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ORIGINAL ARTICLE

Evaluation of solvents' effect on solubility, intermolecular interaction energies and habit of ascorbic acid crystals

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KEYWORDS

Solubility;
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Abstract Solubility of active pharmaceutical ingredient (API) in solvents is very important for drug development and manufacturing. Solubility data may provide further information such as thermochemical properties and intermolecular interactions that may lead to a better understanding of the formation of API crystals. In this study, solubility of ascorbic acid was determined by gravimetric method in four different commonly used polar protic solvents: water, methanol, ethanol and 2-propanol. The solubility of ascorbic acid crystal was also predicted using Conductor-like Screening Model – Realistic Solvent (COSMO-RS) approach. In this computational analysis, the generated ΔG values are based on the solubilities that were experimentally obtained to simulate the intermolecular forces. The intermolecular interaction data from COSMO-RS provide an insight into the relationship between the intermolecular interactions and its crystal habit across four different polar protic solvents. The habit of the crystals was then determined using light microscopy and scanning electron microscopy techniques, while the polymorphic form of the crystals was identified by X-ray powder diffraction and single X-ray diffraction techniques. The solubility and characterization data showed that the solvents with high polarity increased the solubility of ascorbic acid. The data also showed that different solvent polarity influenced the crystal habit, but did not change the crystal structure to form a new polymorph.

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1. Introduction

Ascorbic acid ((5R)-[(1S)-1,2-Dihydroxyethyl]-3,4-dihydroxy furan-2(5*H*)-one, $C_6H_8O_6$) is commonly used as ingredient in pharmaceutical, cosmetic, and dietary supplement [1].

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Nomenclature

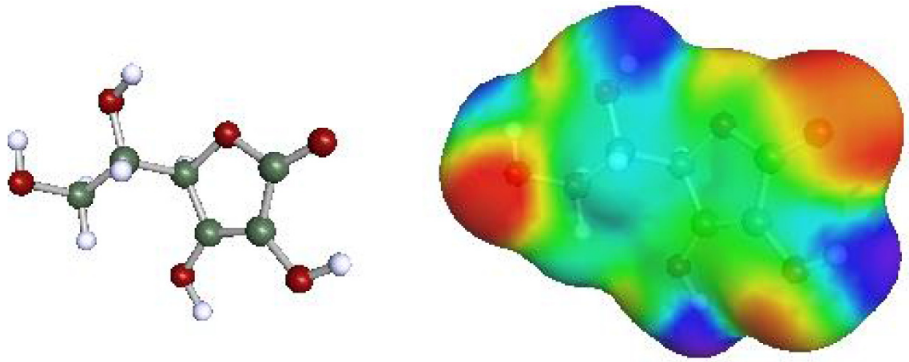
w_d	solute dry weight	a_{eff}	effective surface segment surface area
w_o	initial solute weight	σ	surface-segment charge-density distribution (e/Å2)
w_w	solute wet weight/weight solute and solvent	σ'	electrostatic misfit parameter ((J Å^2)/(mol e^2))
m_1	mass of solute	τ_{vdW}	element specific parameter ((J Å^2)/(mol e^2))
M_1	molecular mass of solute	R	ideal gas constant
M_2	mass of solvent	T_{melt}	melting point temperature (K)
M_2	molecular mass of solvent	π	pi
E_{misfit}	electrostatic misfit energy (J)	ΔHf_{us}	enthalpy of fusion (kJ/kmol)
E_{HB}	hydrogen bond energy (J)	ΔS_{fus}	entropy of fusion (kJ kmol^{-1} K^{-1})
E_{vdW}	van der Waals energy (J)		

Fig. 1 shows the ascorbic acid molecular structure and COSMO cavity image. Ascorbic acid is classified as a polar organic molecule due to the presence of four hydroxyl groups. The habits of ascorbic acid crystals are reported to be cubic, plate or needle-like depending on factors such as the type of solvent used [2]. The selection of solvents may also determine whether the ascorbic acid can exist in the same crystal system or with some habit modifications [3,4].

Ascorbic acid, which is typically produced either from biological or chemical synthesis routes, is separated or purified by crystallization process which requires solubility data as a function of temperature and solvent types or compositions [5]. The solubility data can be obtained experimentally via isothermal-gravimetric method [6–8]. Shalmashi and Eliassi (2008) have reported the solubility of ascorbic acid in various solvents with temperature ranging from 293 to 323 K obtained using isothermal-gravimetric method [9]. Various literatures have also reported the impact of solvents on the habit of ascorbic acid crystals [10–12]. Those crystallized from methanol were reported to be needle-like, while those from water typically formed plate-like prism or cubic [11,13,14].

It has been reported that intermolecular interaction energies such as hydrogen bond (E_{HB}) and van der Waals (E_{vdw}) between solute and solvents play an important role in determining degree of solubility and shape formation of pharmaceutical compound [8,15,16]. To date the molecular interaction energy that leads to the different solubility behavior and crystal habit of ascorbic acid is still poorly understood. The intermolecular interaction can be investigated using Conductor-like Screening Model for Real solvents (COSMO-RS, COSMO*logic* GmbH & Co. KG, Leverkusen, Germany) developed by Klamt and co-workers [17,18]. Besides being able to quickly predict thermodynamics properties of fluids, COSMO-RS is also able to predict molecular interaction in different solutions [19–21].

In this work, the solubilities of ascorbic acid in various polar protic solvents namely water, methanol, ethanol, and 2-propanol were determined using isothermal-gravimetric method and the results obtained were compared with previous works. The solubility data and the molecular interaction energy were also predicted using COSMO-RS simulation. The molecular interaction energy obtained during COSMO-RS calculation is used to find the relationship between the effect of solvents' polarity on ascorbic acid solubility and crystal habit. The ascorbic acid crystals produced were characterized using optical microscopy, scanning electron microscopy (SEM), X-ray powder diffractometry (XRPD) and single X-ray diffractometry (single XRD).



