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CHARACTERIZATION AND QUANTIFICATION OF AMORPHOUS CONTENT IN SOME SELECTED PARENTERAL CEPHALOSPORINS BY CALORIMETRIC METHOD

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Amorphous content of a crystalline drug affects its physical and chemical properties as well as its performance. Consequently it is important to assess the extent of amorphous contents in pharmaceuticals. The present study utilizes the technique of solution calorimetry to quantify the percentage of crystallinity in samples of varying amorphous content in cefazolin sodium monohydrate, ceftriaxone sodium, cefotaxime sodium and cefoperazone sodium. Enthalpy of solution of 100% crystalline and amorphous drugs as well as their physical mixtures over the range 0–100 mass/mass% amorphous content were determined. As expected it has been found that amorphous forms have significantly higher energy than the corresponding crystalline form for all the drugs. Enthalpy of solution ($\Delta_{sol}H$), an extensive thermodynamic property can provide a precise and unambiguous measure of the relative crystallinity provided amorphous and crystalline standards are appropriately chosen. A good correlation has been found between $\Delta_{sol}H$ and the amorphous contents of the drugs.

Keywords: *cephalosporins, crystallinity determination, enthalpy of solution, solution calorimetry*

Introduction

A crystalline substance in general is in a physically and thermodynamically stable state. The technological operations such as grinding, milling, spray drying, tablet compaction, wet granulation, rapid cooling of melt, and lyophilization, induces various kinds of disorder in the form of crystal defects and/or due to generation of amorphous regions. These changes generally affect the chemical and physical properties of the material as well as the corresponding drug product performances [1–6]. The amorphous state is thermodynamically unstable state with higher energy level [7]. Even relatively small amount of amorphous material (<10%) may have a detrimental impact on the stability, manufacturability and dissolution characteristics of the formulated drug product [1, 8]. A material, which is partly amorphous, may have problems regarding stability and hygroscopicity, resulting in transformation to more stable crystalline form during storage [9]. The presence of the amorphous form may determine many particle properties, for example: particle size, particle shape, density, chemical stability, water solubility, hygroscopicity, flow properties, compactibility, etc. Above mentioned physicochemical properties may determine the processability of materials and the bioavailability of dosage forms, so it is important and useful to know the crystallinity of material and to monitor it during formulation development, production processes and storage [1].

Various techniques such as X-ray powder [10–12] diffraction, density measurement [13], isothermal microcalorimetry [14–24], solution calorimetry [25–27], differential scanning calorimetry [4, 28, 29], dynamic vapour sorption [30] and FT-IR spectroscopy [31, 32] are used to characterize and possibly quantify the amorphous phase content of these materials [4]. Out of these techniques solution calorimetry has been found to be most useful for the measurement of small quantities of amorphous material in a crystalline sample. For X-ray powder diffraction a lower cut-off in detection may be at 3% and more whereas with calorimetry it has been claimed that it is possible to detect up to 1% amorphous content [14, 15, 19, 27]. Moreover X-ray powder diffraction study is affected by dimensions of the amorphous and crystal regions and that is why the amorphous content from this method does not produce precise values [22]. Besides this the use of X-ray powder diffraction technique is also limited by cost and hazardousness [14].

In recent years solution calorimetry has been utilized for a wide variety of pharmaceutical applications. Furthermore, directly determined enthalpies of solution ($\Delta_{sol}H$) have been utilized for the characterization of pharmaceuticals [33–40] and for the determination of the extent of crystallinity in drugs and excipi-

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ents [25–27] as well as to study interactions between the drugs and the carriers in conjunction with their solubility and dissolution [36–39, 41]. It has been shown that quantification of amorphous content could be done with much higher accuracy than by the X-ray powder diffraction method [22]. The USP Advisory Panel on Physical Test Methods has made recommendation of solution calorimetry for the crystallinity determination [42]. Enthalpy of solution obtained from van't Hoff plot of log solubility against the reciprocal of temperature suffers from the drawback that these plots are not linear over a wide temperature range [43].

