Solubility of L-Glutamic acid in concentrated Water/Ethanol solutions

Maya Khellaf, Catherine Charcosset, Denis Mangin, Elodie Chabanon

Solubility of L-Glutamic acid in concentrated Water/Ethanol solutions

Maya KHELLAF, Catherine CHARCOSSET, Denis MANGIN, Elodie CHABANON*

Univ Lyon, Université Claude Bernard Lyon 1, CNRS, LAGEPP UMR 5007, 43 boulevard du 11 novembre 1918, F-69100, VILLEURBANNE, France

*: Corresponding author

☎: +33 4 72 43 18 52

Email: elodie.chabanon@univ-lyon1.fr

ABSTRACT

In this work the solubility of the metastable α-form and the stable β-form of L-Glutamic acid in pure water and in different water/ethanol mixtures at high concentrations of ethanol is measured by analytical gravimetric method. The experiments are carried out over a temperature ranging from 283 to 343K. The experimental results show that the solubility of the stable β-form is lower than the metastable α-form regardless of the solvent studied (water or water/ethanol mixtures). The results also highlight that the solubility of both polymorphs decreases with the increase of the antisolvent concentration and increases with the temperature rising. Based on the data obtained, the enthalpy and the entropy of dissolution are estimated thanks to the empirical Van't Hoff correlation. The solubility data of both polymorphs is then correlated by Combined Nearly Ideal Binary Solution (CNIBS/Redlich-Kister) equation and the parameters are determined for the temperature studied.

KEYWORDS:

A1. Crystallization, A1. Solubility, B1. L-Glutamic acid, B. Water/Ethanol mixtures.

1. Introduction

Crystallization is an important unit operation in pharmaceutical industry. It is involved during the process of intermediates products separation and in the final step of active pharmaceutical ingredients manufacturing. Therefore, it represents one of the most sensitive steps in order to reach the desired therapeutic objectives of the final compound. Indeed, properties such as crystal size distribution (CSD), crystal shape, purity and particularly polymorphism have to be perfectly controlled [1]. In fact, the crystallization of a single molecule can lead to different crystalline polymorphs depending on the nature of the crystallization (in the melt state or in solution) and the operating conditions (supersaturation, temperature, nature of the solvent, impurities...) [2]. They have the same chemical composition but exhibit different physical, mechanical and thermal properties such as melting point, density, compressibility, hardness and crystal morphology, as well as solubility and consequently different dissolution rates [1,3,4].

These differences in physical properties can have a significant impact on the stability, the bioavailability (activity/toxicity), the shape of the active ingredient [5] and also on the filtration and the tableting processes of pharmaceutical and chemical products. A revealing example of the lack of control of polymorphism is about the production of the drug Norvir®, having Ritonavir as active ingredient, by Abott laboratory. The industrial production of this compound was stopped following the unexpected appearance of a more stable form. The crystallization of the metastable form obtained was difficult using seeding or priming [6].

Since the crystallization of a selected polymorph is crucial, it is necessary to have an efficient and reliable production process for the targeted polymorph [7].

The current issue is to develop methods enabling a good control of CSD and polymorphisms. Nowadays, antisolvent crystallization in stirred reactor is the most implemented technique at the industrial scale [8]. In spite of the process robustness, micro-mixing heterogeneity can be

encountered, affecting the production repeatability, the final product homogeneity [9] or even the polymorphic phase formed. To limit these problems, reverse antisolvent crystallization is proposed as an alternative method, i.e. the solvent is selectively removed from a solvent/antisolvent solution in order to increase the supersaturation and induce the nucleation. This technique might have some advantages: higher yield, limited phase transition allowing better control of polymorphism and more uniform supersaturation. But, the knowledge of the solubility data of polymorphs in the solvent/antisolvent mixtures is essential to the crystallization process and product quality control. That is the purpose of this study.

L-Glutamic acid, one of the main amino acids used in pharmaceutical and food industries [10], has been chosen as a model compound. This molecule crystallizes under two well-known monotropic polymorphs: the stable polymorph β and the metastable polymorph α, wherein the β-form is needle-like in shape and the α-form is prismatic. The solubility data of both polymorphs in pure water at different temperatures has already been determined in previous works [11–13]. Also, some studies reported the solubility data of α-form and β-form in different solvent/antisolvent mixtures [10,12,14]. However, the data in water/ethanol mixtures are still limited and therefore more consistent results are needed, especially at high ethanol concentration.

In the present work, the solubility data of α-form and β-form of L-Glutamic acid in water/ethanol solutions are measured by a gravimetric method. The enthalpy and the entropy of dissolution of both polymorphs are then determined based on regression of the solubility data thanks to the Van't Hoff equation. Finally, the experimental data in the investigated water/ethanol mixtures are correlated with the thermodynamic model CNIBS/Redlich-Kister based on three parameters related to the binary and ternary interactions between the three species (solute, antisolvent and solvent), which are determined as function of the temperature.

2. Experimental section

2.1.Materials

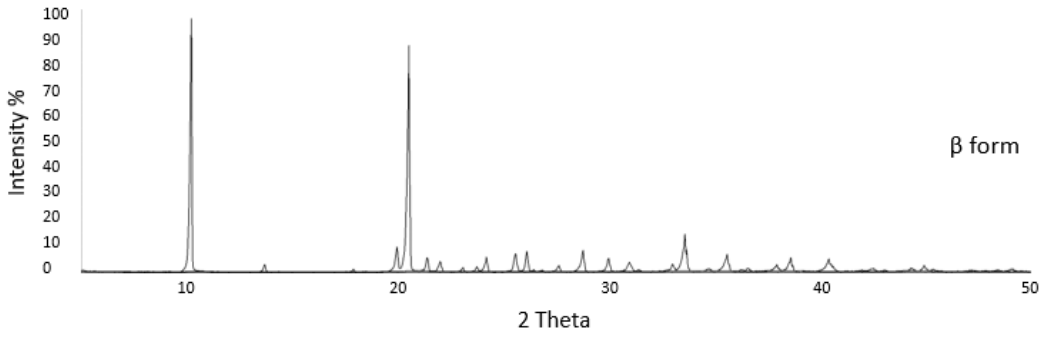
The stable β polymorph of L-Glutamic acid, purchased from Sigma Aldrich Co. Ltd (Lot BCBT9726, purity ≥ 99.5%), absolute anhydrous ethanol for analytical grade from Carlo Erba Reagent S.A.S (chemical purity ≥ 99.9%) and ultrapure water (resistivity = 18.2mΩ.cm) are used to perform the solubility measurements reported below.

