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Solubility determination of raloxifene hydrochloride in ten pure solvents at various temperatures: Thermodynamics-based analysis and solute–solvent interactions

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Acetonitrile (PubChem CID: 6342)
Dimethyl sulfoxide (PubChem CID: 679)
Ethanol (PubChem CID: 702)
Ethyl acetate (PubChem CID: 8857)
Ethylene glycol (PubChem CID: 174)
Isopropyl alcohol (PubChem CID: 3776)
Polyethylene glycol-400 (PubChem CID: 174)
Propylene glycol (PubChem CID: 1030)
Raloxifene hydrochloride (PubChem CID: 54900)
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ABSTRACT

The purpose of the present study was to determine the solubility of raloxifene hydrochloride (RHCl) in ten solvents: water, ethanol, isopropyl alcohol (IPA), ethylene glycol (EG), propylene glycol (PG), polyethylene glycol-400 (PEG-400), Transcutol, 1-butanol, dimethyl sulfoxide (DMSO), and ethyl acetate (EA) at temperatures of 298.2–323.2 K and a pressure of 0.1 MPa. The solubility data obtained was fitted upon "Apelblat and Van't Hoff" equations. The maximum mole fraction solubility of RHCl was obtained in DMSO (5.02×10^{-2} at 323.2 K), followed by PEG-400 (5.92×10^{-3} at 323.2 K), EA (3.11×10^{-3} at 323.2 K), Transcutol (1.22×10^{-3} at 323.2 K), PG (2.19×10^{-4} at 323.2 K), 1-butanol (1.96×10^{-4} at 323.2 K), IPA (1.47×10^{-4} at 323.2 K), ethanol (7.90×10^{-5} at 323.2 K), EG (6.65×10^{-5} at 323.2 K), and water (3.60×10^{-5} at 323.2 K). Similar fashions were noticed at each studied temperature. The higher solubility of RHCl in DMSO, PEG-400, EA, and Transcutol was possibly referable to their lower polarity in comparison with water. The molecular interactions between the solute and solvent molecules were estimated by calculating parameters like activity coefficients, and more prominent solute–solvent molecular interactions were noted for RHCl–DMSO, RHCl–EA, and RHCl–PEG-400 in comparison with the other solute–solvent combinations. The outcomes of the "apparent thermodynamic analysis" showed that the dissolution of RHCl was "endothermic, spontaneous and entropy-driven" in all investigated solvents. The obtained solubility data of RHCl in commonly used solvents could be useful in the purification, recrystallization, and dosage form design of the drug.

1. Introduction

Raloxifene hydrochloride (RHCl; molecular formula: $C_{28}H_{27}NO_4S{\cdot}HCl$; molar mass: 510.045 g mol^{-1}; CAS number: 82640-04-8; Fig. 1) is an oral second-generation selective estrogen receptor modulator utilized in the prevention and management of post-menopausal osteoporosis in women (Ravi et al., 2014). RHCl is a highly lipophilic drug (Log P = 5.69 (Reimao et al., 2014). Almost 60% of the oral dose is absorbed, but its inadequate aqueous solubility and wide-ranging pre-systemic metabolism via glucuronide conjugation limits its oral bioavailability (< 2%) (Hochner-Celnikier, 1999; Ravi et al., 2014). RHCl is almost entirely insoluble in water, which is the primary hurdle for the formulation development of RHCl, particularly for liquid dosage forms. The solubility information of poorly soluble drugs such as RHCl in various commonly used organic solvents and in water has significance to several industrial procedures like "recrystallization, purification, drug discovery, and formulation development" (Almarri et al., 2017; Alshora et al., 2016).