In the present communication we report the $\Delta_{sol}H$ of crystalline and amorphous cephalosporins as a function of concentration ($0.302–4.188 \cdot 10^{-3}$ M) and pH (2–10) using solution calorimetry. Enthalpy of solution data obtained for their physical mixtures (0–100 mass/mass%) has been correlated with the extent of crystalline form. The correlation allows determination of the amorphous contents of unknown samples of drug rather accurately (±1.2%).

Experimental

Chemicals

Cefazolin sodium monohydrate (Surya Medicare Ltd., India) ceftriaxone sodium, cefotaxime sodium, cefoperazone sodium (Orchid Pharmaceutical Ltd., India), were procured as gift samples and were used without further purification. All the drugs were sieved and fractions with particle size 150 μm were used throughout the study.

Buffers

In the present studies phosphate buffers were prepared by mixing solutions of appropriate sodium salts of phosphoric acid in suitable ratio according to the given procedures [44]. The ionic strength of all phosphate buffers was 0.05 M. The pH values of various phosphate buffers were measured using a pH meter (Elico, India) standardized with solutions of pH 4.0, 7.0 and 9.2.

Preparation of amorphous samples

The drugs were dissolved in triply distilled water and placed in a deep freezer (–80°C) for 1 h. They were then lyophilized under 17.2 mTorr with the shelf temperature of –40°C for 48 h or until the frozen ice spheres in the control petri dish completely disappeared. Usually, the temperature at this time was 2°C. The temperature was then increased to 8 and 16°C for 0.5 h each. Finally, the temperature was raised to 25°C and kept overnight to eliminate residual moisture. After the sample was freeze-dried, the vacuum was broken over dry nitrogen. The petri dishes were transferred immediately into a vacuum desiceator and dried over P_2O_5 under vacuum for at least 24 h.

Preparation of amorphous drug mixtures

Dried amorphous and crystalline drugs were sieved to produce a particle size of less than 150 μm and then suitable amounts of each were weighed accurately and thoroughly mixed to obtain powder mixtures of 0–100 mass/mass% amorphous drug, in increments of 10%. Sample storage was at 0% relative humidity in a desiccator over phosphorous pentaoxide, at room temperature (20–25°C).

Methods

Solution calorimetry

The system, Isoperibol solution calorimeter (ISC) model 4300 (Calorimetry Science Corporation, Utah, USA) was used to determine the enthalpies of solution of crystalline, amorphous drugs and mixtures. Before and/or after the dissolution process, the system was calibrated electrically i.e. a known amount of energy is added to the system to match the anticipated thermal energy accompanying the process. The small heat exchange between the environment and the vessel during the reaction and the heat arising from stirring are adjusted (by software 'ISC analyze') using the information obtained from the baseline temperature changes before and after the experiments. The calorimeter consists of a thin-walled 25 mL silvered Dewar flask in a constant temperature bath (37.00±0.0001°C). It is a semi-adiabatic calorimeter with temperature resolution, after noise reduction, close to 1 μK, which corresponds to a heat resolution of 1–4 mJ in a 25 mL reaction vessel. The time constant of the system is 2.05 h.

For measurements of $\Delta_{sol}H$ of the individual samples of pure crystalline drugs or its mixture with amorphous form weighed around 40–60 mg was filled into batch adapter of volume 0.9 mL sealed on both end with o-ring and glass ampoules. This was then inserted into the Dewar flask containing buffer (25±0.01 mL), the batch adapter holding the drug was isolated from the solution. The combined unit was then lowered into the calorimeter water bath held at 37°C. The glass stirrer was rotated at 100 revolution min^{-1} and the system was allowed to equilibrate for 90 min, after which electrical calibration was performed which imparted a known heating signal to the contents of the Dewar. The ampoule was then shattered automatically by means of a plunger, releasing the drug into the buffer and allow-

ing its dissolution. The ensuing heat change was detected by a thermistor within the vessel enabling measurement of the enthalpy of solution.