2.2. Preparation of α L-glutamic acid

First of all, a sample of the commercial L-Glutamic acid is analyzed by X-Ray Diffraction (XRD) in order to confirm the presence of the stable phase β only. The pure α-form is obtained following the protocol described by Tahri et al. [11]. For this purpose, an aqueous solution of L-Glutamic acid (15g/kg of solvent) is rapidly cooled from 50°C to 5°C at a rate of -1.5°C/min and under constant stirring. After about 1 h at 5°C, the nucleation and the growth of the α-form occurs and can be observed thanks to a video probe (EZProbe® 12005) immersed in the reactor. The suspension is then quickly filtered and dried at room temperature. Optical Microscopy (OM) observations are first carried out to identify the crystals obtained. Then, XRD and Scanning Electron Microscopy (SEM) analyses are achieved to confirm the presence of the desired polymorphic form and to observe its morphology, respectively. The XRD patterns are recorded on a Bruker D8 Advance Diffractometer at room temperature with Cu Kα radiation of wavelength 1.54060Å, a tube voltage of 40kV and a tube current of 40mA. The diffraction spectra are recorded by a step scanning method at 2 Theta values between 5° and 50° with a step size of 0.02°. The SEM analyses are carried out with a FEI Quanta 250 FEG microscope. The crystals are deposited on a flat steel holder before being sputtered with 20nm of copper under high vacuum and then observed under an accelerating voltage of 15KV.

Fig. 1. presents the observations obtained by OM and SEM. It is worth noting that, as expected, the α- form is prismatic while the β-form is needle-like. Fig. 2. represents the XRD patterns of both polymorphs. The patterns show the presence of only one polymorph in each case.

Fig. 1. OM (top) and SEM (bottom) micrographs of the stable β-form (a1, a2) and the metastable α-form (b1, b2) of L-Glutamic acid



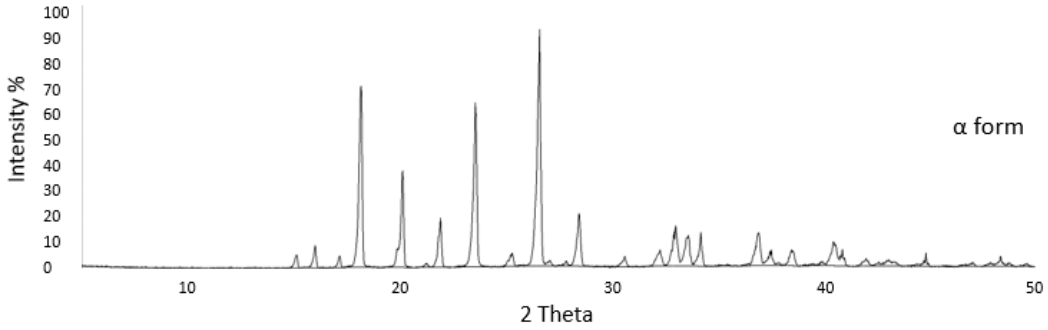
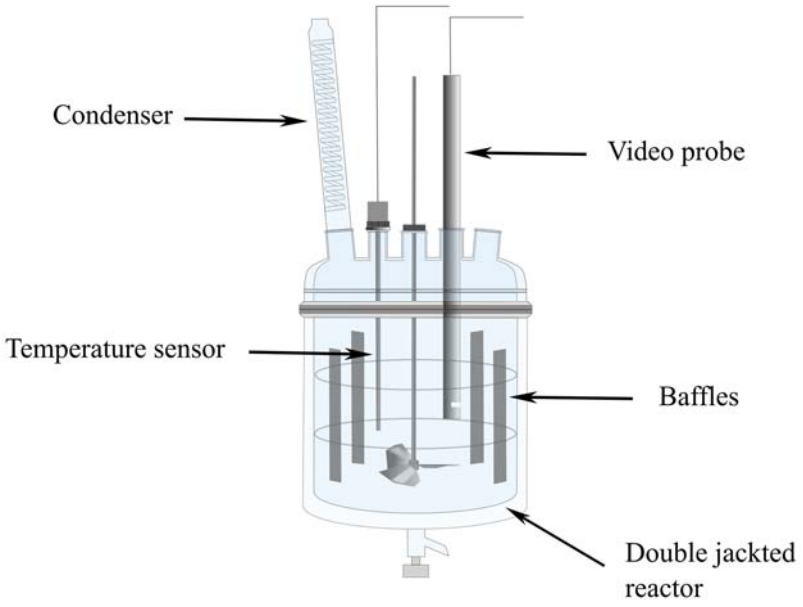


Fig. 2. XRD patterns of the stable β and the metastable α polymorphs of L-Glutamic acid

2.3.Apparatus and procedure for the solubility measurement

The solubility measurements are, first, performed in pure water and compared with the data available in the literature in order to validate the experimental protocol. Then, solubility of both polymorphs are measured in different water/ethanol solutions with x_{EtOH} the initial molar fraction of ethanol determined in the absence of L-Glutamic acid and ranging from 0 to 31.9% (0 to 54.5%wt). To achieve that, a slurry of α-form or β-form is prepared by adding an excess of solute to the solvent mixture in a 100mL stirred double jacketed reactor. The reactor (cf. Fig.3) is equipped with a condenser to avoid any solvent evaporation during the heating phase and agitated with a 3-blade mixel TT® propeller. The temperature is controlled by a bath circulation thermostat (ministat 230, Huber, Germany) equipped with a pt100 sensor and checked by a Platinum resistance thermometer using a multimeter (2700 multimeter, Keithley, US).



