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Solubility of daidzein in propylene glycol plus water cosolvent mixtures

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ABSTRACT

The solubility of daidzein in propylene glycol + water cosolvent mixtures was determined by UV spectrophotometry, and predicted using the Jouyban–Acree model and the mathematical model based on the algebraic rule of mixing. The thermodynamic functions, such as Gibbs energy, enthalpy, and entropy of solution and of mixing and so on, were obtained from these solubility data by using the van't Hoff and Gibbs equations. The results show that the daidzein solubility increases as propylene glycol proportion increases in the mixtures and the solution temperature increases. The Jouyban–Acree model can be used to predict the solubility of daidzein in propylene glycol + water cosolvent mixtures at different temperatures. The driving mechanism for daidzein solubility in water-rich mixtures is the entropy, probably due to water-structure loss around the drug non-polar moieties by effect of propylene glycol, whereas the driving mechanism is the enthalpy above 0.20 mass fraction of propylene glycol, probably due to daidzein solvation increase by the cosolvent molecules. Non linear enthalpy–entropy compensation with negative slope from water up to 0.20 mass fraction of propylene glycol and positive slope beyond this composition up to pure propylene glycol is found.

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1. Introduction

Daidzein (DZ) (7,4′-dihydroxyisoflavone, Fig. 1) is a major isoflavone found in soybean and other leguminous plant, such as kudzu root. Previous studies have shown that DZ has pharmacological and biochemical effects including antioxidant, anti-inflammatory, cell cycle arrest and estrogen-like biological activities in humans [1–4], and is widely used as phytoestrogen for menopausal-related disorders, such as cardiovascular disease [5,6], osteoporosis [7], other menopausal symptoms [8]. Currently, DZ is commercially available as tablets for peroral administration in the China market.

Solubility is an important physicochemical property which plays a basic role in most pharmaceutical and industrial processes. Usually, the low solubility of pharmaceutical compounds causes them to fail during the drug development process, especially of homogeneous liquid pharmaceutical systems. In this way, some water + cosolvent mixtures have been evaluated in order to increase drug solubility and also to permit molecular understanding of solution phenomena and development of homogeneous liquid pharmaceutical products. Propylene glycol (PG), as a hydrogen-donor and hydrogen-acceptor compound, is miscible with water in all proportions, and has been studied in particular as a possible cosolvent in liquid pharmaceutical dosage forms design for several drugs [9]. Moreover, PG has also been used as an evaporation regulator and antimicrobial agent in several liquids formulations [10]. In this study, the solubility of DZ in PG + water cosolvent mixtures at different temperatures was determined.

Experimental solubility determination is a time-consuming and costly process. Several mathematical models have been proposed in the published literature to predict the solubility of drugs in cosolvent + water mixtures [11]. The simplest model to predict drug solubility in cosolvent water mixtures is the one based on the algebraic rule of mixing, which for semipolar compounds in binary mixtures takes the following form:

$$\ln x_m = w_c \ln x_c + w_w \ln x_w \quad (1)$$

where x_m, x_c, x_w, w_c and w_w are the drug solubility calculated in the cosolvent mixture, the drug solubility in the neat cosolvent, the drug solubility in water, the mass fraction of cosolvent in the

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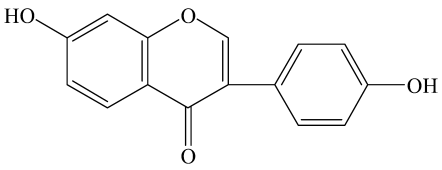

Fig. 1. Molecular structure of daidzein (DZ).

mixture, and the mass fraction of water in the mixture, respectively. In PG + water cosolvent mixtures, a trained version of the Jouyban–Acree model could be a useful tool for solubility prediction purposes in the pharmaceutical industries [12]. The mathematical model for PG + water cosolvent mixtures at various temperatures is:

$$\ln x_m = f_c \ln x_c + f_w \ln x_w + f_c f_w \left[\frac{85.254}{T} + \frac{735.662(f_c - f_w)}{T}\right] \quad (2)$$

where x_m, x_c and x_w are the drug solubility calculated in solvent mixture, PG and water at temperature (T, K), f_c and f_w denote the volume fractions of PG and water in the absence of the solute.

In addition, temperature-solubility dependence allows to perform the respective thermodynamic analysis. So, the objectives of this study are: (1) to measure the solubility of DZ in PG + water cosolvent mixtures at different temperatures; (2) to determine the feasibility of predicting the solubility of DZ in PG + water cosolvent mixtures using two mathematical models; (3) to evaluate the thermodynamic characteristic of DZ dissolved in PG + water cosolvent mixtures based on van't Hoff method, including the respective contributions by mixing of this compound toward the solution processes.