(a) (b)

Fig. 1 L-ascorbic acid (a) molecular structure; and (b) COSMO sigma profile image. Sigma profile of ascorbic acid is color coded by the polarization charge density σ. Red areas denote strongly negative parts of the molecular surface and hence strongly positive values of σ. Deep blue marks denote strongly positive surface regions (strongly negative σ) and green denotes nonpolar surface.

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2. Experimental and computational method

2.1. Materials

The crystalline powder of ascorbic acid used in this work was purchased from Fisher Scientific with a purity of 99.9%. The solvents used are methanol, ethanol, 2-propanol and double distilled water. Except water, all other solvents were of analytical reagent grade with purity of 99.8% purchased from Fisher Scientific. Table 1 tabulates some physical properties of the solvents used. The relative polarity values of solvents tabulated in Table 1 are calculated with respect to the water polarity value.

2.2. Solubility measurements

The solubilities of ascorbic acid in four polar protic solvents, namely 2-propanol, ethanol, methanol and water, were determined at temperatures ranging from 303 K to 323 K using isothermal-gravimetric method [6]. These solvents are used in many other research related to ascorbic acid crystals and processes [22,23]. Excess of ascorbic acid powder was added to glass vials containing 10 mL of the respective solvents. The vials were then shaken at the targeted temperature using a temperature-controlled thermomixer shaker (Eppendorf, Hamburg, Germany) for 8 h to reach equilibrium. The solutions were then filtered using 0.45 μm syringe filters with PTFE membrane to separate the solutions from the solids. The obtained supernatants were transferred to glass petri dishes, which were weighed before the transfer (empty weight, w_o) and weighed again immediately after the transfer (wet weight, w_w). The supernatants on the dishes were then left overnight to evaporate in a vacuum oven at a temperature of 50 °C. The petri dishes were weighed then dried, weighed again and dried repeatedly until constant weights were obtained (dry weight, w_d). The solubility, S of the solute in the solvent at a targeted temperature was calculated as follows:

$$S = \frac{w_d - w_o}{w_w - w_d} \tag{1}$$

The mole fraction solubility, x_1 at the targeted temperature was obtained using the following equation:

$$x_1 = \frac{\frac{m_1}{M_1}}{\frac{m_1}{M_1} + \frac{m_2}{M_2}} \tag{2}$$

where m_1 and m_2 are weight of solute and solvent, respectively in g. M_1 and M_2 are the molecular weight of the solute and solvents, respectively.

Table 1 Some physical properties of solvents used.

Solvent	Chemical formula	Boiling point (°C)	Density (g/mL)	Relative Polarity
Water	H_2O	100	0.998	1
Methanol	CH_4O	64.6	0.791	0.762
Ethanol	C_2H_6O	78.5	0.789	0.654
2-Propanol	C_3H_8O	82.4	0.785	0.546

2.3. COSMO-RS computational method

The 3D single molecular structure of ascorbic acid used for solubility calculation was obtained from Cambridge Crystallographic Data Center (CCDC, Cambridge, UK) [39]. The ascorbic acid molecular structure was optimized using TURBOMOLE program package version 7.0 (COSMOlogic GmbH & Co. KG, Leverkusen, Germany) by applying Density Functional Theory (DFT) with Becke-Perdew triple valence electrons plus polarization function (BP-TZVP) level with the Resolution Identity (RI) approximation. RI approximation, which is also known as density fitting, is a method to reduce the computational load associated with a large number of electron repulsion. The input files for water, methanol, ethanol and 2-propanol were taken directly from the COSMO-RS database.

Conductor-like Screening Model for Real Solvents (COSMO-RS, COSMOlogic GmbH & Co. KG, Leverkusen, Germany) continuum solvation was applied to simulate a virtual conductor environment for ascorbic acid molecule and to evaluate the charge density (σ-profile) [24] on the three dimensions surface molecule. COSMO-RS is based on surface interaction model, considers molecular charge densities rather than the interaction of groups which are obtained by molecular quantum chemical COSMO-RS calculations. The main feature of COSMO-RS is probability distribution of screening charges for the molecule solvated in a perfect conductor environment. σ-profile values have been proven to be an excellent parameter to a predictive quantification of conductor HB energy in COSMO-RS simulation. The statistical thermodynamics of the molecules interaction was used to calculate the interaction of the pair-wise interacting surface segments (σ, σ′). The three main coulomb interactions evaluated were electrostatic energy (E_{misfit}), hydrogen bond (E_{HB}) and van der Waals (E_{vdW}).

The solubility predictions were performed in COSMO*thermX* (COSMOlogic GmbH & Co. KG, Leverkusen, Germany) using solubility tool with BP/TZVP parameterization. The predictions utilized the following iterative algorithm:

$$\log_{10}\left(x_j^{sol(n+1)} = \left[\mu_j^{pure} - \mu_j^S\left(x_j^{sol(n)}\right) - \max\left(0, \Delta G_{fus}\right)\right]/(RT\ln(10))\right) \tag{3}$$

where $x_j^{sol}$is the mole fraction of solid dissolved in the targeted solvent, $\mu_j^{Pure}$is the chemical potential of pure compound j, $\mu_j^L$is the chemical potential of pure compound j at infinite dilution in the solvent, S and $\Delta G_{fus}$is the Gibbs free energy of fusion. The $\Delta G_{fus}$of solute at a particular temperature, T was estimated by reference solubility method. In this work, the solubility data of ascorbic acid at a particular temperature are used to determine ΔG_{fus} by solving Eq. (3).