131

132 **Fig. 3.** Experimental set-up

133 The composition of the saturated solution is determined by gravimetric method which has
134 already been reported in several studies to measure the solubility of L-Glutamic acid [10–12].

135 The first step is to determine the time required for the solution to reach the thermodynamic
136 equilibrium. This has been done at the lowest temperature studied (283K) since the kinetic
137 should be the lowest at this temperature. An excess of solid is added to the solution and two
138 samples are collected every 1h, with a 2mL pipette equipped with a filter, and then, placed in
139 an oven at 358K for 24h. All the samples are weighted before and after drying (at room
140 temperature), using an analytical balance (XA105 DualRange, Mettler Toledo, Switzerland)
141 with ± 0.01mg accuracy, and the solubility of L-Glutamic acid is deduced. Based on the results
142 obtained (cf. Fig.4), the duration of 2h30 for pure water and 2h for water/ethanol mixtures,
143 whatever the molar fraction of ethanol (x_{EtOH}), are selected to measure the solubility of both
144 polymorphs between 283K and 343K following the same gravimetric method described above
145 [11,12,15].

Since α is the metastable form in the whole studied temperature domain, it was important to ensure that no phase transition towards β form occurred during α polymorph solubility measurement [16]. Thus, the suspension was monitored with an *in situ* video probe directly immersed in the stirred vessel and suspension samples were regularly withdrawn and observed by OM (optical microscopy). In fact, for temperature above 328K and ethanol molar fraction under 0.171, it was observed that the phase transition had started at the time of the solubility measurement. However, the dissolution rate of α-form is faster than the growth rate of β-form. As a consequence, although both phases were present in suspension, the solution concentration remained close to the α-polymorph solubility [12,17,18]. This is also in agreement with the Van t'Hoff plot of α-form solubility (see Fig. 6), which does not show any change in slope in the whole temperature domain and whatever the solvent mixture composition. Besides, Long et al. [10] and Tahri et al. [11] have already measured the α polymorph solubility at temperatures up to 343K in pure ethanol and pure water respectively. It will be seen below, that the α-form solubility in water presented in this work is close to the results reported by Tahri et al. Finally, it has to be mentioned that a low phase transition was observed for temperature above 333K and ethanol molar fraction over 0.236 within the experimental time. Indeed, it is well-known that phase transitions are slowed down when solubility is very low.

The molar fraction solubility (x_i) of each polymorph of L-Glutamic acid (i=α or β) in the solvent mixtures is calculated as follow:

$$x_i = \frac{m_i/M_i}{m_i/M_i + m_w/M_w + m_{EtOH}/M_{EtOH}} \quad (1)$$

Where m_i, m_w, and m_{EtOH} represent the masses (in g) of dissolved L-Glutamic acid), water and ethanol, respectively and M_i, M_w and M_{EtOH} are the molecular weights (in $g.mol^{-1}$) of L-Glutamic acid, water and ethanol, respectively.

The error of the solubility measurements is estimated by taking 10 samples at the same temperature. The standard deviation is then calculated, divided by the square root of the number of samples and multiplied by 2.262 (which corresponds to a confidence level of 95%). The error obtained is ± 5.03 10^{-6}.

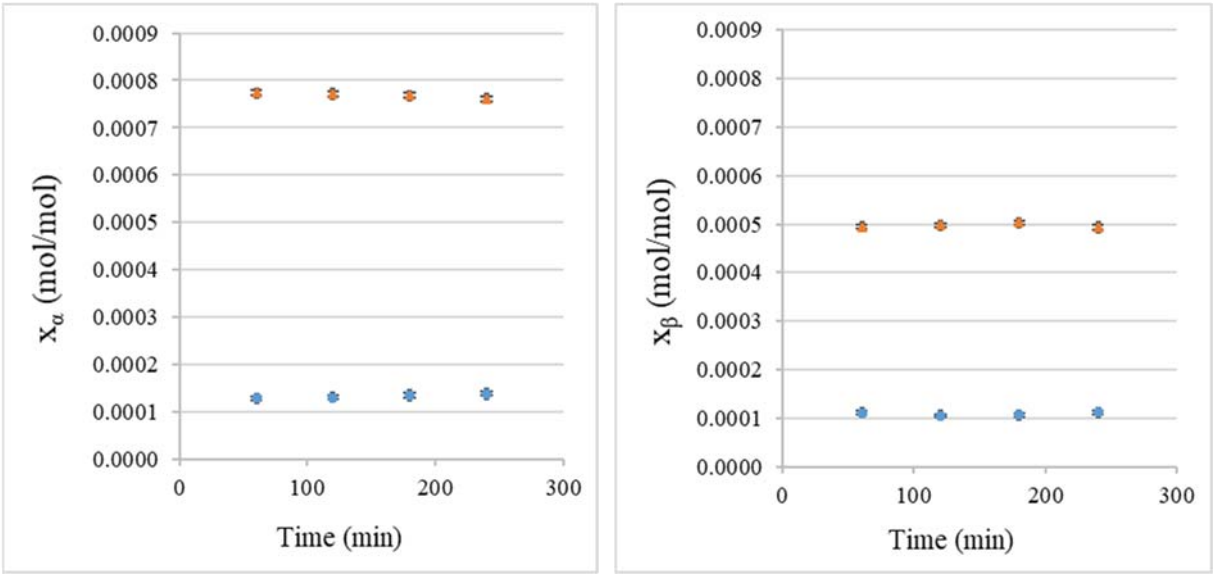


Fig. 4. Thermodynamic equilibrium study of α and β-forms at 283K in (▲) pure water and in (●) x_{EtOH} = 0.236.

