J. Chem. Thermodynamics 94 (2016) 230–233

Contents lists available at ScienceDirect

J. Chem. Thermodynamics

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

Solubility of rosuvastatin calcium in different neat solvents at different temperatures

Doaa H. Alshora [a], Nazrul Haq [b,c], Fars K. Alanazi [c], Mohamed A. Ibrahim [a], Faiyaz Shakeel [b,c,*]

[a] Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia
[b] Center of Excellence in Biotechnology Research, College of Science, King Saud University, P.O. Box 2460, Riyadh 11451, Saudi Arabia
[c] Kayyali Chair for Pharmaceutical Industry, Department of Pharmaceutics, College of Pharmacy, King Saud University, P.O. Box 2457, Riyadh 11451, Saudi Arabia

ARTICLE INFO

Article history:
Received 5 October 2015
Received in revised form 18 November 2015
Accepted 19 November 2015
Available online 2 December 2015

Keywords:
Correlation
Neat solvent
Rosuvastatin calcium
Solubility

ABSTRACT

In the current research work, the solubility of rosuvastatin calcium (ROSCa) in seven different neat solvents such as water, ethanol, 1-butanol, 2-butanol, ethylene glycol (EG), isopropyl alcohol (IPA) and propane-1,2-diol (PG) was measured at five different temperatures *i.e.* T = (298.15 to 318.15) K and atmospheric pressure. Values of the experimental solubility of ROSCa were correlated with Apelblat and ideal models which showed good correlation and model fitting. The solubility (as mole fraction) of ROSCa was recorded highest in PG ($1.89 \cdot 10^{-2}$ at T = 318.15 K) followed by 1-butanol ($8.20 \cdot 10^{-4}$ at T = 318.15 K), ethanol ($6.81 \cdot 10^{-4}$ at T = 318.15 K), IPA ($5.66 \cdot 10^{-4}$ at T = 318.15 K), EG ($5.03 \cdot 10^{-4}$ at T = 318.15 K), 2-butanol ($1.08 \cdot 10^{-4}$ at T = 318.15 K) and water ($1.40 \cdot 10^{-5}$ at T = 318.15 K). The experimental results from this research work would be helpful in the development of conventional and advanced liquid dosage forms of ROSCa.

1. Introduction

Chemically, rosuvastatin calcium (ROSCa) is (E)-7-[4-(4-fluorophenyl)-6-isopropyl-2-[methyl(methylsulfonyl)amino]pyrimidin-5-yl]-(3R,5S)-3,5-dihydroxyhept-6-enoic acid calcium salt (molecular structure is presented in figure 1) [1,2]. It is a synthetic lipid lowering drug which is also used in the treatment of osteoporosis, Alzheimer disease and prostatic hyperplasia [1–3]. Recently, ROSCa also shows potential anticancer effects against Caco-2 cells [4]. It shows poor aqueous solubility due to its crystalline nature [2]. The oral administration of ROSCa presents only 20% bioavailability due to its extensive first pass metabolism and poor aqueous solubility [2,3]. The solubility of drugs/pharmaceuticals in neat solvents are valuable in various fields of pharmaceutical sciences [5–7]. It is very important to measure the solubility of ROSCa in solvents that could enhance the industrial production of ROSCa. Water has been reported as the best solvent for this purpose because it offers several advantages such as low cost, non-toxic and no pharmaceutical limits. Other commonly used neat solvents in pharmaceutical production of poorly soluble drugs are reported as propylene glycol (PG), ethyl alcohol and polyethylene glycols because they are also safe and non-toxic [7–9]. Some pharmaceutical technologies such as liquisolid technology [10], microemulsion technology [11], liquid self-microemulsifying drug delivery system [12], liquid self-nanoemulsifying drug delivery system (SNEDDS) [2,13] and solid SNEDDS [4] have been investigated in order to enhance solubility, dissolution rate and bioavailability of ROSCa. The mole fraction solubility of crystalline ROSCa in water has been reported as $6.08 \cdot 10^{-6}$ at T = 298.15 K [12]. The solubility of crystalline ROSCa in various oils such as vegetable oils, essential oils, semisynthetic oils and medium chain triglycerides, surfactants such as Tween-20, Tween-40, Tween-60, Tween-80, Labrasol, Cremophor-EL and Brij, cosurfactants such as Span-20, Span-80, Captex-100, Caprol-10G-100, Capmul-MCM and Capmul-MCM-C8 had also been reported in literature [2]. Nevertheless, the solubility values with respect to temperature of crystalline ROSCa in various neat solvents such as water, ethanol, PG, ethylene glycol (EG), isopropyl alcohol (IPA), 1-butanol and 2-butanol had not been reported. Hence, in this research work, the solubility of crystalline ROSCa in various neat solvents such as water, ethanol, PG, EG, IPA, 1-butanol and 2-butanol were measured at T = 298.15 K to T = 318.15 K and p = 0.1 MPa using an isothermal method. The results obtained in this research work could be useful in preformulation studies and dosage form design of ROSCa in the pharmaceutical industry.

