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Solubility and thermodynamic function of a bioactive compound bergenin in various pharmaceutically acceptable neat solvents at different temperatures

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ABSTRACT

Bergenin is neither a highly lipophilic nor a highly hydrophilic bioactive compound due to which its dissolution and permeation are poor which results in poor oral bioavailability. The solubility data of bergenin are scarce in literature. Therefore, in this study, the solubility of bergenin was determined in eleven different pharmaceutically acceptable neat solvents namely water, ethanol, isopropanol (IPA), ethylene glycol (EG), propylene glycol (PG), 1-butanol, 2-butanol, ethyl acetate (EA), dimethyl sulfoxide (DMSO), polyethylene glycol-400 (PEG-400) and Transcutol at five different temperatures (T = 298.15 K–318.15 K) and atmospheric pressure (p = 0.1 MPa). Experimental solubility expressed in mole fraction of bergenin was correlated with semi-empirical models. Root mean square deviations were recorded <1% for the Apelblat model and <2% for the van't Hoff model. The mole fraction solubility of bergenin was recorded highest in PEG-400 (4.15×10^{-2} at T = 318.15 K) followed by DMSO (2.30×10^{-2} at T = 318.15 K), Transcutol (2.28×10^{-2} at T = 318.15 K), PG (1.19×10^{-2} at T = 318.15 K), EG (1.17×10^{-2} at T = 318.15 K), ethanol (7.77×10^{-3} at T = 318.15 K), IPA (1.69×10^{-3} at T = 318.15 K), EA (6.71×10^{-4} at T = 318.15 K), 2-butanol (5.14×10^{-4} at T = 318.15 K), 1-butanol (4.92×10^{-4} at T = 318.15 K) and water (1.87×10^{-4} at T = 318.15 K). The results of apparent thermodynamic analysis in terms of standard enthalpy indicated that the dissolution of bergenin is endothermic in all pharmaceutically acceptable neat solvents. The solubility results of this study could be useful in purification, recrystallization and formulation development of bergenin.

1. Introduction

Bergenin [Fig. 1; IUPAC name: 3,4,8,10-tetrahydroxy-2-(hydroxymethyl)-9-methoxy-3,4,4a,10b-tetrahydro-2*H*-pyranol[3,2-c]isochromen-6-one; molecular formula: $C_{14}H_{16}O_9$; molar mass: 328.27 g·mol^{-1} and CAS number: 477-90-7] occurs as white to off-white crystalline powder [1,2]. It is the major compound of Chinese traditional medicine *Bergenia crassifolia* (Family: Saxifragaceae) [1]. A variety of therapeutic activities such as antiulcer, antidiarrheal, anti-tussive, laxative, anti-inflammatory, anti-HIV, anti-arrhythmic, hepatoprotective, neuroprotective, anticancer, antidiabetic, antinociceptive, antimicrobial, antioxidant, immunomodulatory and wound healing activity for bergenin have been reported in literature [3–14]. It is slightly soluble bioactive compound in water [15]. It has been reported neither highly hydrophilic nor highly lipophilic compound due to which its oral bioavailability is poor after oral administration [1,15]. Low solubility and poor permeability are the main barriers in formulation development of bergenin [15]. It is commercially available in solid dosage forms such as tablets, pills and soft gelatin capsules [1]. Due to its low solubility in water, liquid dosage forms of bergenin are not available in market. A knowledge of the solubility of bioactive compounds such as bergenin, diosmin, vanillin, isatin, reserpine and hesperidin in neat aqueous and organic solvents is important in extraction/separation, recrystallization, purifications, drug discovery and formulation development of these compounds [16–24]. Therefore, it is important to determine the solubility of bergenin in solvents which are pharmaceutically acceptable and safe for industrial application. Commonly used pharmaceutically acceptable neat solvents are water, propylene glycol (PG), ethanol

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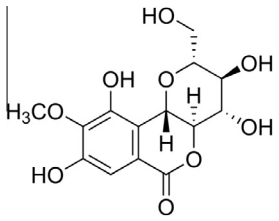

Fig. 1. Molecular structure of bergenin (molar mass: 328.27 g·mol^{-1}).

and polyethylene glycol-400 (PEG-400) [16–19]. Recently, Transcutol has also been investigated as a potential solvent in solubilization of various poorly soluble bioactive compounds [19,22,25]. Some pharmaceutical approaches such as solid dispersions, phospholipid complex, film-coated tablets and surfactants were evaluated in order to enhance solubility, dissolution and oral bioavailability of bergenin in literature [15,26–29]. The solubility of bioactive compound bergenin is poorly reported in literature. Nevertheless, the mole fraction solubility of bergenin in water at T = 298.15 K has been reported as 7.52×10^{-5} [15]. The solubility and thermodynamic functions of bergenin in pharmaceutically acceptable neat solvents such as ethanol, Transcutol, PEG-400, PG, ethylene glycol (EG), isopropanol (IPA), 1-butanol, 2-butanol, ethyl acetate (EA) and dimethyl sulfoxide (DMSO) or aqueous-cosolvent mixtures have not been reported in the literature. Hence, in this study, the solubility (expressed as mole fractions) of crystalline bergenin in eleven different pharmaceutically acceptable neat solvents including water, ethanol, Transcutol, PEG-400, PG, EG, IPA, 1-butanol, 2-butanol, EA and DMSO was determined at five different temperatures *i.e.* T = (298.15 K to 318.15) K and pressure p = 0.1 MPa. Thermodynamic function for dissolution of bergenin was also carried out by van't Hoff analyses. The solubility data of this study could be useful in extraction/separation, recrystallization, purification, and formulation development of bergenin.