2.4. Crystallization of ascorbic acid

Ascorbic acid crystals were prepared by evaporation method [2,11,12]. The method involved dissolving a certain amount of ascorbic acid powder in 25 mL of the respective solvents until they were saturated. Then the saturated solutions were shaken for 8 h at 30 °C in a temperature-controlled thermomixer shaker. After that, the solutions were left unshaken overnight at 30 °C to equilibrate. An aliquot of supernatant from each of the solutions was then filtered using 0.45 μm

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syringe filter. The supernatants were evaporated in a vacuum oven at 50 °C until the solutes crystallized. The crystals produced were then weighed and dried, repeatedly, until constant weights were obtained to ensure they were completely dried.

2.5. Characterization of ascorbic acid crystals

2.5.1. Optical microscopy

The habit of the ascorbic acid crystals was observed and captured using an optical microscope, Nikon Diaphot 300, equipped with DinoXScope camera (Nikon, Tokyo, Japan) operating at a standard 4× magnification.

2.5.2. Scanning electron microscopy (SEM)

The habit of the ascorbic acid crystals was further observed and captured using Scanning Electron Microscope, Evo 50 (Zeiss, Jena, Germany). A small amount of samples were scattered on double-sided adhesive carbon tabs mounted on SEM stubs and coated with gold (Au). The samples were examined by Evo 50 operating at 15 kV.

2.5.3. X-ray powder diffractometry (XRPD)

The identity of ascorbic acid crystals was determined using XRPD with D8 Advanced – Bruker axS model (Bruker, Massachusetts, USA). Samples of ascorbic acid were gently grounded with mortar and mounted onto a flat silicone sample holder. The samples were scanned from 5.0° to 60.0° of 2θ range using exposure of 0.1 s/step and 0.025 step size [11]. The data from XRPD were evaluated using DIFFRAC.EVA software (Bruker, Massachusetts, USA).

2.5.4. Single crystal X-ray diffractometry (SCXRD)

Diffraction data were collected by ω-scan technique on a Bruker SMART APEX II CCD diffractometer (Bruker, Massachusetts, USA) equipped with CuKα radiation (λ = 1.5418 Å). The unit cell parameters were determined by the least-squares methods using 1292 reflections in the 2θ range 5.5–55.6°. The data were corrected for Lorentz-polarization and absorption effects. The structure was solved by direct methods using the SHELXS program and refined by a full-matrix least-squares calculation on F2 using SHELXL. All H atoms were placed at calculated positions and treated using a riding model, fixing the C–H distances at 0.96 Å and U iso (H) = 1.2U eq (C)].

3. Results & discussion

3.1. Effects of polar protic solvents on ascorbic acid solubility

The experimental solubility data of ascorbic acid in water, methanol, ethanol and 2-propanol from 303 to 323 K in comparison with those obtained by Shalmashi and Eliaasi (2008) [9] are presented in Fig. 2. Based on the figure, the experimental solubility data obtained in the current work are in agreement with those reported in the previous work with only 2% of average deviation. The deviations may result from differences in equipment, samples and measured conditions.

As shown in Fig. 2, the solubility of ascorbic acid in each solvent increases as the temperature increases. This is because the higher the temperature, the higher the molecules' kinetic

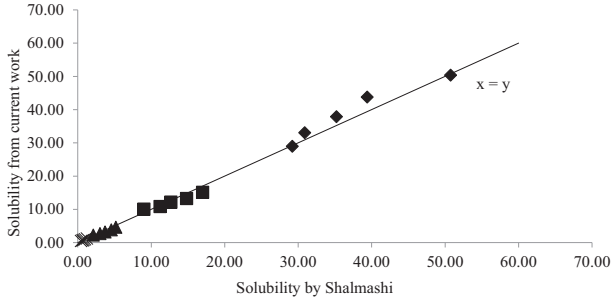


Fig. 2 Comparison between solubility data of current work and work done by Shalmashi (2008) for solubility of ascorbic acid in water (◆), methanol (■), ethanol (▲) and 2-propanol (×). Solid lines represents linear line x = y.

energies, which in turn leads to more effective collision and intermolecular interactions between solute and solvents molecules [25]. Within a temperature range of 303–323 K, the order of ascorbic acid solubility is the highest in water followed by methanol, ethanol, and 2-propanol. This order indicates that the solubility of ascorbic acid increases with the decrease in molecular size and the increase in polarity of the solvents. It also can be observed from the solubility data that the solubilities of ascorbic acid in various solvents are in the same order as the solvents' polarity tabulated in Table 1, which is the highest in water followed by methanol, ethanol and 2-propanol. The solvent with high polarity value tends to demonstrate high hydrogen bonding acceptor (HBA) and hydrogen bonding donor (HBD) propensity [26] as compared to lower polarity solvents.

3.2. Thermodynamic properties of the saturated solutions of ascorbic acid.

van't Hoff plots of the experimental solubility of ascorbic acid in water, methanol, ethanol and 2-propanol at temperatures between 303 K and 328 K are presented in Fig. 3. The enthalpy of dissolution (ΔH_{diss})and entropy of dissolution (ΔS_{diss})can then be respectively calculated from each of the plot using van't Hoff equation:

$$\ln x = -\frac{\Delta H_{diss}}{RT} + \frac{\Delta S_{diss}}{R} \quad (4)$$

where x is the solubility of ascorbic acid in mole fraction. Knowing the values of $\Delta H_{diss}$and ΔS_{diss}, the change of Gibbs free energy (ΔG) of the ascorbic acid dissolution in different

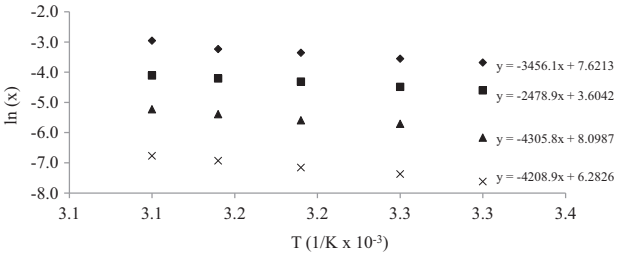


Fig. 3 van't Hoff plot of ascorbic acid in water (◆), methanol (■), ethanol (▲) and 2-propanol (×).

