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Equilibrium solubility, dissolution thermodynamics and preferential solvation of 6-methyl-2-thiouracil in aqueous co-solvent mixtures of methanol, *N*-methyl-2-pyrrolidone, *N,N*-dimethyl formamide and dimethylsulfoxide

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ABSTRACT

The experimental solubility behavior of 6-methyl-2-thiouracil in co-solvent mixtures of (methanol, *N*-methyl-2-pyrrolidone, *N,N*-dimethyl formamide or dimethylsulfoxide) + water were measured by the isothermal dissolution equilibrium method at elevated temperatures between 278.15 K and 323.15 K under about 101.2 kPa. The solubility of 6-methyl-2-thiouracil increased positively with increasing temperature and molar fraction of organic solvents in each binary system. The minimum solubility was observed in neat water. At the same temperature and mass fraction of the organic solvent, the solubility of 6-methyl-2-thiouracil was greater in (dimethylsulfoxide + water) than in the other three mixed solvents. The solid phase 6-methyl-2-thiouracil was tested by X-ray power diffraction, which showed that no polymorphic transformation, solvate formation or crystal transition during entire experiments conclusively. The measured solubility data was correlated with the Jouyban-Acree model, Van't Hoff-Jouyban-Acree model and Apelblat-Jouyban-Acree model. The calculated data was in good agreement with the experimental values within the temperature range studied and the maximum of relative average deviation and root-mean-square deviation were 3.64×10^{-2} and 5.68×10^{-4}, respectively. The dissolution process of 6-methyl-2-thiouracil in the four co-solvent mixtures was endothermic. The solvent effect analysis indicates that the hydrogen bond acceptor capacity and dipolarity-polarizability of solvent control mainly the variation in the solubility. Furthermore, the preferential solvation parameters were derived from their thermodynamic solution properties by using the inverse Kirkwood–Buff integrals. For the four co-solvent mixtures with intermediate composition and co-solvent-rich mixtures, 6-methyl-2-thiouracil was preferentially solvated by co-solvent. It could act mainly as a Lewis acid interacting with proton-acceptor functional groups of the co-solvents.

1. Introduction

Equilibrium solubility is an essential thermodynamic property in pharmaceutical field of liquid dosage forms from both practical and theoretical viewpoints [1–4]. Faced with low aqueous solubility of some drugs and drug-like molecules, among the approaches employed to influence the solubility, co-solvency is one of the most effective methods in the pharmaceutical industry [5–7]. Aqueous solution with co-solvent mixtures are used i.e. in pharmaceutical formulations of dosage forms in drug's crystallization from synthetic reaction solutions or from solutions prepared upon dissolving natural products. Therefore, the solubility behavior of drugs in aqueous co-solvent mixtures is evaluated essentially for the purposes of starting material purification and understanding of the mechanisms about the physical and chemical stability of pharmaceutical dissolutions [2,6–8]. Furthermore, the solubility data enables us to look for the most suitable solvent system to purify drugs by way of solvent crystallization. For these reasons mentioned above, it is very important to systematically determine drug solubilities in different aqueous and organic solvent mixtures [2,3,6–8]. Although solvent mixing as a solubilization technique has been widely employed in pharmacy and chemistry, recently the mechanisms involved in increasing or decreasing drugs'

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solubility have started to be investigated by analysis of the preferential solvation of the solutes by the solvent components in the saturated solutions [9–11].

The derivatives of uracil deserve particular attention among all series of derivatives of nucleic pyrimidine bases since they play an important role in the field of biology as fundamental constituents of nucleic acid with some derivatives of uracil exhibiting significant biological activity. Thiouracils are an important class of modified nucleo bases derived from uracil. Thio-derivatives of uracil have come to play increasingly important roles in biology and medicine as numerous sulphur-substituted pyrimidines and have found applications as clinically useful drugs. 6-Methyl-2-thiouracil (CAS Reg. NO. 56-04-2, chemically named 2,3-dihydro-6-methyl-2-thioxo-4(1*H*)-pyrimidinone, molecular structure shown in Fig. S1 of Supporting material) is classified by the one of most representative thiouracil derivatives with unique structural features containing active (—HN—CS—NH—) and pyrimidine heterocyclic group which has a variety of good biological and antifungal activity as an active pharmaceutical ingredient [12–18]. Primarily, it is an indispensable intermediate used for synthetizing cardiovascular drugs named dipyridamole [16–18]. Literature survey shows that 6-methyl-2-thiouracil have been used as a potent antithyroid drug, hyperthyroidism inhibitor. It induces modifications in the thyroid, such as, an increase of the hypothyroidism effect on blood [19] or a dietary product due to the effects on thyroid activity suppression [20,21]. In recent years, various medical values of 6-methyl-2-thiouracil have gradually drawn people's attention so as to urge increasing demand in pharmacological fields. In order to extend the drug's use in various fields, it is necessary to determine systematically their solubilities for liquid pharmaceutical systems. The solubility of 6-methyl-2-thiouracil in water has been studied in the literatures [22–25]. Nevertheless, despite the usefulness of this drug, the study on physicochemical properties of 6-methyl-2-thiouracil in aqueous solutions has not been made up to now. For these reasons, it is of importance to systematically determine drug solubilities in different aqueous co-solvent mixtures [6,8].