3. Result and discussion

3.1.Solubility data

In this work, the solubility data of both polymorphs of L-Glutamic acid in pure water and in water/ethanol mixtures are investigated on a temperature range from 283K to 343K. The crystal shape is checked by OM observation for each measurement.

The results obtained are listed in Table 1 and presented in Fig. 5 where x_α and x_β represent the molar fraction solubility of α-form and β-form, respectively, and x_{EtOH} denotes the molar fraction of ethanol in the solvent mixture (without considering the L-Glutamic acid).

As it can be seen on Fig. 5, the solubility data reached in pure water in this work are in good agreement with the data available in the literature [11,12].

Table 1 shows that the solubility of both polymorphs increases with increasing the temperature. Another point is that the α-form has a higher solubility than the β-form over the entire temperature range studied, confirming, thus, that β-form is the thermodynamically stable form and α the metastable one. However, it can be noticed from Table 1 that the solubility of the stable β-form and the α-form are 0.93 and 0.82 respectively at T=283 K and x_{EtOH} =0.319; Similarly, the solubility of the stable β-form and the α-form are 1.4 and 1.37 respectively at T=293 K and x_{EtOH} =0.319. These solubilities are not in agreement with the respective stability of α and β forms. Nevertheless, at such high concentrations of ethanol and low temperatures, the solubilities of both polymorphs are extremely low and are nearly similar, the difference between the two values is within the error range of ± 5.03 10^{-6}.

According to the results obtained, it has to be noted that the solubility of the polymorphs decreases with the increase of the antisolvent, i.e. the ethanol, concentration.

The relative standard deviation (RSD) of the solubility measurements of α-form and β-form are calculated based on the results obtained by the equation (2):

$$\mathrm{RSD} = \frac{\sigma_i}{\bar{x}_i} \times 100 \quad \text{with} \quad \sigma_i = \sqrt{\frac{\sum_{i=1}^{n}(x_i - \bar{x}_i)^2}{n-1}} \qquad (2)$$

where σ_i is the standard deviation of the solubility measurement (mol/mol) at temperature T, x_i and $\bar{x}_i$ are respectively the solubility value of the polymorph i (i.e. α or β) and the average solubility (mol/mol), n is the number of samples.

For instance, the RSD is about 3.07% and 3.05% for 0.236 ethanol molar fraction at 283K for α and β forms respectively, and 0.7% and 0.89% in pure water at 283K for α and β forms respectively. These values are less than 5%, indicating the validity of the solubility measurements.

Table 1

Molar fraction solubility of α-form (x_α) and β-form (x_β) in pure water and in water/ethanol mixtures with different molar fractions of ethanol (x_{EtOH}) as a function of temperature T.

T (K)	$10^4 \times x_\alpha$	$10^4 \times x_\beta$	T(K)	$10^4 \times x_\alpha$	$10^4 \times x_\beta$	T(K)	$10^4 \times x_\alpha$	$10^4 \times x_\beta$
Pure water			**x_{EtOH} =0.051**			**x_{EtOH}=0.116**		
283	7.69	5.15	**283**	3.63	3.18	**283**	2.14	1.76
293	11.40	7.81	**293**	5.85	5.06	**293**	3.13	2.88
303	16.45	11.82	**303**	9.50	7.54	**303**	5.42	4.53
313	23.33	17.11	**313**	14.21	10.67	**313**	8.69	7.12
323	33.51	24.17	**323**	20.67	16.69	**323**	13.29	11.16
333	44.90	33.87	**333**	30.82	23.64	**333**	19.96	16.27
343	61.30	47.01	**343**	43.19	34.95	**343**	29.64	24.17
x_{EtOH}=0.171			**x_{EtOH}=0.236**			**x_{EtOH}=0.319**		
283	1.38	1.18	**283**	1.14	1.09	**283**	0.82	0.93
293	2.43	1.99	**293**	1.82	1.65	**293**	1.37	1.41
303	3.98	3.25	**303**	2.95	2.45	**303**	2.00	1.98
313	6.33	5.18	**313**	4.60	3.79	**313**	3.29	2.79
323	9.64	7.85	**323**	6.96	5.43	**323**	4.64	3.98
333	14.29	11.74	**333**	10.32	7.80	**333**	6.52	5.62
343	21.32	17.62	**343**	15.07	11.76	**343**	9.57	7.94
Pure EtOH								
283	0.28	0.11						
293	0.44	0.17						
303	1.12	0.21						