Table 2 Calculated ΔH, ΔS and ΔG from van't Hoff linear plot.

	ΔG at 308 K kJ mol^{-1}	ΔH kJ mol^{-1}	ΔS kJ mol^{-1}
Water	12.82	21.84	42.24
Methanol	13.48	25.25	44.38
Ethanol	20.75	36.06	68.38
2-Propanol	21.18	40.48	69.79

solvents can then be calculated using the Gibbs-Helmholtz equation:

$$\Delta G_{diss} = \Delta H_{diss} - T\Delta S_{diss} \quad (5)$$

The determined values for ΔH_{diss}, $\Delta S_{diss}$and $\Delta G_{diss}$are tabulated in Table 2. All values are positive, which indicates that the dissolution processes were endothermic [27], entropy driven and not spontaneous. The highest values of $\Delta H_{diss}$and ΔG_{diss}were obtained during the dissolution of ascorbic acid in 2-propanol, which indicates low solubility or poor solute–solvent interactions. $\Delta H_{diss}$and ΔG_{diss}were the lowest ones in water, which indicate high solubility. The increase of $\Delta H_{diss}$with the decrease in solvent polarity shows that ascorbic acid dissolution absorbed more energy as the polarity of the solvent decrease. This suggests that in order for ascorbic acid to dissolve in less polar solvent, more energy will be required to overcome its solute–solute intermolecular forces. $\Delta G$is at its lowest in water, which suggest that the ascorbic acid crystal formed from water is the most stable as compared to the other solvents.

3.3. Solubility prediction and intermolecular interaction energies

Fig. 4 shows sigma profile (σ-profile) of water, methanol, ethanol and 2-propanol. A σ-profile is used to estimate the interaction between solute and solvent. Water has been found to have two peaks at strongly positive and negative parts of the σ-profile, which indicates water as a stable organic molecule that is able to accept or donate its partial charges to form hydrogen bond. A molecule that shows a peak at σ-region beyond ± 1 e/Å^2 is considered as strongly polar and therefore has a greater potential to form hydrogen bond [28]. The σ-profiles of methanol, ethanol and 2-propanol show the same peak value at 2σ as water in the positive σ-range indicating that all solvents have almost the same negatively polar hydrogen contributed in forming hydrogen bond. However, in the negative σ-range, the intensity of the peak for other solvents as compared to water is less than 50%. This is an indication that methanol, ethanol and 2-propanol have less positive polar hydrogen, hence lesser capacity to accept partial charges to form hydrogen bond, in comparison to water. In addition, similar polarity between solvent and solute will improve the solute solubility. Due to this, it might be easier for hydroxyl groups in ascorbic acid molecule to establish hydrogen bonds with water molecule, and consequently contribute to the high solubility value.

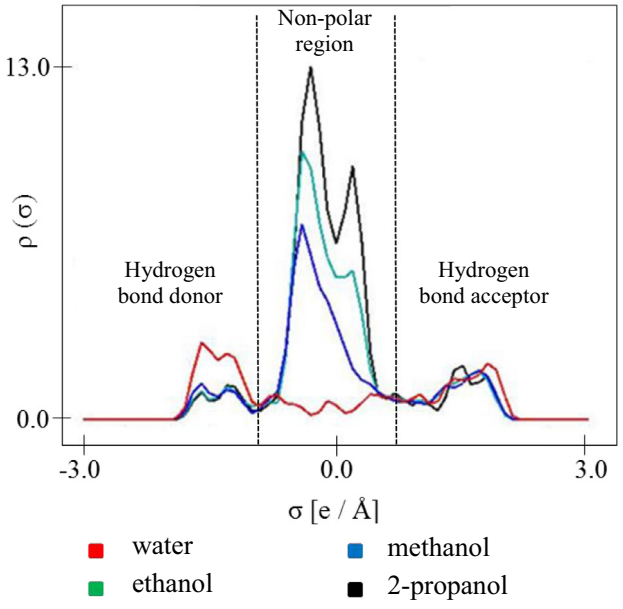


Fig. 4 σ-profiles of water, methanol, ethanol and 2-propanol.

COSMO-RS normally predicts the solubility of a compound based on the compound's enthalpy of fusion (ΔH_f) and melting temperature (T_m). However, ascorbic acid, which has four hydroxyl groups, practically possess no definitive T_m as the compound decomposes before it can reach its melting temperature [29]. The presence of a multiple hydroxyl groups contributes to the compound's high melting temperature because of the formation of many hydrogen bonds, while at the same time it exhibits low decomposition temperature because of the rise in reactivity due to the presence of multiple hydroxyls group. An alternative approach has been used to predict the solubility of ascorbic acid, which is based on its ΔG that was obtained using Eq. (4).