* Corresponding author at: Center of Excellence in Biotechnology Research, College of Science, King Saud University, Riyadh, Saudi Arabia. Tel.: +966 537507318.
E-mail address: faiyazs@fastmail.fm (F. Shakeel).

http://dx.doi.org/10.1016/j.jct.2015.11.019
0021-9614/

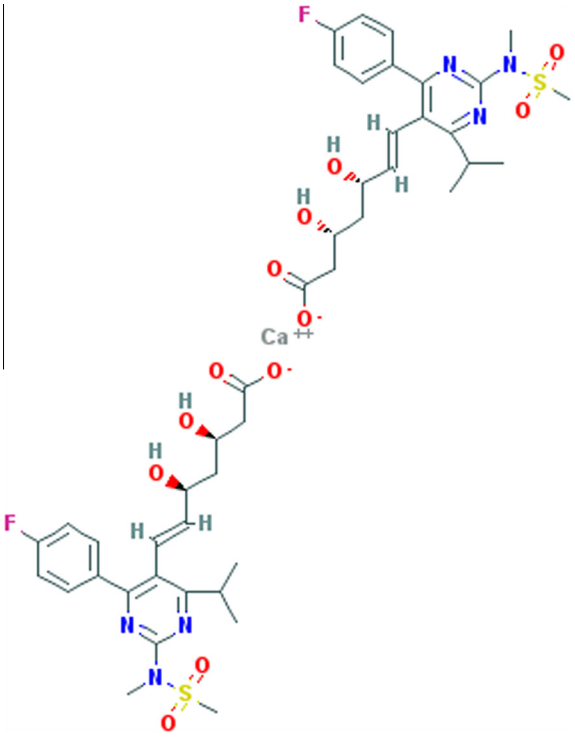

FIGURE 1. Molecular structure of rosuvastatin calcium (ROSCa).

2. Experimental

2.1. Materials

ROSCa was obtained from Beijing Mesochem Technology CO. Ltd. (Beijing, China). EG (IUPAC name: ethane-1,2-diol) and PG (IUPAC name: propane-1,2-diol) were obtained from Sigma Aldrich (St. Louis, MO). IPA (IUPAC name: 2-propanol), ethyl alcohol (IUPAC name: ethanol), 1-butyl alcohol (IUPAC name: 1-butanol) and 2-butyl alcohol (IUPAC name: 2-butanol) were procured from Scharlau Chemicals (Berlin, Germany). The other material used was water which was collected from Milli-Q water unit. The information regarding materials used in this research work is presented in table 1.