313	2.43	0.33
323	3.68	0.38

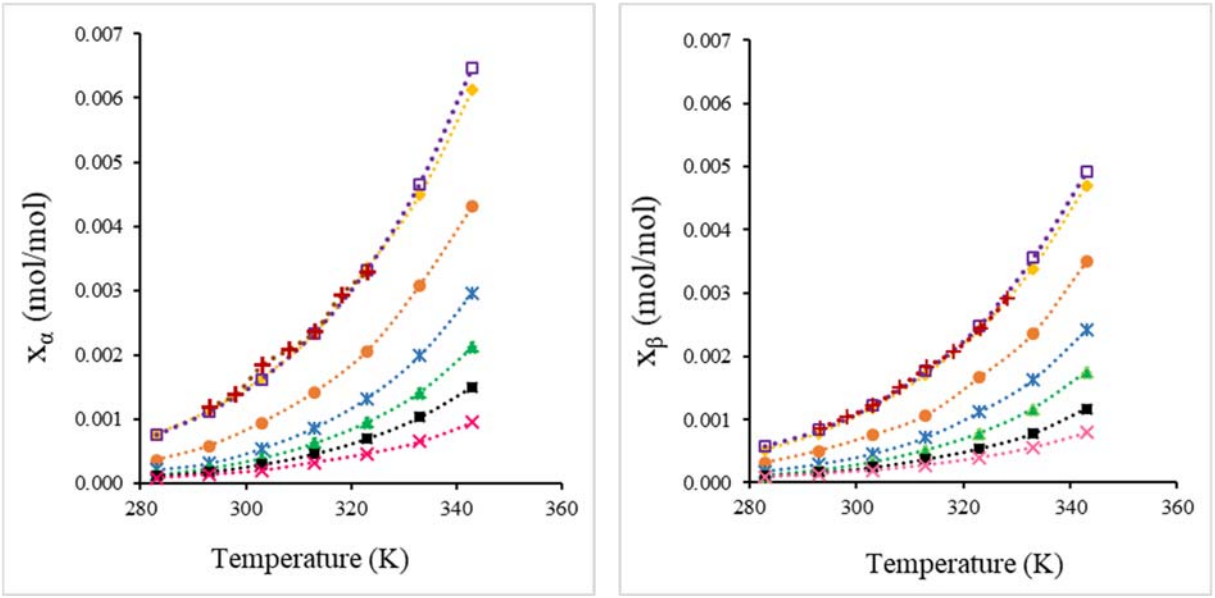


Fig. 5. Solubility curves of α and β forms in (◆) pure water; (●) x_{EtOH} = 0.051; (∗) x_{EtOH} = 0.116; (▲) x_{EtOH} = 0.171; (■) x_{EtOH} = 0.236; (×) x_{EtOH} = 0.319; (□) and (+) solubility in water in [11] and [12].

3.2.Solubility correlation

3.2.1. Van't Hoff empirical correlation

In order to confirm the results obtained, the solubility data of both polymorphs at different temperatures is correlated by the Van't Hoff equation.

The Van't Hoff equation is the representation of the neperien logarithm of the molar fraction solubility x_i of each polymorph as a function of the reciprocal absolute temperature for each composition studied (cf. Fig.6). It is a simplification of the rigorous thermodynamics equation given below [10] :

$$\ln(x_i\,\gamma_i) = -\frac{\Delta H_f}{RT}\left[1-\frac{T}{T_f}\right] - \frac{1}{RT}\int_{T_f}^{T}\Delta C_p\ dT + \frac{1}{R}\int_{T_f}^{T}\frac{\Delta C_p}{T}\ dT \quad (3)$$

Where x_i is the molar fraction (-) of L-Glutamic acid polymorph i (i.e. α or β) in the solution at equilibrium, γ_i is the activity coefficient in the solution at equilibrium (-), T is the absolute temperature (K), ΔH_f and T_f are, respectively, the enthalpy ($kJ.mol^{-1}$) and the temperature of fusion (K) of the considered polymorph, R is the ideal gas constant ($J.mol^{-1}.K^{-1}$) and ΔC_p is the difference between the heat capacity of the considered polymorph in the molten and the solid state ($J.mol^{-1}.K^{-1}$). In the equation (3), the first term on the right side is more important than the other two terms containing ΔC_p, which are often negligible and leads to the following equation (assuming $\Delta C_p \approx 0$) [2,10] :

$$\ln(x_i\,\gamma_i) = -\frac{\Delta H_f}{RT}\left[1-\frac{T}{T_f}\right] = -\frac{\Delta H_f}{RT} + \frac{\Delta S_f}{R} \quad (4)$$

The activity coefficient γ_i is linked to the excess Gibbs free energy. Since the Gibbs free energy of dissolution is the sum of the excess Gibbs free energy and of the Gibbs free energy of fusion, equation (4) can then be rewritten by introducing the enthalpy and the entropy of dissolution ΔH_d and ΔS_d, respectively. This leads to a reasonable simplification of equation (3) which is commonly used [2] :

$$\ln x_i = -\frac{\Delta H_d}{RT} + \frac{\Delta S_d}{R} \quad (5)$$

Fig.6 shows the Van't Hoff plots obtained for this work. It has to be noted that the curves present a good linearity and have the same trend for each solvent mixture. From the slope and the intercept point of the resulting straight lines, the enthalpy and the entropy of dissolution of both polymorphs in each water/ethanol solutions are determined. The results are reported in Table 2. Assuming that the slopes have the physical significance indicated by equation (5) (i.e. $-\Delta H_d$), the difference in slopes reflects the differences in heats of dissolution of both polymorphs of L-Glutamic acid according to the ethanol molar fraction.

As presented in Table 2, the enthalpy and the entropy of dissolution of both polymorphs increase with the increase of the ethanol molar fraction in the solvent mixture until a maximum value (at x_{EtOH} =0.171) then it tends to decrease significantly. Moreover, β-form exhibits a higher dissolution enthalpy in water than α-form but starting from a water/ethanol composition x_{EtOH} of 0.171, there is an inverse trend.

Table 2

Dissolution enthalpy and entropy of α and β forms of L-Glutamic acid in different water/ethanol mixtures.

