J. Chem. Thermodynamics 104 (2017) 218–229

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

journal homepage: www.elsevier.com/locate/jct

Solubility measurement, model evaluation and thermodynamic analysis of rivaroxaban polymorphs in organic solvents

Jinghuan Zhai, Zhenzhen Chen, Xijian Liu, Lijuan Zhang, Jie Lu *

School of Chemistry & Chemical Engineering, Shanghai University of Engineering Science, Shanghai 201620, China

ARTICLE INFO

Article history:
Received 18 April 2016
Received in revised form 24 September 2016
Accepted 26 September 2016
Available online 28 September 2016

Keywords:
Solubility
Polymorph
Rivaroxaban
Measurement
Thermodynamic modelling

ABSTRACT

This work measured the solubility of forms I and II of anticoagulant drug rivaroxaban in a series of organic solvents in which the solubility of form II was firstly reported as supplementary to the work of Zhang et al. [22]. A dynamic dissolution method was used to determine the solubility of both forms in acetonitrile, methyl acetate, acetone, 2-butanone, 3-pentanone and 2-hexanone from (273.15 to 318.15) K and in 1,4-dioxane from (288.15 to 333.15) K. The results showed that, the solubility of both forms generally increased with the temperature and decreased with an increase in the carbon number of ketones at the same temperature. The two forms were monotropically related and form II was the metastable form giving a higher solubility than form I. Meanwhile, such semiempirical thermodynamic models based on local composition concept as Wilson, nonrandom two-liquid (NRTL) and universal quasi chemical (UNIQUAC) equations with the correlation between model parameters and temperature were employed to model the studied solid-liquid equilibrium. It was found that UNIQUAC was the most appropriate model among the selected thermodynamic equations for the correlation of the solubility of rivaroxaban polymorphs in organic solvents. Finally, the apparent standard enthalpy change of dissolution was acquired from the experimental solubility data and the positive values of the apparent standard enthalpy change revealed that the dissolution of both forms of rivaroxaban in the selected solvents was an endothermic process.

1. Introduction

Crystallization refers to the formation of solid particles from a vapor, the solidification from a liquid melt or the formation of dispersed solids from a solution, which is extensively applied in food, pharmaceutical and chemical industries [1,2]. The solubility of a compound can provide vital thermodynamic information required to design crystallization processes, engineer crystal size distribution and understand phase behaviors in multiple-phase systems [3,4]. Meanwhile, as to a given compound particularly organic one, it usually has different polymorphs which normally have different solubilities. Therefore, it is necessary to acquire the solubility data of different polymorphs of a compound in various solvents over an abroad temperature range for the purpose of separation and purification through crystallization process [5,6].

However, the experimental determination of solubility in pure or mixed solvents is usually time-consuming, expensive and sometimes impracticable when a large quantity of the objective compound is unavailable. Reliable solubility prediction using validated thermodynamic models is being received much attention currently [7]. To date, a number of thermodynamic models that can be used to model liquid-liquid phase equilibrium have been improved to model solid-liquid equilibrium, including semiempirical models founded by local composition concept such as Wilson equation [8,9], UNIQUAC equation [10,11], NRTL equation [12] and UNIQUAC functional group activity coefficients (UNIFAC) equation [13], though their modelling performance is system-dependent. Han et al. [14] employed van't Hoff equation, modified Apelblat equation, λh equation, Wilson equation and NRTL equation to correlate the experimental solubility of ethyl 5-amino-4-cyano-3-(2-ethoxy-2-oxoethyl)-2-thiophene carboxylate in methanol, ethanol, 1-butanol, *n*-propanol, isopropanol, toluene, ethyl acetate, acetonitrile and acetone, and found that all the equations could agree well with the experimental data in which Wilson equation gave better correlation results than other models. Long et al. [15] compared the correlated solubility of benzoic acid in acetone, 2-propanol, acetic acid and cyclohexane by van't Hoff equation, λh equation, Wilson equation, NRTL equation and UNIQUAC equation with the experimental data, and concluded that the three-parameter NRTL equation could give the best correlation results. Yu et al. [16] used Scatchard-Hildebrand, Wilson, NRTL