Only a few reports are available on the solubility of RHCl. The "mole fraction solubility" of RHCl in water at temperature (T) = 298.2 K was reported as 1.01×10^{-5} and 2.21×10^{-5} by Chauhan (2015) and Bikiaris et al. respectively (Bikiaris et al., 2009; Chauhan, 2015). Chauhan (2015) also reported the solubility (3.73×10^{-5}) of RHCl in isopropyl alcohol (IPA) at T = 298.2 K (Chauhan, 2015). Elsheikh et al. reported the solubility of RHCl in propylene glycol (PG) (8.99×10^{-5}) and Transcutol (6.83×10^{-4}) at T = 303.2 K and "atmospheric pressure" (Elsheikh et al., 2012). Nevertheless, the solubilities of RHCl in other pure solvents like

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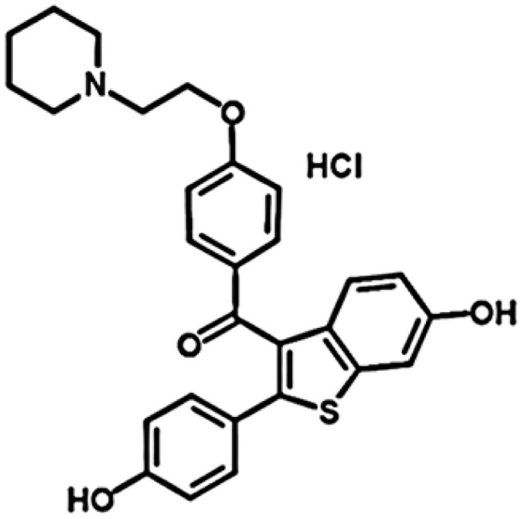

Fig. 1. Molecular structure of RHCl.

ethanol, ethylene glycol (EG), polyethylene glycol-400 (PEG-400), 1-butanol, dimethyl sulfoxide (DMSO), and ethyl acetate (EA) have not been reported until now. It is essential to precisely appraise the solubility of RHCl in distinct pure solvents at different temperature ranges to obtain the complete physicochemical information of RHCl. Therefore, the purpose of present study is to found out the solubility of RHCl in ten pure solvents (i.e. water, ethanol, IPA, EG, PG, PEG-400, Transcutol, 1-butanol, DMSO, and EA) at "T = 298.2–323.2 K" and "pressure (p) = 0.1 MPa" in order to obtain physicochemical information of RHCl in these solvents. An "apparent thermodynamic analysis" of the RHCl solubility data was implemented following the "Van't Hoff and Krug et al. analysis" to obtain the dissolution behavior of RHCl (Holguin et al., 2012; Krug et al., 1976; Ruidiaz et al., 2010). Finally, the activity coefficients were calculated to evaluate the molecular solute–solvent interactions. The solubility data of RHCl recorded in this work would be useful in "purification, recrystallization and dosage form design" of RHCl in pharmaceutical industries.

2. Materials and methods

2.1. Materials

RHCl was purchased from "Ark Pharm, Inc. (Libertyville, IL, USA)". EA was purchased from "Winlab Ltd. (Leicestershire, UK)". DMSO and 1-butanol were procured from "BDH Laboratory Supplies (Poole, UK)". Ethanol was procured from "Sigma-Aldrich (St. Louis, MO, USA)". IPA was received from "Panreac Química, S.A.U. (Barcelona, Spain)". PEG-400 was acquired from "Merck Schuchardt (Munchen, Germany)". Transcutol was received from "Sigma-Aldrich (St. Louis MO, USA)". EG and PG were obtained from "Anova Chem (Hurden, Switzerland)". Milli-Q water was obtained from a Millipore water purification system (Millipore SAS, Molsheim, France). The information of these materials are presented in Supplementary Table (Table S1).

2.2. High-performance liquid chromatographic (HPLC) analysis of RHCl

The RHCl analysis was accomplished with an ultraviolet HPLC system "(Shimadzu, Japan)". A C_{18} HPLC column was used for the analysis "(Nucleodur®; 5 µm, 250 × 4.6 mm; Macherey-Nagal, Germany)". The mobile phase included 50 mM potassium dihydrogen orthophosphate buffer pH 3.0 (64%) and acetonitrile (36%). The flow rate was 0.5 mL min^{-1} and the wavelength was set at 287 nm.