The performance of the system was checked using potassium chloride and tris(hydroxymethyl) aminomethane, as reference materials. A good agreement (±0.03 kJ mol^{-1}) was found with the published values. The precision of any individual measurement was better than 0.02 kJ mol^{-1} for three consecutive experiments and agreed with the recommended value within ±0.03 kJ mol^{-1}. The concentration is within ±0.005 M due to uncertainty in mass (for 5 mg sample). For each sample three replicate investigations were performed, with results quoted as mean values.

Solubility determination

Excess amount of drug were placed in 25 mL stoppered conical flask, 5 mL of buffer pH 7.40 was added to conical flask and were placed in water bath shaker maintained at 37±0.5°. The speed of shaker was set at 100 rpm for 24 h, then the shaker was switched off and temperature of bath maintained for 6 h, this was done to avoid forced solubility due to shaking. Then the solutions from the conical flask were filtered (during filtration the temperature was maintained at 37°C). The solutions were suitably diluted with respective buffers and analyzed spectrophotometrically at corresponding lambda maximum by using plain buffer as a blank. The study was carried out in triplicate. The concentration of samples of drugs is determined from the standard plot constructed for each drug using same buffer.

Results and discussion

Enthalpy of solution

The structural formulae of the drugs for which the $\Delta_{sol}H$ have been determined are given in Table 1. The $\Delta_{sol}H$ of cefazolin sodium, cefotaxime sodium, ceftriaxone sodium, and cefoperazone sodium determined using solution calorimeter as function of concentration and pH are given in Tables 2–5. it can be seen that $\Delta_{sol}H$ of cefazolin sodium and cefoperazone sodium in buffered solution indicates that dissolution process is endothermic. For cefotaxime sodium and ceftriaxone sodium $\Delta_{sol}H$ is exothermic below pH 4 and approaches endothermic behavior in pH above 4. However, $\Delta_{sol}H$ of all the drugs is nearly independent of concentration ($0.302–4.188\cdot10^{-3}$ M). Therefore an average value has been taken for $\Delta_{sol}H$ of a drug at a particular pH. The net measured response for the enthalpy of solution is a summation of several components. The first stage corresponds to wetting of the powder, followed by dissolution, that involves the disruption of the bonding between molecules in the solid-state. The solvation of the solute by the solvent molecules is the final step. There may also be rearrangement of contacts within the solvent in order to accommodate the solute, besides protonation and deprotonation of molecules depending on pH of the buffer. The endothermic behavior indicates weak interaction between drug and solvent molecules.

Enthalpy of solution of amorphous samples prepared by lyophilization were also determined as function of pH and concentration (Tables 2–5). It can be seen that amorphous ceftriaxone sodium and cefotaxime sodium show exothermic behaviour over the entire pH range. While amorphous cefazolin sodium and cefoperazone sodium exhibit decrease in the endothermicity compared to corresponding crystalline samples. The difference in behavior is due to the fact that more disordered state gives lower enthalpy of solution due to absence of lattice energy in the solid sample. Therefore, lower values for $\Delta_{sol}H$ of amorphous than for crystalline drugs is expected and justified.