2. Experimental

2.1. Materials

Bergenin, ethyl alcohol (IUPAC name: ethanol), 1-butyl alcohol (IUPAC name: 1-butanol), (*RS*)-2-butyl alcohol [IUPAC name: (*RS*)-2-butanol] and IPA (IUPAC name: isopropanol) were obtained from Sigma Aldrich (St. Louis, MO). Transcutol (IUPAC name: diethylene glycol monoethyl ether) was obtained from Gattefosse (Lyon, France). PEG-400 (IUPAC name: polyethylene glycol-400), (*RS*)-PG [IUPAC name: (*RS*)-1,2-propanediol], EA (IUPAC name: ethyl acetate), DMSO (IUPAC name: dimethyl sulfoxide) and EG (IUPAC name: 1,2-ethanediol) were obtained from E-Merck (Berlin, Germany). Water was collected from a Milli-Q water unit. The description and purity of these materials are listed in supplementary information (Table S1).

2.2. Quantification of bergenin

The amount of bergenin in solubility samples was quantified using reversed phase high performance liquid chromatography (HPLC) coupled with ultra-violet (UV) detector (HPLC-UV) at 254 nm. The analysis was carried out at 298.15 K with the help of HPLC system (Waters, USA). The system was equipped with an isocratic 1515 HPLC pump, 717 auto sampler, binary pumps and dual λ UV–visible detector (Waters, 2487). The column used for analysis of bergenin was Nucleodur (150 × 4.6 mm) RP C_8 with 5 µm packing. The binary mixture of ethanol:methanol (50:50% v/v) was utilized as the mobile phase. The mobile phase was degassed via sonication for 15 min. The elution of solute was carried at a flow rate of 1.0 mL·min^{-1} at 254 nm. The calibration curve between the concentration and HPLC peak area of bergenin was plotted which was found to be linear in the range of (1–100) µg·g^{-1} with correlation coefficient (R^2) of 0.9971. The regressed equation was obtained as $y = 5648.4x + 12{,}158$; in which x is the concentration of bergenin and y is the HPLC peak area.

2.3. Determination of bergenin solubility

Bergenin solubility in eleven different pharmaceutically acceptable neat solvents was measured using an isothermal method [30]. Experiments were carried out at T = (298.15–318.15) K and atmospheric pressure (p = 0.1 MPa). The excess quantity of bergenin was added in known amounts of each pharmaceutically acceptable neat solvent. Experiments were performed in triplicates. All the samples were kept into biological shaker (Julabo, PA) for continuous shaking at 100 rpm for 3 days. After 3 days, each sample was removed from the shaker and allowed to settle bergenin particles overnight. After overnight settling of bergenin particles, supernatants from each sample were carefully withdrawn, diluted and subjected for analyses of bergenin content by HPLC-UV method described above at 254 nm. Values of the experimental solubility (expressed as mole fraction) of bergenin (x_e) were calculated by adopting the standard formula of x_e reported previously in literature [18,19].

3. Results and discussion

3.1. Experimental solubility values of bergenin and its literature comparison

The x_e values of bergenin in eleven different pharmaceutically acceptable neat solvents at T = (298.15 K–318.15 K) and p = 0.1 MPa are presented in Table 1. The solubility of bergenin at different temperatures in these neat solvents has not been reported in literature. However, the solubility (as mole fraction) of bergenin in water at T = 298.15 K has been reported as 7.52×10^{-5} [15]. In this study, the solubility (as mole fraction) of bergenin in water at T = 298.15 K was recorded as 7.57×10^{-5}. Observed solubility of bergenin was very close with reported solubility of bergenin in water. This observation indicated good agreement of our results with literature value of bergenin in water [15]. Zhou et al. (2008) also reported the solubility of bergenin in aqueous solutions of different pHs such as 1, 3 and 5 at five different temperatures ranging from (298.15 to 333.15) K [1]. They observed that the solubility of bergenin was not significantly changed by changing the pH of aqueous solution [1]. However, the solubility of bergenin was significantly enhanced with the rise in temperature. In this study, the x_e values of bergenin were also enhanced significantly with the rise in absolute temperature in all eleven pharmaceutically acceptable neat solvents (Table 1). With respect to temperature, our results are in good agreement with those reported by Zhou et al. [1]. Zhou et al. (2008) also found that bergenin was sufficiently decomposed at neutral and alkaline pHs, therefore the solubility of bergenin in neutral and alkaline solutions was not determined by Zhou et al. [1]. Due to the reported decomposition of bergenin in neutral water (pH = 7.0), we have also determined the decomposition of bergenin in deionized water. The pH of deionized water in the air atmosphere was recorded as (5.5 ± 0.1) which was possible due to CO_2. The decomposition study of bergenin was carried out in deionized water (pH = 5.5) at T = 298.15 K. The stock solution of bergenin (100 µg·g^{-1}) was prepared in fresh deionized water in triplicates. The prepared stock solution was transferred to biological shaker controlled at 298.15 K. The samples were taken from