Plots of the predicted versus experimental results for solubility of ascorbic acid in water, methanol, ethanol and 2-propanol are presented in Fig. 5. Data of the predicted experimental results for solubility of ascorbic acid are presented in Table 3. The pattern of the curves of the predicted and experimental results are comparable. The values of the predicted solubility of water, however, are at least 50% higher than the experimental values. The reason of this difference is maybe due to limitation of predicted approach using Gibbs energy that it does not take into account the additional strength of hydrogen bond due to the highly polar ascorbic

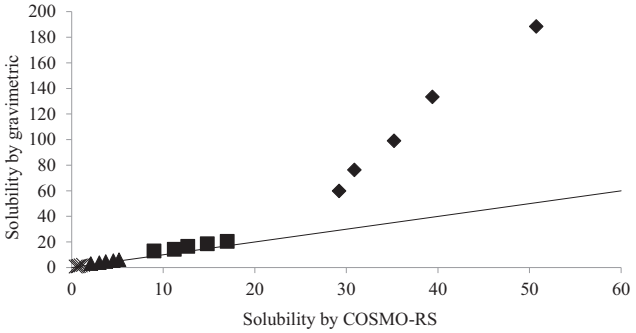
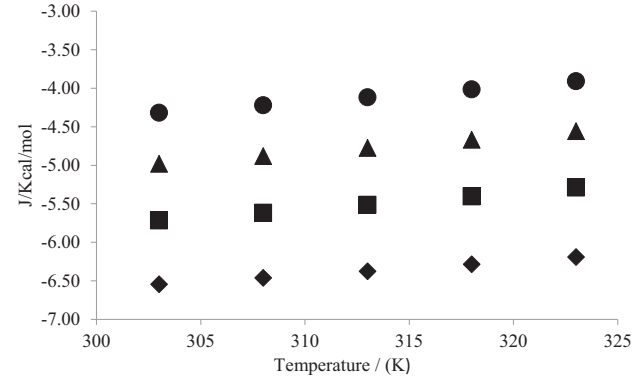


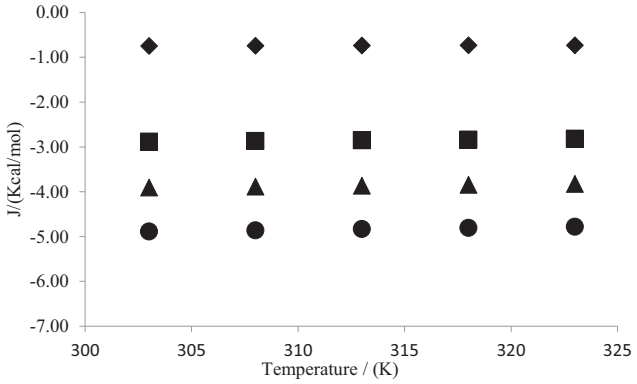
Fig. 5 Comparison between ascorbic acid solubility data of current work and solubility data obtained by COSMO-RS in water (◆), methanol (■), ethanol (▲) and 2-propanol (×). Solid lines represents linear line x = y.

Table 3 Saturated mole fraction solubility x of ascorbic acid in different organic solvents at experimental pressure (0.1 MPa) and temperatures T from (303 to 323) K.

Solvent	T (K)	$10^3 x_{exp}$	$10^3 x_{COSMO}$	Standard deviation for x_{exp}
Water	303	25.20	59.90	0.02
	308	28.70	76.40	0.03
	313	35.00	99.10	0.03
	318	39.40	133.50	0.03
	323	52.10	188.50	0.04
Methanol	303	10.10	13.00	0.04
	308	11.30	14.30	0.02
	313	13.50	16.50	0.05
	318	14.90	18.50	0.05
	323	16.50	20.40	0.07
Ethanol	303	2.10	3.20	0.04
	308	3.30	3.90	0.05
	313	3.70	4.70	0.04
	318	4.60	5.50	0.07
	323	5.40	6.10	0.06
2-Propanol	303	0.50	0.80	0.08
	308	0.60	1.00	0.07
	313	0.80	1.20	0.08
	318	1.00	1.70	0.10
	323	1.20	2.10	0.09



(a) Hydrogen bond



(b) Van der Waals

Fig. 6 The intermolecular strength in water (◆), methanol (■), ethanol (▲) and 2-propanol (●).

acid and water solvent-solute interaction. Although the absolute solubility of ascorbic acid cannot be predicted, COSMO-RS can quantitatively determine a reasonable and comparable solubility in different solvents. Since measuring solubility of an API in different solvents is highly time consuming task, the introduction of a fast and reliable method to predict the solubility of an API in any given solvent is the way forward. The method would be particularly useful in the screening for a suitable solvent.

Fig. 6 illustrates the hydrogen bonding and van der Waals interaction versus temperature for each solvent used in this work. These interactions were quantified from the solubility calculation based on the local surface polarization charge densities in a virtual conductor environment. The negative or positive value of the energy indicates exothermic or endothermic process, respectively [17].

Based on Fig. 6, water is found to have the strongest H-HB interaction due its high propensity as hydrogen bonds donor (HBD) and acceptor (HBA) on its molecule as compared to other solvents. Ascorbic acid solubility is found higher in solvent with high HBA. High HBA is highly favorable in the dissolution process of ascorbic acid because it provides more binding sites for ascorbic acid's hydroxyl's group to form hydrogen bonds with solvent and improve ascorbic acid solubility. The strength of H-HB interaction decreases from water > methanol > ethanol > 2-propanol.

Van der Waals energy on the other hand was very low in water due to the small size of water molecule. However, with the increasing of carbon atom in solvent molecule, van der Waals interaction can be seen increasing consistently from methanol < ethanol < 2-propanol. Both intermolecular forces are slightly effected by temperature because local surface polarization charge densities in a virtual conductor environment is constant with temperature.