2.3. Solid state characterization of RHCl

Solid state characterization was performed using "differential scanning calorimetry (DSC)", "thermogravimetry (TGA)" and "powder X-ray diffraction (PXRD) analysis" for pure RHCl and equilibrated RHCl (solid obtained from bottom phase of equilibrated sample). The equilibrated RHCl was obtained from solubility sample in water by evaporation (Alshehri and Shakeel, 2017; Shakeel et al., 2017c).

DSC analysis was performed using "DSC 8000 instrument (Perkin Elmer, USA)" for the pure and equilibrated RHCl, at a heating rate of 10 °C/min and in the temperature range of "323.2–573.2 K" (Babanejad et al., 2017).

TGA analysis on pure and equilibrated RHCl was performed with "Pyris 1 TGA (Perkin Elmer, USA)". In brief, 3.885 mg of the samples were heated at a rate of 10 °C/min from 313.2 K to 973.2 K under dynamic nitrogen atmosphere. While for PXRD analysis, the samples were tested by "Ultima IV Diffractometer (Rigaku Inc. Tokyo, Japan)" equipped with "Cu–Kα radiation 1.5406 Å". Samples were analyzed in the 2θ range from 3° to 60° using a step size of 0.02° (Babanejad et al., 2017).

2.4. Measurement of RHCl solubility

The solubility (mole fraction) of RHCl in the ten pure solvents was measured at "T = 298.2–323.2 K" and "p = 0.1 MPa" using a "static equilibrium method" (Higuchi and Connors, 1965). During each experiment, surplus RHCl was placed in known quantities of each solvent and vortexed (10 min) in a vigorous manner, and then transferred to a "shaking water bath (Model 1083; GFL GmbH, Burgwedel, Germany)" at 100 rpm for 72 h. Then, each solute–solvent mixture was withdrawn from the shaker bath and allowed to sit for 24 h to allow the RHCl particles to settle (Ahad et al., 2017). After 24 h, the supernatant was pipetted out carefully, suitably diluted with mobile phase, and analyzed for RHCl content using HPLC. The experimental solubility of RHCl (x_e) in the mole fraction was calculated using Eq. (1) (Almarri et al., 2017):

$$x_e = \frac{m_1/M_1}{m_1/M_1 + m_2/M_2} \quad (1)$$

Here, the symbols m_1 and m_2 are the masses of pure RHCl and the respective solvent (g), respectively. The symbols M_1 and M_2 are the molar masses of RHCl and the respective solvent (g mol^{-1}), respectively.

3. Results and discussion

3.1. Solid state characterization of RHCl

The solid state characterization of RHCl in pure and equilibrated form was carried out in order to investigate possible transformation of RHCl after equilibrium. Fig. 2A presents the DSC visual representation of pure RHCl, which showed a crystalline sharp peak at the fusion temperature (T_{fus}) of 543.3 K, with a fusion enthalpy (ΔH_{fus}) of 54.95 kJ mol^{-1} (Fig. 2A). The sharp crystalline peak of the drug indicated that RHCl was in a crystalline form and did not show evidence of polymorphic transformation. The DSC thermogram of equilibrated RHCl also showed a crystalline sharp peak at T_{fus} of 541.55 K with ΔH_{fus} value of 52.76 kJ mol^{-1} (Fig. 2B). The DSC spectra of pure and equilibrated RHCl were almost similar which suggested that it exists in pure crystalline form and did not transform to amorphous or polymorphic form after equilibrium. The T_{fus} value of 543.3 K for pure RHCl obtained in the present work is in good correspondence to the reported T_{fus} value of RHCl of 546.07 K (Shah et al., 2015).

TGA spectra of pure RHCl and equilibrated RHCl presented mass loss at around 561.38 K and 561.09 K respectively (Fig. 3A and B). The similar TGA spectra of pure and equilibrated RHCl indicated that it did not transform to amorphous or polymorphic form after equilibrium.