* Corresponding author.
E-mail address: lujie@sues.edu.cn (J. Lu).

http://dx.doi.org/10.1016/j.jct.2016.09.036
0021-9614/

and UNIQUAC equations to correlate the experimental solubility data of phosphoric acid, P, P′-1,4-phenylene P, P, P′, P′-tetraphenyl ester (PAPTE) in methanol, ethanol, acetone, ethyl acetate, acetonitrile, methyl acetate, toluene, ether, *n*-propanol and *i*-propanol, and declared that all the equations could give satisfying correlations in which UNIQUAC worked best.

Rivaroxaban (5-chloro-N-{[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl] methyl}thiophene-2-carboxamide, as shown in Fig. 1) is a low molecular weight oral anticoagulant drug, which can directly inhibit the active form of serine protease Factor Xa (FXa) [17]. Today rivaroxaban has been used for the prevention and treatment of thromboembolic diseases, deep vein thrombosis (DVT) [18], pulmonary embolism (PE) and peripheral arterial occlusive diseases [19]. Rivaroxaban has been reported to have forms I, II, III in which form I (medicinal form) is regarded as the most stable form and form III seems a disappearing form [20,21]. In our previous work, Zhang et al. [22] have reported the solubility of form I of rivaroxaban in the binary mixtures of ethyl acetate with N,N-dimethylformamide, N,N-dimethylacetamide and tetrahydrofuran at temperatures ranging from (278.15 to 318.15) K. Sun et al. [23] have measured the solubility of the same form in the binary solvent mixtures of 1-methyl-2-pyrrolidinone with water, methanol, ethanol and isopropanol from (273.15 to 323.15) K. But, to the best of our knowledge, there is not any report on the solubility of form II. For expanding the fields of usage and the purification of rivaroxaban polymorphs, this work measured the solubility of forms I and II of rivaroxaban in acetonitrile, methyl acetate, acetone, 2-butanone, 3-pentanone and 2-hexanone from (273.15 to 318.15) K and in 1,4-dioxane from (288.15 to 333.15) K. Meanwhile, the applicability of Wilson, NRTL and UNIQUAC in the modelling of studied solid-liquid equilibrium was evaluated using the experimental solubility data. Finally, the apparent standard enthalpy change of dissolution was calculated by means of the modified van't Hoff analysis.

2. Experimental

2.1. Materials

Rivaroxaban (mass fraction purity greater than 0.995) was provided by Miss Boyle Chemical Co., Ltd. (Shanghai, China). All solvents used in this work were purchased from Sinopharm Reagent Co., Ltd. (Shanghai, China) with analytical reagent grade and used as received without further purification. More detailed information about the materials used in this work was listed in Table 1.

2.2. Preparation and characterization of polymorphs

Form I was obtained as the raw material, whereas form II was prepared in-house as described in reference [20]. Both forms of rivaroxaban were characterized by powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and Fourier transform infrared spectroscopy (FTIR).

PXRD was performed on a Rigaku Ultima-IV powder X-ray diffractometer (Woodlands, TX) with Cu Kα radiation (λ = 1.5418 Å) at 30 kV and 15 mA. The forms I and II were scanned from 5° to 40° (2θ) at a scanning rate of 0.02° s^{-1}. As shown in Fig. 2, the characteristic peaks of form I were at 8.9° and 24.7° while those of form II were at 12.8° and 20.8°.