	α-form			**β-form**		
x_{EtOH}	ΔH_d (kJ.mol^{-1})	ΔS_d (kJ.mol^{-1}K^{-1})	R^2	ΔH_d (kJ.mol^{-1})	ΔS_d (kJ.mol^{-1}K^{-1})	R^2
0	27.96	39.03	0.9997	29.66	41.82	0.9999
0.051	33.30	51.85	0.9998	31.92	45.66	0.9982
0.116	35.99	56.38	0.9981	35.27	52.59	0.9997
0.171	35.51	55.29	0.9998	36.24	52.81	0.9999
0.236	34.86	47.51	0.9998	31.82	36.21	0.9983
0.319	32.73	37.52	0.9990	28.54	23.47	0.9983

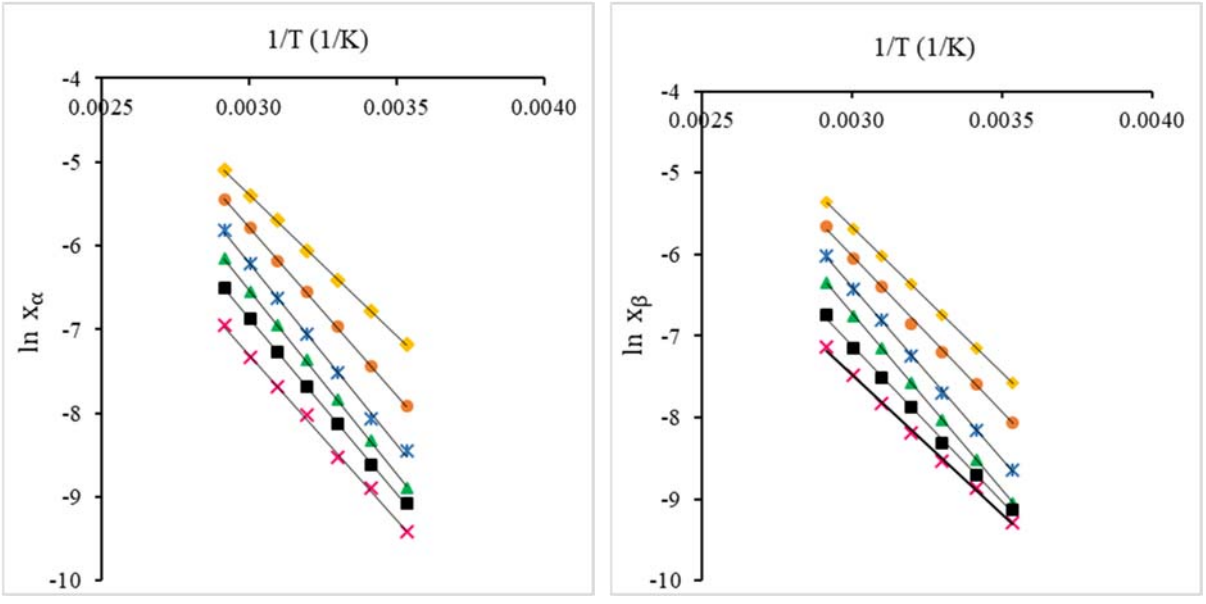


Fig. 6. Van't Hoff plot for α and β forms in (◆) pure water; (●) x_{EtOH} = 0.051; (∗) x_{EtOH} = 0.116; (▲) x_{EtOH} = 0.171; (■) x_{EtOH} = 0.236; (×) x_{EtOH} = 0.319.

3.2.2. Thermodynamic modeling

The solubility data in water/ethanol mixtures are also described by the Combined Nearly Ideal Binary Solvent CNIBS/Redlich-Kister model suggested by Acree [19] and also used in different studies [12,20,21].

$$\ln x_i = x_w \ln(x_i)_w + x_{EtOH} \ln(x_i)_{EtOH} + x_w x_{EtOH} \sum_{k=0}^{N} F_k (x_w - x_{EtOH})^k \quad (6)$$

Where x_w and x_{EtOH} refer in equation (6) to the initial molar fraction (-) respectively of water and ethanol determined in the absence of L-Glutamic acid polymorph i (α or β), $(x_i)_j$ is the molar fraction solubility of the solute i, i.e. L-Glutamic acid polymorph, in pure solvent j (-), F_k are the parameters of the model; they relate the solute-solvent and solvent-solvent interaction terms and are computed using a no-intercept least-squares analysis for each binary solvent system (-) [21] and N is a number ranging from 0 to 3 for a ternary system (-).

Equation (6) describes how the solubility of a crystalline solute dissolved in a binary solvent mixture evolves as a function of the composition of the medium at a fixed temperature.

By substituting x_w by (1- x_{EtOH}) in equation (6), for N=2 [21] and with a subsequent rearrangement and simplification, it leads to equation (7):

$$\ln x_i = \ln(x_i)_w + [\ln(x_i)_{EtOH} - \ln(x_i)_w + F_0 + F_1 + F_2]\, x_{EtOH} + [-F_0 - 3F_1 - 5F_2] x_{EtOH}^2 + [2F_1 + 8F_2] x_{EtOH}^3 + [-4F_2] x_{EtOH}^4 \quad (7)$$

To solve the equation, the solubility of the β-form in pure ethanol is measured by the gravimetric method described above while the solubility values of the α-form are taken from the study of Long et al. [10].

The values of the parameters F_0, F_1 et F_2 of equation (7) are listed in Table 3 together with the root-mean square deviation (rmsd) defined by equation (8):

$$\text{rmsd} = \left[\frac{1}{n}\sum_{i=1}^{n}\left(x_i^{cal} - x_i^{exp}\right)\right]^{\frac{1}{2}} \quad (8)$$

Where n is the number of experimental points, x_i^{cal} is the polymorph solubility calculated from equation (7) and x_i^{exp} is the experimental polymorph solubility. Both are expressed here in mol/mol.

The numerical results are presented in Fig.7 together with the experimental data taken from Table 3. As expected, at constant temperature, the solubility of both forms of L-Glutamic acid decreases with the increase of ethanol molar fraction. The experimental results can be well described with the correlation (7) using two different parameter sets of the two polymorphs. Thus, the model applied with N=2 and based on three parameters, is well adapted to take into account the effect of the solvent composition on the solubility.