The variation of $\Delta_{sol}H$ with pH is due to presence of different species of the drugs in varying amounts

Table 1 Chemical structure of cephalosporins

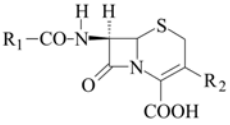
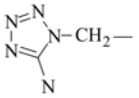
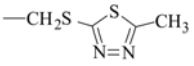
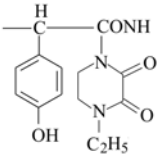
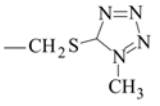
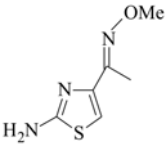
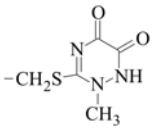
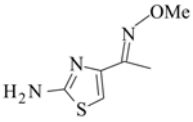
	R_1	R_2
		
cefazolin pKa_1=2.1		
cefoperazone pKa_1=2.6 pKa_2=9.55		
ceftriaxone pKa_1=2.70; pKa_2=3.30; pKa_3=4.10		
cefotaxime pKa_1=2.10 pKa_2=3.4		–CH_2OCOCH_3

Table 2 Molar enthalpy of solution of crystalline and amorphous cefazolin sodium (CF) at pH range 1–8 and fractions of various species

pH	f	f^-	10^3[CF] (M)	$\Delta_{sol}H_{crys}$/kJ mol^{-1}	$\Delta_{sol}H_{amor}$/kJ mol^{-1}
			0.404±0.0002	16.33±0.099	2.65±0.099
1	0.9264	0.0736	0.485±0.0002	16.34±0.082	2.67±0.082
			0.566±0.0002	16.35±0.071	2.64±0.071
			0.404±0.0002	18.38±0.111	4.96±0.111
2	0.5573	0.4427	0.485±0.0002	18.36±0.092	4.97±0.092
			0.566±0.0002	18.39±0.077	4.95±0.077
			0.647±0.0003	20.83±0.062	7.75±0.062
3	0.1118	0.8882	0.809±0.0003	20.85±0.049	7.74±0.049
			0.971±0.0004	20.86±0.041	7.76±0.041
			0.647±0.0003	21.37±0.063	8.37±0.063
4	0.0124	0.9876	0.809±0.0003	21.38±0.051	8.38±0.051
			0.971±0.0004	21.39±0.042	8.39±0.042
			1.213±0.0005	21.42±0.033	8.43±0.033
5	0.0013	0.9987	1.618±0.0007	21.45±0.025	8.44±0.025
			2.022±0.0008	21.43±0.020	8.45±0.020
			1.213±0.0005	21.43±0.033	8.46±0.033
6	0.0001	0.9999	1.618±0.0007	21.42±0.025	8.45±0.025
			2.022±0.0008	21.45±0.020	8.47±0.020
			1.213±0.0005	21.46±0.033	8.46±0.033
8	–	0.9999	1.618±0.0007	21.47±0.025	8.48±0.025
			2.022±0.0008	21.44±0.020	8.43±0.020

crystalline	ΔH=15.92 kJ mol^{-1}	ΔH^-=21.45 kJ mol^{-1}
amorphous	ΔH=2.19 kJ mol^{-1}	ΔH^-=8.45 kJ mol^{-1}

due to protonation or deprotonation. The corresponding fractions of the drug species determined from their pKa's values are also reported (Tables 2–5). The pKa values are taken from [45] and are given in Table 1.

At a particular pH, $\Delta_{sol}H$ can be represented by the following equation.

$$\Delta_{sol}H = \sum_{i=0}^{n} f_i \Delta_{sol} H_i \quad (1)$$

where f_i represents the fraction of species '*i*' of the drug at a particular pH calculated from its ionization constant (*s*) and $\Delta_{sol}H_i$ represents its enthalpy of solution.

Values of $\Delta_{sol}H_i$ corresponding to various species of the drugs calculated by solving the simultaneous Eq. (1) using measured values of $\Delta_{sol}H$ at different pH. These are utilized to calculate the enthalpy of ionization and combining these values with ionization constants a number of thermodynamic quantities for ionization of the drug have been calculated and are given in Table 6. It is satisfying to note that the values of enthalpy of ionization as determined from $\Delta_{sol}H_i$ calculated for crystalline and amorphous forms are nearly the same. Small differences may arise due to uncertainties in Ka values used for calculating fraction of different species at a particular pH.