2. Experimental

2.1. Materials

All chemicals used in experimental part are listed in Table 1. The compounds were used without further purification. The redistilled and deionized water with conductivity <2 μS cm^{-1} was used throughout.

2.2. Solubility determinations

An excess of DZ was added to approximately 10 g of each PG + water cosolvent mixture or neat solvent in the stoppered brown glass flasks, which all PG + water cosolvent mixtures were prepared by mass using a AG135 analytical balance (Mettler Toledo, Switzerland) with sensitivity ±0.1 mg. The flasks with the solid–liquid mixture were placed in a SHA-C thermostatic water bath shaker (Jiangsu Zhengji Instruments Co. Ltd., Jiangsu, China) and kept at 298.15, 303.15, 308.15, 313.15 or 318.15 K (uncertainty in temperature was ±0.05 K) for at least 5 days to reach the equilibrium. The equilibrium time was established by measuring DZ concentrations in the solutions till they became constant. Hereafter, the supernatant solutions were filtered through a 0.22 μm Millipore membrane filter, added to a volumetric flask, and diluted with methanol to an appropriate concentration for UV analysis.

To determine the DZ concentration in the solution, the absorbances of the standard and sample were measured by an SP-2000UV UV–vis spectrophotometer (Shanghai Spectrum Instruments Co. Ltd., Shanghai, China) at the wavelength 254 nm. The calibration curve ($y = 30{,}034.44x - 0.01$, $r^2 = 0.9993$) for estimating of DZ concentrations was prepared using the standard solutions in the appropriate concentration range (1.57×10^{-6} to 23.60×10^{-6} mol/L).

All the solubility experiments were run in triplicates. In order to transform molar concentrations to mole fractions, the density of the saturated solutions was determined with a digital density meter (DMA 45 Anton Paar) connected to the same re-circulating thermostatic baths, accordingly to procedures described in the literature [13].

2.3. DSC analysis

Melting point (T_{fus}) and enthalpy of fusion (ΔH_{fus}) of DZ were determined by DSC (DSC 822^e Mettler Toledo, Zurich, Switzerland). Thermal analyses were performed at a heating rate of 10 K min^{-1} under nitrogen atmosphere. Nearly 2.5 mg of DZ was accurately weighed directly into aluminium pans. The pans were then covered with lids and sealed using the crucible sealing press. Before each scan, a baseline was recorded with the same heating rate and then subtracted from the experimental scan. The DSC curves were recorded and analyzed using the STAR^e software. Temperatures and enthalpies were calibrated using indium phase transition (99.99% pure; heat of fusion, 28.45 J g^{-1}; melting point, 429.76 K).

The heat capacities (C_p) of the super-cooled liquid and crystalline forms of daidzein were measured using DSC. Three runs were made for each heat capacity experiment: empty pan for baseline determination, sapphire for calibration and sample scans. All scans were conducted at a heating rate of 1 K min^{-1} under nitrogen atmosphere. The DSC curves were recorded and analyzed using the STAR^e software. The pans and lids were weighed and only those having mass differences within 0.1% tolerance were used in the experiments. The heat capacity values were measured in a range from 273.15 K to 333.15 K. The supercooled liquid form of daidzein was prepared for thermal analysis by in situ melting and cooling of the crystalline material in DSC.

2.4. Solubility prediction

Solubilities of DZ in PG + water cosolvent mixtures at different temperatures were predicted by two methods: (I) the mathematical model based on the algebraic rule of mixing (Eq. (1)) and (II) the trained version of the Jouyban–Acree model (Eq. (2)). The percentage deviations (PD) and the mean percentage deviations (MPD) were used to check the accuracy of the prediction method and were calculated using Eqs. (3) and (4).

$$\mathrm{PD} = 100 \times \frac{\text{Predicted} - \text{Experimental}}{\text{Experimental}} \quad (3)$$

$$\mathrm{MPD} = \frac{100}{N} \sum \frac{|\text{Predicted} - \text{Experimental}|}{\text{Experimental}} \quad (4)$$

in which N is the number of solubility data points.

Table 1
Suppliers and purities of the chemicals.

Substance	Certified purity (%)	Method	Supplier
Daidzein	99.0	HPLC	Xi'an Guanyu Bio-tech Co. Ltd. (Xi'an, China)
Propylene glycol	99.8	–	Tianjin Kermel Chemical Reagent Co. Ltd. (Tianjin, China)
Aluminum oxide (α-phase)	99.99	–	Aladdin Industrial Corporation (Shanghai, China)
Water	–	–	Redistilled and deionized

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