Table 3

Fitting parameters of equation (7) for α and β forms in different water/ethanol mixtures.

	α-form				**β-form**			
T (K)	**F_0**	**F_1**	**F_2**	**10^5rsmd**	**F_0**	**F_1**	**F_2**	**10^5rsmd**
283	-5.400	-3.020	-1.689	2.55	-3.536	-1.908	-0.970	1.49
293	-5.209	-2.891	-1.596	3.18	-3.185	-1.661	-0.790	1.65
303	-4.870	-2.551	-1.298	1.68	-2.997	-1.548	-0.720	1.41
313	-4.674	-2.357	-1.130	1.05	-2.827	-1.427	-0.635	2.84
323	-4.502	-2.237	-1.044	3.45	-2.206	-1.017	-0.347	2.13

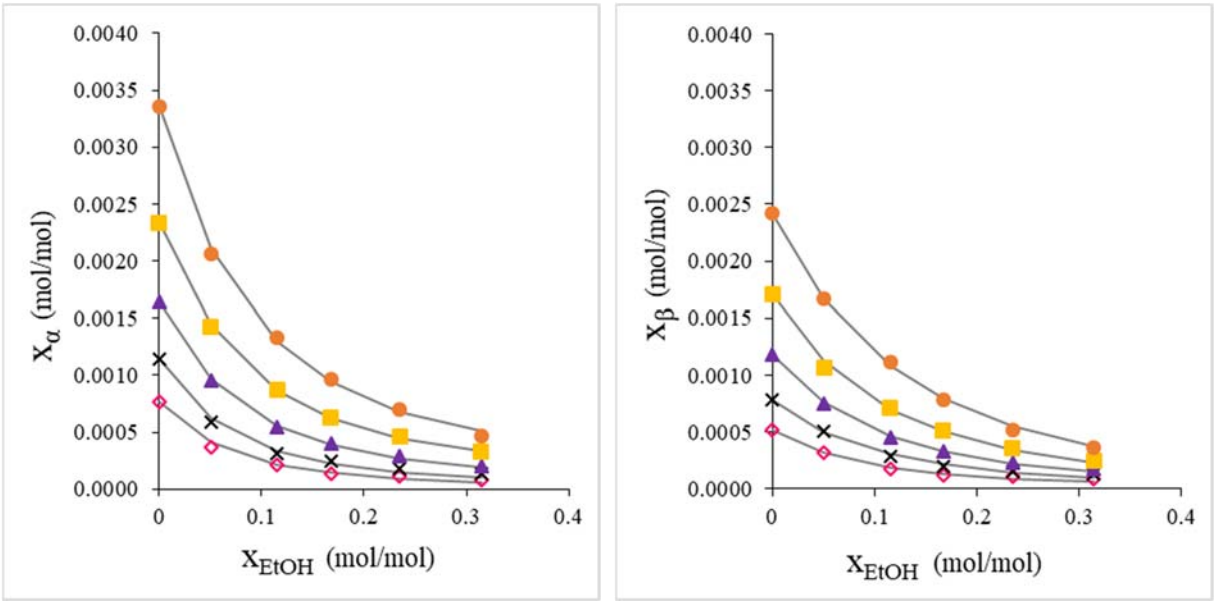


Fig. 7. Molar fraction solubility of α-form and β-form in binary water/ethanol mixtures at (●) T= 323K; (■) T= 313K; (▲) T= 303K; (×) T= 293K; (◇) T= 283K; (—) calculated from equation (7).

4. Conclusion

In this work, the solubility of both polymorphs of L-Glutamic acid in different water/ethanol mixtures at temperature ranging between 283K and 343K are measured by a gravimetric method. The results show that the solubility of the stable β-form is lower than the metastable α-form regardless of the medium studied (water or water/ethanol mixtures). The results also highlight that the solubility of both forms decreases with the increase of the antisolvent concentration and increases with the temperature rising. The dissolution enthalpy and entropy are also estimated by correlating the solubility measurements and the temperature using the Van't Hoff equation. The measured solubility data are modeled by the CNIBS/Redlich equation. Three parameters linked to the binary and ternary interactions between the three species (solute, antisolvent and solvent) are determined using a no-intercept least-squares analysis for each binary solvent system. This model gave a satisfactory correlation for a binary mixture with optimized parameters.

Finally, the investigation of L-Glutamic acid's solubility in this work is prominent to the study of reverse antisolvent crystallization method and may also provide an indication for the screening of the solvent system in industry.

List of symbol

x	molar fraction ($mol.mol^{-1}$)
m	mass (g)
M	molecular weight ($g.mol^{-1}$)
ΔH_d	enthalpy of dissolution ($kJ.mol^{-1}$)
ΔH_f	enthalpy of fusion ($kJ.mol^{-1}$)
ΔS_d	entropy of dissolution ($kJ.mol^{-1}.K^{-1}$)
ΔS_f	entropy of fusion ($kJ.mol^{-1}.K^{-1}$)
R	gas constant ($J.mol^{-1}.K^{-1}$)
T	temperature (K)
ΔC_p	heat capacity ($J.mol^{-1}.K^{-1}$)

List of indices

i	polymorphic form α or β
α	α polymorph of L-Glutamic acid
β	β polymorph of L-Glutamic acid
EtOH	Ethanol
w	water

Acknowledgments

We would like to thank Ruben Vera for the X-ray diffraction measurements (Centre de Diffractométrie Henry Longchambon, Université Lyon 1, Villeurbanne - France) and Eloise Thomas for the SEM images (Centre Technologique des Microstructures, Université Lyon 1, Villeurbanne - France).

References

[1] S. Veesler, F. Puel, Crystallization of Pharmaceutical Crystals, in: Handbook of Crystal Growth, Elsevier, 2015: pp. 915–949. https://doi.org/10.1016/B978-0-444-56369-9.00021-6.

