Journal of Molecular Liquids 219 (2016) 350–353

Contents lists available at ScienceDirect

Journal of Molecular Liquids

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

Solubility and thermodynamic functions of deferasirox in different solvents

Hadi Chahiyan Boroujeni, Farrokh Gharib *

Chemistry Department, Shahid Beheshti University, G. C., Tehran, Evin, Iran

ARTICLE INFO

Article history:
Received 3 November 2015
Received in revised form 14 March 2016
Accepted 15 March 2016
Available online xxxx

Keywords:
Deferasirox
Solubility
Thermodynamic functions
Apelblat equation

ABSTRACT

The total solubility of deferasirox was determined in pure methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, acetonitrile, 1,4 dioxane and DMSO, at 25.0 °C as well as in aqueous solutions of methanol from 20.0 to 80.0% (v/v) methanol in a temperature range of 25.0–40.0 °C and constant ionic strength (0.1 mol·dm^{-3} NaCl). The UV–Vis spectrophotometric results have shown that by increasing both temperature and methanol mole fraction as well as decreasing the dielectric constant of the medium causes an increase in solubility of the drug with an exception in DMSO. The solubility data were correlated by the Apelblat equation and the thermodynamic functions of dissolution were calculated at the mean temperature (T_m) at different mole fractions of methanol using the modified Van't Hoff method. Considering the dielectric constant and the polarity/polarizability parameter of the solvents used, the relation between the nature of solvents, solubility, $\Delta H°$, and $\Delta S°$ of dissolution were determined and discussed.

1. Introduction

A disorder in the synthesis of hemoglobin known as thalassaemia is one of the most common genetic disease all over the world; unfortunately, with the birth of at least 60,000 infants with this problem every year [1]. Thalassemia is one of the first hereditary diseases which has been investigated and characterized during the past four decades [2]. A useful way to treat thalassemia major is blood transfusion [3]. However, frequent blood transfusions can result in iron overload in the body [4]. Excess iron accumulated in the body can also result from the hereditary causes, even in the absence of transfusions. The rate of intestinal absorption of dietary iron is lower than that related to chronic transfusions [5]. Although, iron is an essential element for humans and is required for many functions such as oxygen transport, energy production, mitochondrial aspiration, DNA synthesis, etc. [4,6], but the excess iron leads to the formation of insoluble complexes which are deposited in the internal organs such as liver and causing severe damaging them [4,7]. In the patients who have thalassemia major, congestive heart failure and arrhythmias that arises from iron overload are the leading cause of death [8].

Chelation therapy is the most convenient way to remove the excess iron from the body and consequently save the life of these patients [9]. There are some chelating agents for treatment of iron overload such as deferoxamine, deferiprone and deferasirox which form water soluble complexes with iron to remove it through kidney [10]. Deferasirox is a tridentate chelating drug that was authorized by the US Food and Drug Administration at 2005 [4]. This triazole compound has been designed using molecular modeling method [11] and has high selectivity to form complexes with iron even in the presence of other ions such as copper and zinc [12].

A basic step in characterization of a drug or any chemical substance is to determine its solubility behavior, which can give a demonstrative description of its physicochemical properties and thermodynamic functions [13]. One of the major problems in the pharmaceutical industry is low aqueous solubility of new chemical entities during their formulations. Unfortunately, at least 40% of new discovered drugs are practically insoluble in water [14]. There are a wide range of physical and chemical techniques for solubility enhancement of poorly soluble drugs which are described in detail in the literature [15]. In pre-formulation studies of the pharmaceutical industry, measuring the solubility of a drug in several conditions (different solvents and various temperatures and so forth), is an essential step. The corresponding information and plotted solubility-temperature curve is very useful [13]. Furthermore, the solubility behavior of a drug in the mixture of two or more solvents is very important because co-solvent blends have a wide application in purification methods and pre-formulation studies [16].

Although, deferasirox seems to control the total iron overloaded in humans, there is only a few literature data about its solubility and its thermodynamic functions [17–18]. So, the main objective of this study is to determine the total solubility of deferasirox in different solvents and temperatures to achieve a thermodynamic insight of the drug. In the present work, we have evaluated the effect of the co-solvent composition on the solubility and dissolution thermodynamics of deferasirox in some water-methanol mixtures in a temperature range between 25.0 and 40.0 °C and constant ionic strength (0.1 mol·dm^{-3} NaCl as

* Corresponding author.
E-mail address: f-gharib@sbu.ac.ir (F. Gharib).

http://dx.doi.org/10.1016/j.molliq.2016.03.044
0167-7322/

the supporting electrolyte). Furthermore, the solubility of the drug was determined in eight pure solvents at 25.0 °C and discussed.

2. Experimental

2.1. Materials

Deferasirox, scheme 1, supplied from Arasto Pharmaceutical Chemicals Inc. (Iran). Its purity was determined by an alkalimetric titration to be higher than 99.5%. For fixing the ionic strength in each experiment, the NaCl solutions were prepared by weighing appropriate pure salt that previously dried in an oven at 110 °C for 2 h. The organic solvents used including methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, acetonitrile, 1,4 dioxane and DMSO were all purchased from Merck as reagent grade materials and used without further purification. All solutions and dilution processes were performed using double-distilled water with a conductance equal to (2.0 ± 0.1) μS.