DSC was conducted on a PerkinElmer DSC 8000 differential scanning calorimeter (Waltham, MA). The calibrations of the temperature and the enthalpy of fusion were performed with the extrapolated onset temperature and the enthalpy of the phase transition of indium (mass fraction purity, ⩾0.99999; onset temperature, 429.75 K; enthalpy of fusion, 3.2723 kJ·mol^{-1}) as the standard material [24]. All measurements for the calibration were repeated at least 3 times. In each DSC measurement (6–10 mg of sample was placed in an alumina crucible while an identical empty crucible was used as reference. The sample was scanned at 10 K·min^{-1} from the room temperature to 673.15 K under a nitrogen purge. The DSC thermograms of forms I and II of rivaroxaban are shown in Fig. 3. The melting point of form I was obtained at 501.41 K and its enthalpy of fusion was calculated as 46.68 kJ·mol^{-1}. The standard uncertainties were evaluated to be 3.90 K for temperature and 0.93 kJ·mol^{-1} for enthalpy of fusion. Meanwhile form II presented an exothermic peak at 464.84 K and the enthalpy of transition to form I was calculated as 5.29 kJ·mol^{-1}. The standard uncertainties were calculated to be 3.90 K for temperature and 0.11 kJ·mol^{-1} for enthalpy of transition. Compared with our previous work [22,23], the large standard uncertainties for phase transition temperatures may be resulted from sample preparation (particle size, stacking mode, weight, etc.), crystallinity or polymorphic impurities in samples, etc. Because there was no other peak between the points of transition and melting, forms I and II should be monotropically related according to the rule of heat-of-transition [25]. On the other hand, according to the heat-of-fusion rule [25], the enthalpy of transition of form II to form I could be expressed by:

$$\Delta H_{\mathrm{II}\to\mathrm{I}}(T = T_{m,\mathrm{I}}) \approx \Delta H_{fus,\mathrm{II}} - \Delta H_{fus,\mathrm{I}} + \frac{\Delta H_{fus,\mathrm{II}} - \Delta H_{c,\mathrm{II}}}{T_{m,\mathrm{II}} - T_{c,\mathrm{II}}} \times (T_{m,\mathrm{I}} - T_{m,\mathrm{II}}) \quad (1)$$

where $\Delta H_{\mathrm{II}\to\mathrm{I}}$ represents the enthalpy of transition of form II to form I, $\Delta H_{fus,\mathrm{I}}$ and $\Delta H_{fus,\mathrm{II}}$ are the enthalpy of fusion of form I and form II, respectively, $\Delta H_{c,\mathrm{II}}$ is the enthalpy of crystallization of form II, $T_{c,\mathrm{II}}$ is the crystallization temperature of form II, $T_{m,\mathrm{I}}$ and $T_{m,\mathrm{II}}$ are melting point of form I and form II, respectively. The melting point of form II ($T_{m,\mathrm{II}}$) is 476.15 K from reference [20]. Assuming that the fusion

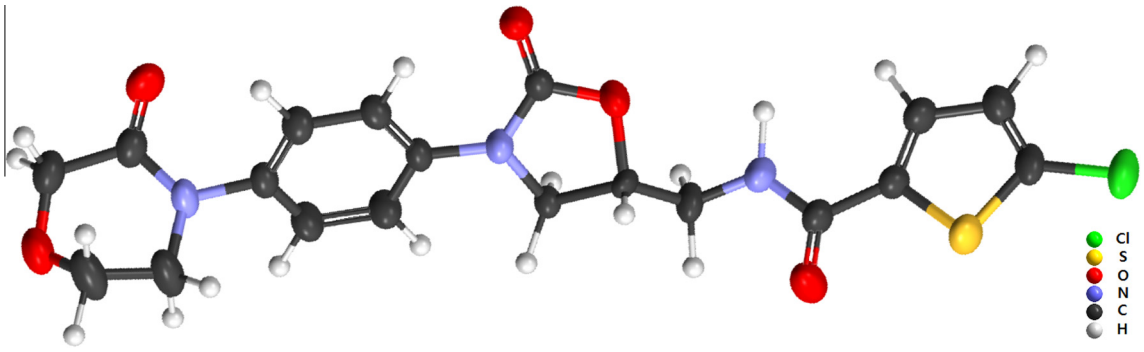

Fig. 1. Molecular structure of rivaroxaban.