[2] J.W. Mullin, Crystallization, 4th ed, Butterworth-Heinemann, Oxford ; Boston, 2001.

[3] H.G. Brittain, K.K. Arora, S.X.M. Boerrigter, S.R. Byrn, P.W. Cains, A.J. Florence, D.J.R. Grant, Polymorphism in pharmaceutical solids, 2nd ed, Informa Healthcare, New York, 2009.

[4] Z. Liu, L. Zhong, P. Ying, Z. Feng, C. Li, Crystallization of metastable β glycine from gas phase via the sublimation of α or γ form in vacuum, Biophysical Chemistry. 132 (2008) 18–22. https://doi.org/10.1016/j.bpc.2007.10.003.

[5] D. Mangin, F. Puel, S. Veesler, Polymorphism in Processes of Crystallization in Solution: A Practical Review, Organic Process Research & Development. 13 (2009) 1241–1253. https://doi.org/10.1021/op900168f.

[6] J. Bauer, S. Spanton, R. Henry, J. Quick, W. Dziki, W. Porter, J. Morris, Ritonavir: An Extraordinary Example of Conformational Polymorphism, (2001) 8.

[7] K. Srinivasan, P. Dhanasekaran, Nucleation control and crystallization of l-glutamic acid polymorphs by swift cooling process and their characterization, Journal of Crystal Growth. 318 (2011) 1080–1084. https://doi.org/10.1016/j.jcrysgro.2010.11.050.

[8] E. Chabanon, D. Mangin, C. Charcosset, Membranes and crystallization processes: State of the art and prospects, Journal of Membrane Science. 509 (2016) 57–67. https://doi.org/10.1016/j.memsci.2016.02.051.

[9] N.S. Tavare, Micromixing limits in an MSMPR crystallizer, Chemical Engineering & Technology. 12 (1989) 1–11. https://doi.org/10.1002/ceat.270120102.

[10] B. Long, J. Li, Y. Song, J. Du, Temperature Dependent Solubility of α-Form L -Glutamic Acid in Selected Organic Solvents: Measurements and Thermodynamic Modeling, Industrial & Engineering Chemistry Research. 50 (2011) 8354–8360. https://doi.org/10.1021/ie200351b.

[11] Y. Tahri, E. Gagnière, E. Chabanon, T. Bounahmidi, D. Mangin, Investigation of the l-Glutamic acid polymorphism: Comparison between stirred and stagnant conditions, Journal of Crystal Growth. 435 (2016) 98–104. https://doi.org/10.1016/j.jcrysgro.2015.11.019.

[12] Y. Mo, L. Dang, H. Wei, Solubility of α-form and β-form of l-glutamic acid in different aqueous solvent mixtures, Fluid Phase Equilibria. 300 (2011) 105–109. https://doi.org/10.1016/j.fluid.2010.10.020.

[13] E. Manzurola, A. Apelblat, Solubilities of l-glutamic acid, 3-nitrobenzoic acid, p-toluic acid, calcium-l-lactate, calcium gluconate, magnesium-dl-aspartate, and magnesium-l-lactate in water, The Journal of Chemical Thermodynamics. 34 (2002) 1127–1136. https://doi.org/10.1006/jcht.2002.0975.
[14] H. Shi, F. Li, X. Huang, T. Wang, Y. Bao, Q. Yin, C. Xie, H. Hao, Screening and Manipulation of l-Glutamic Acid Polymorphs by Antisolvent Crystallization in an Easy-to-Use Microfluidic Device, Ind. Eng. Chem. Res. 59 (2020) 6102–6111. https://doi.org/10.1021/acs.iecr.9b06566.
[15] A. Shalmashi, A. Eliassi, Solubility of Salicylic Acid in Water, Ethanol, Carbon Tetrachloride, Ethyl Acetate, and Xylene, Journal of Chemical & Engineering Data. 53 (2008) 199–200. https://doi.org/10.1021/je7004962.
[16] M. Kitamura, Polymorphism in the crystallization of L-glutamic acid, Journal of Crystal Growth. 96 (1989) 541–546. https://doi.org/10.1016/0022-0248(89)90049-3.
[17] J. Cornel, C. Lindenberg, M. Mazzotti, Experimental Characterization and Population Balance Modeling of the Polymorph Transformation of l-Glutamic Acid, Crystal Growth & Design. 9 (2009) 243–252. https://doi.org/10.1021/cg800387a.
[18] J. Schöll, D. Bonalumi, L. Vicum, M. Mazzotti, M. Müller, In Situ Monitoring and Modeling of the Solvent-Mediated Polymorphic Transformation of L -Glutamic Acid, Crystal Growth & Design. 6 (2006) 881–891. https://doi.org/10.1021/cg0503402.
[19] W.E. Acree, Mathematical representation of thermodynamic properties Part 2. Derivation of the combined nearly ideal binary solvent (NIBS)/Redlich-Kister mathematical representation from a two-body and three-body interactional mixing model, Thermochimica Acta. 198 (1992) 71–79.
[20] Q. Chen, Y. Wang, X. Wu, J. Wang, Solubility of 11β-Hydroxypregna-1,4,16-triene-3,20-dione in Different Solvents, Journal of Chemical & Engineering Data. 53 (2008) 1414–1416. https://doi.org/10.1021/je800174u.
[21] A. Jouyban, H.-K. Chan, N.Y.K. Chew, M. Khoubnasabjafari, Jr. William Eugene Acree, Solubility Prediction of Paracetamol in Binary and Ternary Solvent Mixtures Using Jouyban–Acree Model, Chemical and Pharmaceutical Bulletin. 54 (2006) 428–431. https://doi.org/10.1248/cpb.54.428.