2.2. Measurement of ROSCa solubility

The solubility of crystalline ROSCa in seven neat solvents was measured by an isothermal method [14]. Each experiment was conducted at $T = 298.15$ K to $T = 318.15$ K and $p = 0.1$ MPa. The excess amount of crystalline ROSCa was added in known amounts of each neat solvent in 10 g capacity glass vials. Each experiment was conducted in triplicate at controlled temperature. The glass vials containing concentrated suspension of ROSCa were transferred to a biological shaker (Julabo, PA) at 100 rpm for 120 h. Preliminary studies were carried out to optimize equilibrium time and it was recorded as 120 h. After 120 h, the glass vials were removed from the biological shaker. All the glass vials were allowed to settle ROSCa particles for 2 h [6,7]. After settling of ROSCa particles, supernatants were carefully withdrawn from each sample, diluted and subjected for analysis of ROSCa content spectrophotometrically at 244 nm [2]. The applied analytical technique was observed to be linear in the range of (1 to 25) $\mu g \cdot g^{-1}$ with correlation coefficient (R^2) of 0.9974. Values of the experimental solubility of crystalline ROSCa as mole fraction (x_e) were calculated according to methods reported in literature [7,9].

3. Results and discussion

3.1. Solubility of ROSCa

Values of the experimental solubility of ROSCa in seven different neat solvents at five different temperatures and atmospheric pressure are presented in table 2. The solubility of crystalline ROSCa with respect to temperature in various neat solvents such as water, ethanol, PG, EG, IPA, 1-butanol and 2-butanol had not been reported. The solubility of ROSCa (as mole fraction) in water has been reported as $6.08 \cdot 10^{-6}$ at $T = 298.15$ K [12]. In this research work, the solubility of ROSCa (as mole fraction) in water was recorded as $5.40 \cdot 10^{-6}$ at $T = 298.15$ K. This value was very close to the reported solubility value of ROSCa in water which indicates good agreement of experimental values data with those reported. It is observed that the x_e values of ROSCa increase nonlinearly with the rise in temperature in all seven neat solvents. The x_e values of crystalline ROSCa were recorded highest in PG $1.89 \cdot 10^{-2}$ at $T = 318.15$ K) followed by 1-butanol ($8.20 \cdot 10^{-4}$ at $T = 318.15$ K), ethanol ($6.81 \cdot 10^{-4}$ at $T = 318.15$ K), IPA ($5.66 \cdot 10^{-4}$ at $T = 318.15$ K), EG ($5.03 \cdot 10^{-4}$ at $T = 318.15$ K), 2-butanol ($1.08 \cdot 10^{-4}$ at $T = 318.15$ K) and water ($1.40 \cdot 10^{-5}$ at $T = 318.15$ K) at all five temperatures investigated. Generally, the x_e values of ROSCa are higher in neat solvents with alcoholic groups (–OH) such as ethanol, IPA, 1-butanol, 2-butanol, EG and PG in comparison with water. This observation was probably due to strong molecular solvation of ROSCa with solvents with –OH groups because ROSCa also has several –OH groups in its molecular structure. The x_e values of ROSCa in PG were significantly higher than its x_e values in EG. Although, EG and PG have two –OH groups in their molecular structures but the solubilities of ROSCa were significantly different in these solvents. This observation was possible because PG is less polar than EG and molar mass of PG is also higher than EG. This observation indicated that the polarity of solute and solvents have greater impact on solubility. Although, only one –OH is present in ethanol, IPA, 1-butanol and 2-butanol, the solubility of ROSCa was sufficiently higher in ethanol, IPA and 1-butanol in comparison with 2-butanol. This observation could be possibly due to similar polarity of ROSCa as that of

TABLE 1
A sample table for materials used in this research work.

Materials	Mass fraction purity	Purification method	Analysis method	Source
Rosuvastatin calcium	0.993	None	HPLC	Beijing Mesochem Technology
Ethanol	0.999	None	GC	Scharlau Laboratory
Ethylene glycol	0.994	None	GC	Sigma Aldrich
Propylene glycol	0.995	None	GC	Sigma Aldrich
IPA	0.997	None	GC	Scharlau Laboratory
1-Butanol	0.995	None	GC	Scharlau Laboratory
2-Butanol	0.993	None	GC	Scharlau Laboratory
Water		None		Milli-Q unit