually hydroxyl, methoxyl, or glycosyl, are attached to various positions [1]. The recent explosion of interest in the bioactivity of flavonoids is due to the potential health benefits of these compounds. It is well-known that diets rich in fruits and vegetables are protective against cardiovascular diseases and certain forms of cancer [2]. Flavonoids continue to provide valuable therapeutic agents, both in modern medicine and in traditional systems and are useful compounds because of their multiple biological characters excluding cardio protective effects, anti-inflammatory, antimicrobial, and antiviral activities [3–5]. They prevent and treat cancer [6] and neurodegenerative diseases [7] and prevent skin damage [8] and osteoporosis [9].

Flavonoids are also known to have excellent antioxidant activity [10]. The pharmacological effects are related to the antioxidant activity of flavonoids, arising through their ability to scavenge free radicals. When generated in excess, free radicals can damage biomolecules, and are therefore implicated in the etiology of several diseases and ageing [11]. Radical scavenging by flavonoids occurs via electron donation from the free hydroxyls on the flavonoid nucleus with the formation of a less reactive flavonoid aroxyl radical, which is stabilized by resonance and therefore plays only a moderate role in the propagation of radical-induced damage in biological systems [12].

Morin with molecular structure shown in Scheme 1 is a famous bioactive constituent belonging to the group of flavonols and is found in old fustic (*Chlorophora tinctoria*), osage orange (*Maclura pomifera*), almond, mill (*Prunus dulcis*), fig (*Chlorophora tinctoria*), onion, apple, and other moraceae which are used as dietary agents and also as herbal medicines [13–14]. Morin acts as a potent antioxidant and can chelats to metal ions, and possesses various biological and biochemical effects such as antioxidation, anti-mutagenesis, anti-inflammation, anti-neoplastic, cardio protective activities, anticancer, xanthine oxidase inhibition, protein kinase C inhibition, and cell proliferation inhibition [15–17]. In addition to the inhibition of P-gp(p-glycoprotein), morin can control the activities of the metabolic enzymes including cytochrome P450 (CYPs) [18]. Also, the importance of morin and related compounds as anti-tumors drugs has been widely recognized [19]. Moreover, it has been shown to be acting as a chemopreventive agent in contrast to oral carcinogenesis in vitro and in vivo [20].

Some factors such as solubility in solvent extraction, diffusivities of solutes in solvents, and mass transfer parameters in order to optimize the process, are important in food industrial applications and pharmaceutical technology [21]. The presence of solvents in all steps of pharmaceutical processes (reaction, separation and formulation) is essential

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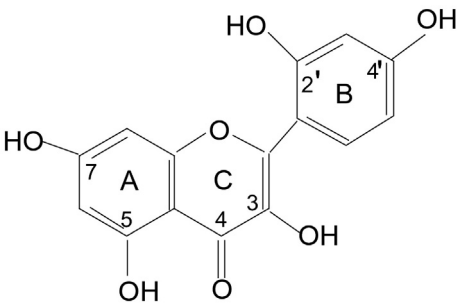

Scheme 1. Chemical structure of morin.

and the medium often affects the overall reaction rate, selectivity or yield. Low solubility of many drugs in water decreases their absorbance and thus diagnosis and treatment effects of drugs will be changed. The solubility behavior of drugs in cosolvent mixtures is important in purification, preformulation, and the dosage used in treatment processes. Further, temperature-solubility dependence allows a thermodynamic analysis inside the molecular mechanisms involved in the solution processes.

Solubility is usually influenced by several parameters such as the molecular structure (ionic species), pH, temperature, ionic strength, nature and concentration of salts and medium. Due to this, there is an increasing availability of these data in literatures. Solubility of flavonoids is very low in water [22]. From the other hand, the functions of flavonoids are controlled and limited by their low aqua- and lipo-solubility and causes low bioavailability [23–24]. An effectual method to develop the functionalities and usage in human diet is lipophilisation of flavonoids into fatty acid esters [25]. Several studies have been dedicated to increasing information about the solubility of these compounds and their thermodynamic and structural properties [26].

This paper aims to present solubility data of morin hydrate in some pure alcohols including methanol, ethanol, propan-1-ol, propan-2-ol, and butan-1-ol as well as in aqueous solutions of ethanol with composition ranging up to 80% (v/v) and different temperatures (298.15–313.15 K) to achieve a thermodynamic insight of the compound dissolution.