The values of molar free energy of solution has been calculated using the following equation.

$$\Delta G = -RT\log s \quad (2)$$

where s=solubility of the drug in mol L^{-1}.

The values of s at pH 7.4 and 310.15 K have been determined by shake-flask method. The molar entropies of solution of drugs calculated from the equation $\Delta_{sol}S=(\Delta_{sol}G-\Delta_{sol}H)/T$ are given in Table 6. The positive values of entropy of solution indicate that the dissolution in all the four cases is largely entropically driven.

No direct calorimetric data are available in literature for comparison with our results except for the enthalpy of solution of cefazolin sodium monohydrate (18.41 kJ mol^{-1}) [46]. The pH of the solution is not specified in these studies. Assuming the resulting pH of about 7 the literature values are in reasonable agreement for our values at pH between 6–7 for crystalline cefazolin sodium. However, the literature value for amorphous sample were –22.59 kJ mol^{-1} and it is difficulty to compare with our experimental values (8.45 kJ mol^{-1}).

Crystallinity determination

A sharp exothermic peak is observed for ceftriaxone sodium and cefotaxime sodium when amorphous drug is loaded. For a mixture of the amorphous and the crystalline forms, the peak area of the exothermic heat flow

was proportional to the amorphous content. When mixture containing 50 mass/mass% amorphous drug was loaded, an initial exothermic behaviour was observed, followed by an endothermic response. This was due to the fact that amorphous drug is more readily soluble in water than the crystalline form, so the exotherm for dissolution of the amorphous form is seen before the endotherm for the dissolution of the crystalline material. For cefazolin sodium and cefoperazone sodium the peak area of endotherm was found to be decreased with increasing amorphous content. The technique is sensitive enough to detect a 0.5% amorphous content, and in each case the limit of detection may be further lowered by increasing the sample size. In order to avoid the possibility of error due to water vapour penetration into the ampoule, resulting in crystallization of the amorphous content, ampoule was sealed twice with wax. If the enthalpy of solution is additive for the crystalline and amorphous components, then

$$\Delta_{sol}H_{mix}=\Delta_{sol}H_1x/100+\Delta_{sol}H_2(100-x)/100$$

or

$$\Delta_{sol}H_{mix}=[(\Delta_{sol}H_1-\Delta_{sol}H_2)/100]x+\Delta_{sol}H_2$$

where x is the mass% of crystalline drug in the sample. $\Delta_{sol}H_1$ and $\Delta_{sol}H_2$ are the enthalpies of solution for crystalline and amorphous samples.

Similarly if

$$A=(\Delta_{sol}H_1-\Delta_{sol}H_2)/100 \text{ and } B=\Delta_{sol}H_2$$

We obtain

$$\Delta_{sol}H_{mix}=Ax+B$$

Although A and B can be calculated from $\Delta_{sol}H_1$ and $\Delta_{sol}H_2$ but we have obtained the values of A and B by plotting $\Delta_{sol}H$ *vs*. x (Fig. 1). The enthalpy of solution plotted against the crystalline% drug (x) yields a linear relationship with a R^2 value within range 0.98 to 0.99. The regression line intersects the ordinate at

Table 3 Molar enthalpy of solution of crystalline and amorphous cefoperazone sodium (CPZ) at pH range 1–10 and fractions of various species