3.4. Ascorbic acid crystals habit

Ascorbic acid crystallized by evaporation from water, methanol, ethanol and 2-propanol presents in various crystal habits as presented by microscopic image in Fig. 7. Based on the data obtained from CCDC, the ascorbic acid crystal was reported to exist in various habits, including prism [30], cubic [2] and needle [31] and is consistent with the findings. Habit is determined by the symmetry of the internal crystal structure, as well as the relative growth rates of the crystal faces. The latter relates to the energetics of molecule attachment to the crystal surfaces which can be influenced by the relatively weak solute-solvent interactions [32]. Solvent with more HBA site has higher potential to form hydrogen bonds with ascorbic acid thus giving it more directional strength to form particular type of crystal. At supersaturation point, the solvent used evaporate thus increasing the intermolecular attraction between solute-solute to form a crystal solid. The distance between solute molecules in a crystal lattice becomes smaller and regular. Intermolecular forces constrain the motion of the molecules more severely than in the liquid state. Well-structured molecules generally have relatively high

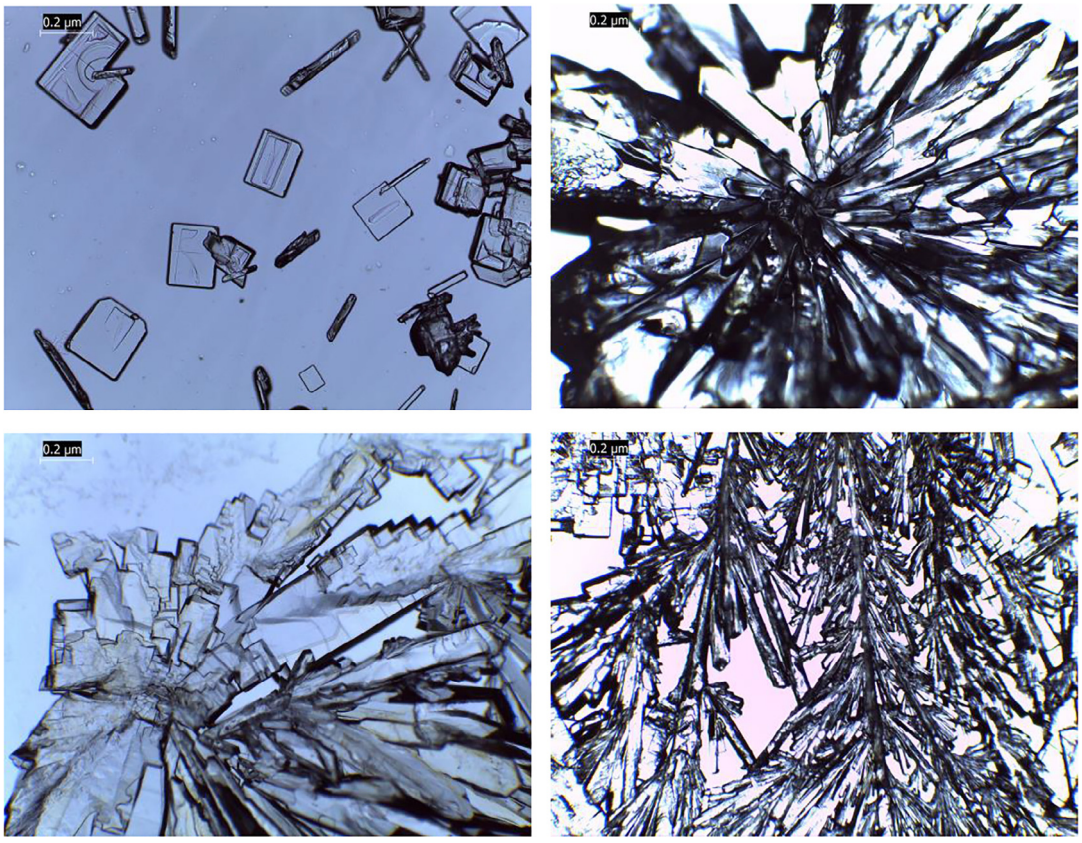


Fig. 7 Ascorbic acid crystal by natural evaporation from [A] water [B] methanol [C] ethanol [D] 2-propanol.