2. Experimental

2.1. Chemicals

Morin hydrate, Scheme 1, supplied from Sigma. The number of water molecules attached to one morin molecule was determined equal to 2, using Karl-Fisher procedure [27]. The purity of morin hydrate was checked by alkalimetric titration method. Methanol, ethanol, propan-1-ol, propan-2-ol, and butan-1-ol were all from Merck as reagent grade materials. For fixing the ionic strength in different percent of aqueous solutions of ethanol, sodium chloride (from Merck) solution was prepared by weighting enough pure salt that previously dried in an oven. Double-distilled water with a (2.0 ± 0.1) μS conductance used in all solutions. The details on chemicals used in this work are given in Table 1.

2.2. Procedure

The solubility of morin hydrate in pure and mixed solvents were performed by preparing saturated solutions by addition of an excess of the compound to the corresponding pure solvents or different percents of ethanol. The mixtures were sonicated for a few minutes, stirred in a mechanical shaker at least for 2 h. To reach solid–liquid equilibrium, the mixtures were placed directly in a constant temperature thermostatic bath with a temperature accuracy of ± 0.1 at least for 48 h. The equilibrium time was established by quantifying the compound concentration up to obtain a constant value. After this time, the mixtures were filtered through a micro porous membrane (at isothermal conditions) to ensure that they were free of particulate matter before sampling. The absorbances of the appropriate diluted solutions were then recorded on a UV–Vis Shimadzu 2100 spectrophotometer in the range of 300–450 nm using thermostated matched 10 mm quartz cells. The concentrations of the samples were then determined using the calibration curves that previously prepared for all the mixed and pure solvents. All the experiments were done at atmospheric pressure (84.8 ± 10) kPa.

3. Results and discussion

3.1. Solubility of Morin hydrate in pure alcohols

The total solubility of morin, *S*, was determined at 298.15 K in five pure alcohols (methanol, ethanol, propan-1-ol, propan-2-ol, and butan-1-ol) which are listed in Table 2. Unfortunately, there is no data reported in the literature for solubility of morin hydrate for comparison. The only one value for solubility of morin hydrate is reported in the Sigma Product Information. It can be seen from Table 2 that the minimum and the maximum solubility of morin in different alcohols used are in methanol and butan-1-ol, respectively. A comparison between the alcohols used, Table 2, shows that by increasing the number of carbon in hydrocarbon chain of the alcohols used, which is accompany with decreasing their dielectric constants, causes the solute molecules preferentially solvated better by the less polar solvent and increases the solubility of morin hydrate which has a low polarity nature in its neutral form. It is worthy to note that the solubility of morin hydrate versus the dielectric constant of the alcohols used shows almost a linear plot, Fig. 1.

The absorption spectra of saturated morin hydrate in different aqueous solutions of ethanol are shown in Fig. 2. An inspection of Fig. 2 reveals that the spectra exhibit one broad absorption band in the wavelength range 350–400 nm and their λ_{max} are shifted to higher wavelengths from 356.7 in 10% to at most 374.5 nm in 80% (v/v) ethanol. In the different percent of aqueous solutions of ethanol (10 to 80% v/v) no changes in the shape of the spectra were observed, indicating that there is no aggregation between morin hydrate molecules.

The solubility data of morin hydrate in the binary system of water-ethanol solutions (10 to 80% v/v ethanol) are presented in Table 3. From Table 3, it can be seen that the solvent composition of the mixtures have a very important effect on the dissolution process of morin hydrate. The solubility value shows an increasing trend from 10 to higher percent of ethanol and reaches the highest value at 80% (v/v) of ethanol.

Table 1
The details of chemicals used.

IUPAK name	Purity	Purification method	Molecular formula	Molar mass
2-(2,4-Dihydroxyphenyl)-3,5,7-trihydroxychromen-4-one	91.6	Used as received	$C_{15}H_{10}O7, 2H_2O$	338.24
Methanol	99.5	Used as received	CH_3OH	32.04
Ethanol	99.5	Used as received	C_2H_5OH	46.07
Propan-1-ol	99.0	Used as received	$CH_3CH_2CH_2OH$	60.10
Propan-2-ol	99.8	Used as received	$CH_3CH(OH)CH_3$	60.10
Butan-1-ol	99.5	Used as received	$CH_3(CH_2)_3OH$	74.12
Sodium chloride	99.5	Dried 2 h at 383 K	NaCl	58.44