pH	f	f^-	f^{2-}	10^3[CPZ] (M)	$\Delta_{sol}H_{crys}$/kJ mol^{-1}	$\Delta_{sol}H_{amor}$/kJ mol^{-1}
1	0.9755	0.0245	–	0.599±0.0002 0.899±0.0004 1.198±0.0005	6.32±0.067 6.31±0.044 6.33±0.034	–1.46±0.067 –1.47±0.044 –1.45±0.034
2	0.7992	0.2008	–	0.599±0.0002 0.899±0.0004 1.198±0.0005	7.34±0.067 7.36±0.044 7.35±0.034	–0.37±0.067 –0.38±0.044 –0.40±0.034
3	0.2848	0.7152	–	0.599±0.0002 0.899±0.0004 1.198±0.0005	10.34±0.067 10.35±0.044 10.33±0.034	2.82±0.067 2.81±0.044 2.84±0.034
4	0.0383	0.9617	–	1.198±0.0005 1.498±0.0006 1.797±0.0007	11.76±0.033 11.78±0.027 11.75±0.022	4.33±0.033 4.34±0.027 4.36±0.022
5	0.0040	0.9960	–	1.198±0.0005 1.498±0.0006 1.797±0.0007	11.94±0.033 11.95±0.027 11.96±0.022	4.57±0.033 4.56±0.027 4.54±0.022
6	0.0004	0.9993	0.0003	1.198±0.0005 1.498±0.0006 1.797±0.0007	11.97±0.033 11.98±0.027 11.96±0.022	4.57±0.033 4.58±0.027 4.55±0.022
7	–	0.9972	0.0028	2.097±0.0008 2.396±0.0010 2.696±0.0011	12.02±0.019 12.00±0.017 12.04±0.015	4.61±0.019 4.62±0.017 4.60±0.015
8	–	0.9726	0.0274	2.097±0.0008 2.396±0.0010 2.696±0.0011	12.20±0.019 12.20±0.017 12.20±0.015	4.82±0.019 4.81±0.017 4.80±0.015
9	–	0.7801	0.2199	2.097±0.0008 2.396±0.0010 2.696±0.0011	13.78±0.019 13.78±0.017 13.78±0.015	6.41±0.019 6.42±0.017 6.43±0.015
10	–	0.2619	0.7381	2.097±0.0008 2.396±0.0010 2.696±0.0011	18.02±0.019 18.02±0.017 18.02±0.015	10.77±0.019 10.76±0.017 10.75±0.015

crystalline	ΔH=6.18 kJ mol^{-1}	ΔH^-=11.98 kJ mol^{-1}	ΔH^{2-}=20.16 kJ mol^{-1}
amorphous	ΔH=–1.62 kJ mol^{-1}	ΔH^-=4.58 kJ mol^{-1}	ΔH^{2-}=12.95 kJ mol^{-1}

the enthalpy of solution of pure amorphous form. We found close agreement (±0.2%) between calculated values of A and B and their corresponding values from the linear relationship. The values of (x) crystallinity can be calculated from $\Delta_{sol}H_{mix}$.

$\Delta_{sol}H_{mix}=8.33+0.127x$ for cefazolin sodium

$\Delta_{sol}H_{mix}=4.77+0.071x$ for cefoperazone sodium

$\Delta_{sol}H_{mix}=-18.77+2.849x$ for ceftriaxone sodium

$\Delta_{sol}H_{mix}=-11.943+0.191x$ for cefotaxime sodium

We observed excellent (±1.5%) agreement between the value determined from experimental $\Delta_{sol}H$ and correlation and the true values of crystallinity in the mixture proposed by us. The method can be extended to determine the crystallinity of the drug in a formulation provided that there are no chemical interactions and wetting problems between drug and excipients by determining the enthalpy of solution of the formulation with and without drug. As expected amorphous forms of a compound are energy rich and had lower enthalpy of solution than corresponding crystalline form (Tables 2–5). In general the energy difference was large approx. 8–35 kJ mol^{-1}. The technique described in this paper has been found useful for detecting amorphous content in cephalosporins accurately. This will help in our overall programme in studying the impact of small quantities of amorphous material on the quality attributes of the formulation.