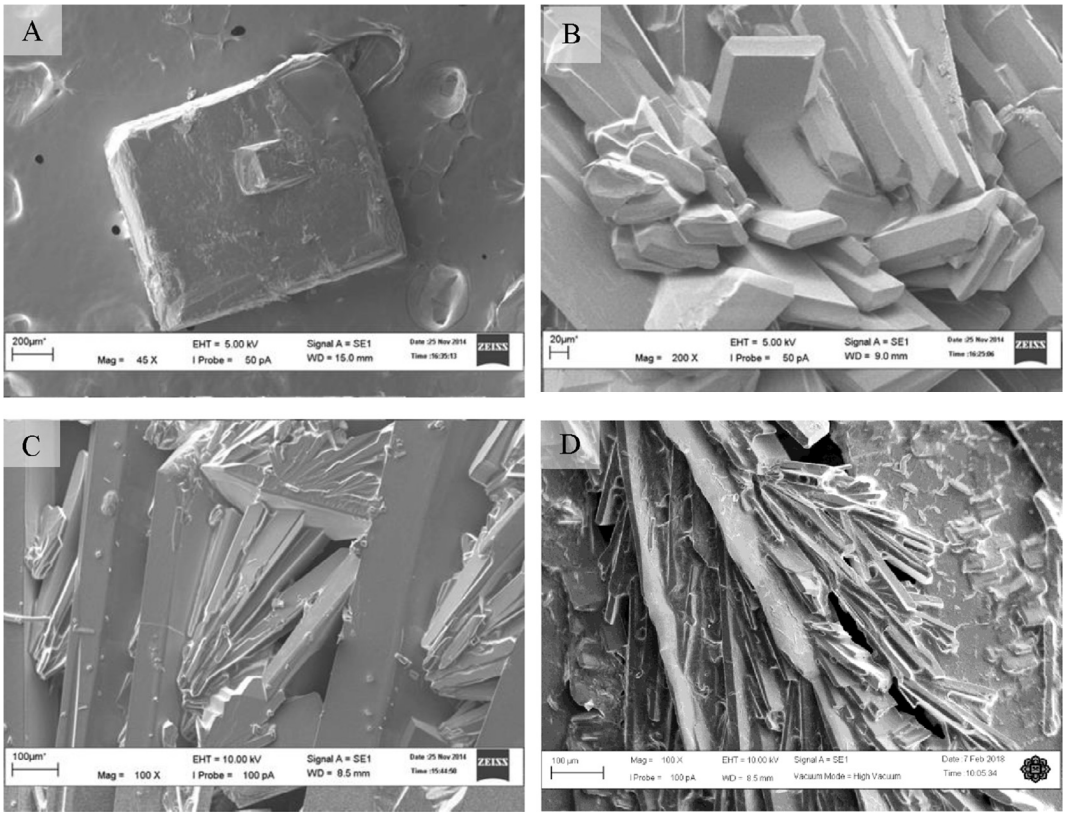


Fig. 8 Scanning Electron Microscope image of ascorbic acid that crystallised from solvents [A] water [B] methanol [C] ethanol.

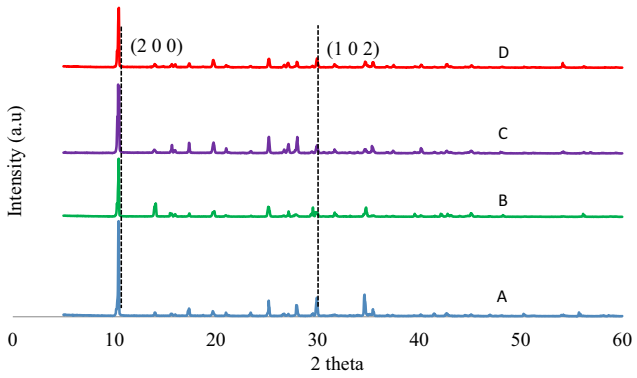
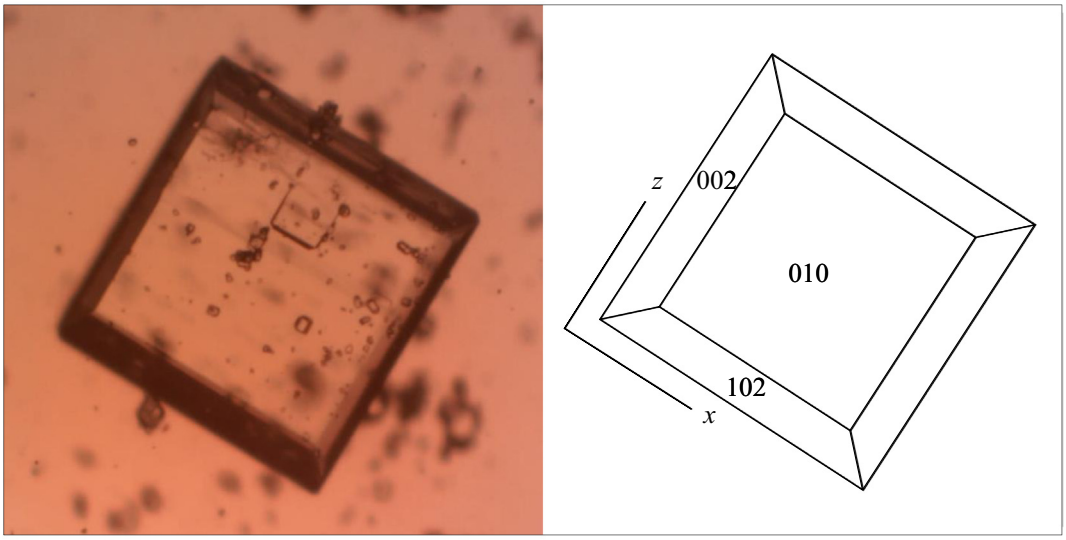


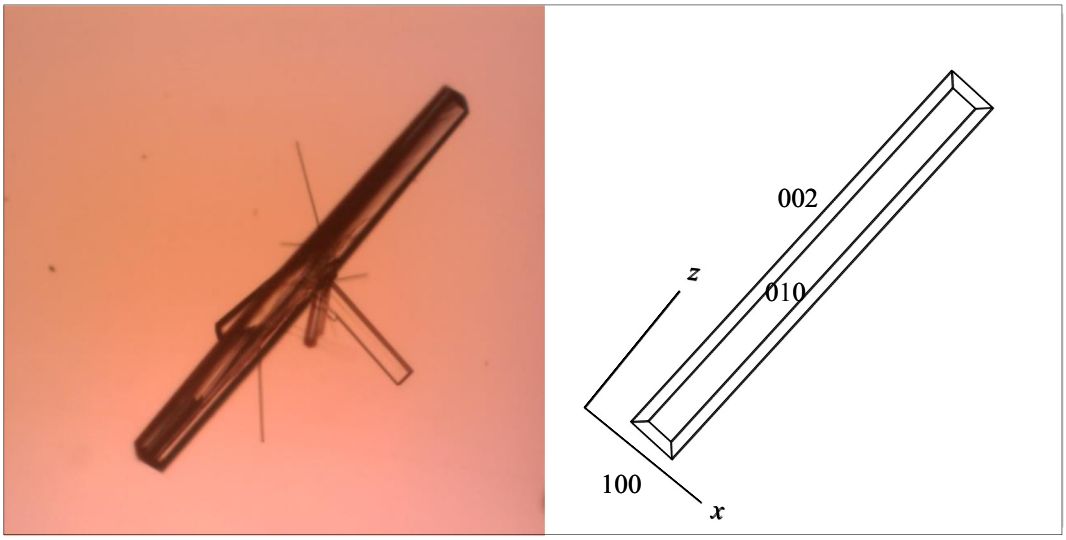
Fig. 9 XRPD pattern from ascorbic acid crystallized in [A] ascorbic acid – water [B] ascorbic acid – methanol [C] ascorbic acid – ethanol [D] ascorbic acid – 2-propanol.