2.2. Procedure and measurements

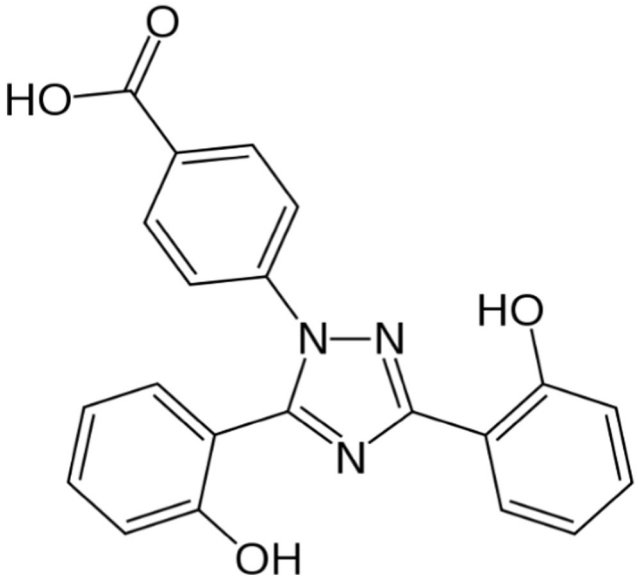
To determine the solubility of deferasirox in pure and mixed solvents, the saturated solutions were prepared by addition of an excess of the drug to the corresponding solutions containing various pure solvents or different mole fractions of methanol. The mixtures were sonicated for a few minutes and then were stirred in a mechanical shaker at least for 2 h. The mixtures were allowed to stand in a water bath at the appropriate temperature (±0.1 °C) at least 72 h to reach the equilibrium. The supernatant solutions were centrifuged for 15 min at the rate of 13,000 rpm and filtered through a cellulose membrane (at isothermal condition) to ensure that they were free of particulate matter before sampling. The absorbance of the diluted solutions were then recorded on a UV–Vis Shimadzu 2100 spectrophotometer in the range of 200 to 300 nm using thermostated matched 10 mm quartz cells. The concentration of the drug in each solution was then calculated using a calibration curve previously prepared.

3. Results and discussion

3.1. Solubility of deferasirox

Table 1 shows the total solubility of deferasirox in pure methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, acetonitrile, DMSO, and 1,4 dioxane at 25.0 °C. It can be seen from Table 1 that the minimum and the maximum solubility of deferasirox in the solvents used are in water and DMSO, respectively. Also, the total solubility of the drug is decreased by increasing the dielectric constant and π^* (polarity/polarizability parameter) of the solvents, due to the low polarity nature of deferasirox, except in the case of DMSO. Although, the polarity of DMSO is higher than the other organic solvents used [19], but the solubility of the drug in DMSO is significantly higher than acetonitrile, alcohols and dioxane. To describe this, it should be noted that solubility is the result and dependent to different forces like Van der Waals interactions and hydrogen bonding between the solute and solvent molecules as well as the polarity of solvent used [21–22], which was described in detail by Clark et al. [23].

A comparison between the alcohols used, Table 1, shows that by lengthening the hydrocarbon chain which is accompany with decreasing their polarity, causes the solute molecules preferentially solvated better by the less polar solvent and increases the solubility of the drug. The solubility data of deferasirox in the binary system of water-methanol solutions are listed in Table 2 and shown in Fig. 1 at different temperatures ranging from 25.0 to 40.0 °C. Plotting the logarithm of the solubility data versus the methanol mole fraction at each temperature, gives a linear curve with a positive slope. Also, the solubility of deferasirox can be roughly estimated in pure water by extrapolating the curves to the zero mole fraction of methanol.



Scheme 1. Chemical structure of deferasirox.

Table 1
The solubility of deferasirox in 8 pure solvents at 25.0 °C.

Solvent	Dielectric constant[a]	π^*[a]	Solubility mol·dm^{-3} [b]
Water	78.36	1.09	1.00×10^{-5}
DMSO	46.45	1.00	>0.8
Acetonitrile	35.94	0.66	1.74×10^{-3}
Methanol	32.66	0.60	3.41×10^{-3}
Ethanol	24.55	0.54	1.33×10^{-2}
1-Propanol	20.45	0.52	1.68×10^{-2}
2-Propanol	19.92	0.48	1.85×10^{-2}
1-Butanol	17.51	0.47	2.11×10^{-2}
Dioxane	2.10	0.49	1.91×10^{-1}

[a] The values are obtained from Ref. [20].
[b] The uncertainties in the solubility values are 0.01 or lower.

3.2. Apelblat model

Between the different methods, the modified semi-empirical Apelblat model is a suitable way to correlate solubility data against temperature [24–25]. This equation, Eq. (1), which is based on solid-liquid equilibrium theory, can provide excellent solubility data for dissolution of a solid in a solvent [22],

$$\ln S = A + B/T + C \ln T \quad (1)$$

Table 2
The solubility of deferasirox at different portions of methanol and various temperatures.

Methanol		Temperature, °C			
Percent v/v	Mole fraction	25.0	30.0	35.0	40.0
		$10^3 S$ (mol·dm^{-3}) [a]			
20.0	0.100	0.018	0.026	0.038	0.052
30.0	0.161	0.029	0.040	0.060	0.079
40.0	0.229	0.043	0.060	0.082	0.099
50.0	0.309	0.104	0.129	0.173	0.211
60.0	0.401	0.243	0.298	0.357	0.442
70.0	0.510	0.668	0.774	0.925	1.066
80.0	0.641	1.744	2.041	2.339	2.592

[a] The uncertainties in the solubility values are 0.003 or lower.