Although a large number of solid-liquid equilibrium models can be employed to predict drug solubilities in solvent mixtures, the accuracy and repeatability of experimental values is still fundamental for the pharmaceutical scientists [2,3,11]. Commonly and practically, the cosolvency, mixing a green organic solvent with water, is the most available technique to increase the aqueous solubility of drugs. Methanol (MeOH) is not used to develop liquid medicines due to its high toxicity. But in some cases methanol is used in drug purification procedures [26], as well as solvent in some drug microencapsulation techniques [27]. Moreover, methanol is widely used as mobile phase in high performance liquid chromatography [28]. *N,N*-Dimethylformamide (DMF) is a very interesting co-solvent to investigate the interrelation between drug solubility and medium polarity because it is aprotic and completely miscible with water [29]. Water DMF mixtures are strongly non ideal and can act in the solute solvation process via hydrophobic interactions and preferential solvation [30,31]. Solubility in dimethyl sulfoxide (DMSO) is one of the important parameters considered by pharmaceutical companies during early drug discovery [32,33]. *N*-Methyl-2-pyrrolidone (NMP) is a very strong solubilizing agent [34] and is an important solvent in extraction, purification, and crystallization of drugs [35]. Based on the above considerations, the main purpose of this work is to determine the equilibrium solubility of 6-methyl-2-thiouracil (3) in co-solvent mixtures of methanol (1) + water (2), NMP (1) + water (2), DMF (1) + water (2) and DMSO (1) + water (2) at temperatures ranging from (278.15–323.15) K under atmospheric pressure in order to evaluate the respective thermodynamic quantities of the solution. In this way, this research expands the available solubility data about drug in neat organic solvents and solvent mixtures [2,22] and also allows the thermodynamic analysis of the respective dissolution and specific solvation process.

2. Experimental

2.1. Materials and apparatus

6-Methyl-2-thiouracil was purchased from Shanghai D.B. Chem. Tech. Co., Ltd. with a mass fraction of 0.980. It was purified three times via crystallization in methanol. The final content of 6-methyl-2-thiouracil employed for solubility determination was 0.995 in mass fraction, which was confirmed by using a high-performance liquid chromatography (HPLC, Agilent-1260). In this work, all solvents (MeOH, NMP, DMF and DMSO) provided by Sinopharm Chemical Reagent Co., Ltd., China were of analytical grade, which purity was all no <0.994 in mass fractions determined by gas chromatography (GC, FULI 9790, China). Distilled deionized water (conductivity < 2 μS cm^{-1}) prepared in our laboratory was used throughout the measurement process. The detailed information of these chemicals used in this work was tabulated in Table 1.

In this work, the experimental apparatus used for the solubility measurements was given in Fig. S2 of Supporting material, which included a 100 ml jacketed glass vessel with a magnetic stirrer and a circulating (water + isopropanol) system employed for controlling the system temperature. The temperature of circulating (water + isopropanol) was kepted by a thermostatic bath (Model: QYHX-1030) with a standard uncertainty of 0.05 K, which was purchased from Shanghai Joyn Electronic Co., Ltd., China. A mercury glass micro thermometer (standard uncertainty: 0.02 K) inserted in the inner chamber of the jacket glass vessel displayed the real temperature of mixture. A condenser was connected with the jacketed glass vessel to prevent the solvent from escaping. An analytical balance (model: BSA224S) having a standard uncertainty of 0.0001 g was produced by Satorius Scientific Instrument (Beijing). Before experiment, the reliability of the apparatus was verified via determining the benzoic acid solubility in toluene [36,37].

2.2. Solubility determination

The equilibrium solubility of 6-methyl-2-thiouracil in several co-solvent mixtures of {MeOH (1) + water (2)}, {NMP (1) + water (2)}, {DMF (1) + water (2)} and {DMSO (1) + water (2)} were determined in this work with the isothermal dissolution equilibrium method [36–39], and the high-performance liquid phase chromatograph (HPLC, Agilent-1260) was employed to determine the solubility of 6-methyl-2-thiouracil in equilibrium liquid phase.

Saturated solutions of 6-methyl-2-thiouracil were prepared in the jacketed glass vessel for each experiment. An excessive amount of 6-methyl-2-thiouracil was added into the jacketed glass vessel filled with about 60 ml solvent mixtures. The mass fractions of MeOH, NMP, DMF or DMSO in the binary solvent mixtures varied from 0 to 1.0. Continuous stirring was obtained by using a magnetic stirrer at a fixed temperature in order to mix the suspension intensively. The system was kept at a desired temperature by circulating water from the smart thermostatic bath through the outer jacket. In order to determine the equilibration time of the studied systems, about 1 ml liquid phase was extracted out every one hour using a 2 ml of preheated syringe equipped with a pore syringe filter (PTFE 0.2 μm), and then analyzed by the high-performance liquid phase chromatograph (HPLC, Agilent-1260). Once the analysis results didn't vary, the system was assumed to be in equilibrium. Furthermore, in order to ensure that sampling was performed at equilibrium conditions, two types of experiments were carried out, one starting from a supersaturated solution, in which the solid phase precipitated to reach equilibrium and the other starting from