intermolecular forces since molecules could pack together more closely. During this process, the solute molecule must displace the hydrogen bonded solvent molecule to grow on a crystal face. The stronger the hydrogen bond form, the slower the displacement process thus slowing the growth rate of the crystal face. On the same point, another study [23] reported that by adding more alcoholic solvent, it reduces the rate of mass transfer for ascorbic acid crystal growth, which is in agreement with the current study.

Fig. 8 shows SEM images of ascorbic acid crystals evaporated from water, methanol, ethanol and 2-propanol. SEM images are presented to confirm the images from microscope analysis and the results obtained are consistent. The crystal formed a cubic crystal from growth in water. The shape of ascorbic acid changes into longer but smaller as it grew in methanol and ethanol. The growth of ascorbic acid crystal is more elongated to one direction from prism/cubic to needle



[A] Water



[B] Ethanol

Fig. 10 Comparison of ascorbic acid crystal from [A] water and [B] ethanol to miller indices representation of prism crystal.

shaped crystal (acicular habit) by reducing the solvents' polarity. The ascorbic acid crystal habit is stretched and minimized due to the build up in highly polar solvents like water as compared to less polar solvents like methanol, ethanol and 2-propanol respectively.

The XRPD patterns obtained in this work, shown in Fig. 9, were identified as ascorbic acid by DIFFRAC.EVA. Ascorbic acid appears to be in monoclinic cell and space group P21 which are consistent with the works conducted by previous researchers [10,11,33]. Fig. 9 shows a good fit between growth crystal and data from the Crystallography Open Database (COD) because the crystals share a prominent peak and no obvious change in peak position. Fig. 10 illustrates the preferred orientation of ascorbic acid crystal based on microscopic image and the XRPD peaks. From the XRPD peaks, the ascorbic acid crystals have a preferred orientation at (0 0 2) crystal surface which indicates that it has a tendency to grow along (0 0 2) direction. However, when ascorbic acid was grown in water, besides (0 0 2) in *z*-axis, the XRPD intensity on the other plane like (1 0 2) is also significantly high. The crystal which grown in water has a tendency to grow in two directions, forming a prismatic crystal. Water which consists of multiple HBA and HBD enables water molecules to form hydrogen bond with ascorbic acid. Hydrogen bond interaction tends to stabilize molecular pair, decrease the entropy and direct the molecule involve into its polar direction [34,35]. This interaction increases the probability of ascorbic acid to grow in other direction besides (0 0 2). In lower polar solvents like methanol, ethanol and 2-propanol, the ascorbic acid crystals grow rapidly along (0 0 2) and less growth on the other plane resulting in long needle like crystals that are typically described as thin prism. It can also be observed from Fig. 10 that the peak is broader for crystals obtained by evaporation from 2-propanol suggesting that the crystal is poorly arranged or having a structural defect [36,37].

Ascorbic acid crystal grown in water, methanol and ethanol were analyzed using single XRD analysis to confirm that all crystals are of the same polymorph. Ascorbic acid from 2-propanol were unable to be tested due to insufficient amount of sample but it is expected to show similar characteristics with crystals formed from methanol and ethanol. Ascorbic acid crystal is from monoclinic system with α and γ values of 90° and β not equal to 90° [11,33]. The unit cell parameter is consistent with the literature values [2,38] The axial length and angles of single crystal of ascorbic acid from previous and current works are presented in Table 4. In the current work, the ascorbic acid crystals were found to have two symmetry faces with β axial angle of between 99°32′ to 102°18′. Single crystal data also confirmed that ascorbic acid crystals, despite forming different habits upon growing in different solvents, they are having the same crystal lattice; hence they are not polymorphic.

Table 4 The axial length and angles of single crystal of ascorbic acid from previous and current works.

Crystal unit cell parameter	[27]	[28]	Current work		
			water	methanol	ethanol
a (Å)	16.95	17.299	17.300	17.310	17.30
B (Å)	6.32	6.35	6.353	6.348	6.348
C (Å)	6.38	6.411	6.411	6.409	6.405
α (Å)	N/A	N/A	90.00	90.00	90.00
β (Å)	102° 30′	102°11′	102°18′	100°32′	99°32′
γ (Å)	N/A	N/A	90.00	90.00	90.00

4. Conclusions

The ascorbic acid solubility has been studied in four different polar protic solvents; water, methanol, ethanol and 2-propanol at temperatures ranging from 303 to 323 K using isothermal-gravimetric methods and compared with a simulation by COSMO-RS. It was found that the solubility values decreased with the decreasing of solvent polarity and increase of van der Waals interaction. The solubility results obtained show a consistent pattern between experimental, literature and simulation data force estimation, which indicates that higher hydrogen bonding propensities in the solvents contributed to higher solubility of ascorbic acid. A systematic change in crystal habits were observed with the change of solvent's polarity during crystallization process. The ascorbic acid crystal habit is flat cubic when crystallized by evaporation from water and becomes more elongated as the polarity reduces. The insights into this behavior of ascorbic acid crystals would be useful toward the control of crystal habits.

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