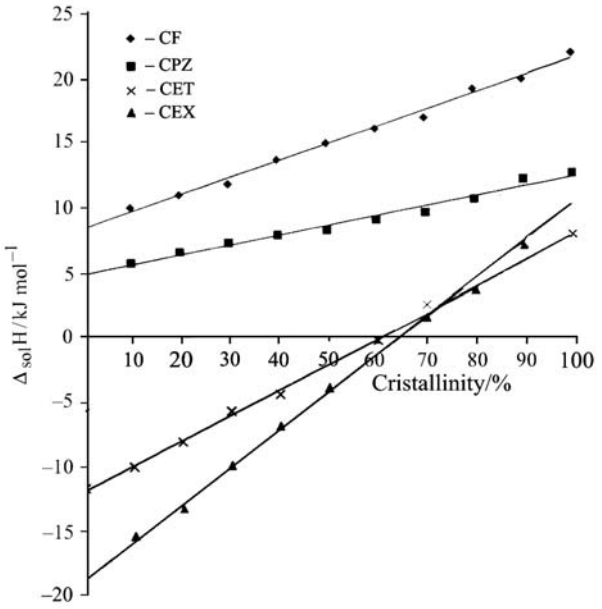


Fig. 1 Linear relation between enthalpy of solution ($\Delta_{sol}H$) and crystalline% content of drugs at pH 8.0

Table 4 Molar enthalpy of solution crystalline and amorphous ceftriaxone (CEX) sodium at pH range 2–10 and fractions of various species

pH	f^{2+}	f^{+}	f	f^{-}	10^3[CEX] (M)	$\Delta_{sol}H_{crys}$/kJ mol^{-1}	$\Delta_{sol}H_{amor}$/kJ mol^{-1}
1	0.9803	0.0146	0.0001	–	0.302±0.0001 0.423±0.0002 0.544±0.0002	–14.24±0.132 –14.26±0.094 –14.25±0.073	–47.35±0.132 –47.34±0.094 –47.37±0.073
2	0.8249	0.1646	0.0104	0.0012	0.302±0.0001 0.423±0.0002 0.544±0.0002	–13.38±0.132 –13.38±0.094 –13.38±0.073	–46.74±0.132 –46.76±0.094 –46.75±0.073
3	0.2297	0.4582	0.2891	0.0230	0.605±0.0003 0.907±0.0004 1.209±0.0005	–7.84±0.066 –7.84±0.044 –7.84±0.033	–39.97±0.066 –39.94±0.044 –39.95±0.033
4	0.0042	0.0808	0.5100	0.4051	0.605±0.0003 0.907±0.0004 1.209±0.0005	2.66±0.066 2.67±0.044 2.68±0.033	–27.95±0.066 –27.96±0.044 –27.97±0.033
5	–	0.0018	0.1116	0.8866	0.605±0.0003 0.907±0.0004 1.209±0.0005	9.06±0.066 9.05±0.044 9.07±0.033	–20.82±0.066 –20.84±0.044 –20.82±0.033
6	–	–	0.0124	0.9876	1.814±0.0007 2.116±0.0008 2.418±0.0010	10.27±0.022 10.28±0.019 10.27±0.017	–19.21±0.022 –19.20±0.019 –19.22±0.017
7	–	–	0.0013	0.9987	1.814±0.0007 2.116±0.0008 2.418±0.0010	10.39±0.022 10.40±0.019 10.38±0.017	–19.02±0.022 –19.01±0.019 –19.00±0.017
8	–	–	0.0001	0.9999	1.814±0.0007 2.116±0.0008 2.418±0.0010	10.42±0.022 10.43±0.019 10.41±0.017	–19.00±0.022 –18.99±0.019 –18.98±0.017

crystalline	ΔH^{2+}=–14.40 kJ mol^{-1}	ΔH^{+}=–9.88 kJ mol^{-1}	ΔH=–1.23 kJ mol^{-1}	ΔH^{-}=10.42 kJ mol^{-1}
amorphous	ΔH^{2+}=–47.68 kJ mol^{-1}	ΔH^{+}=–42.24 kJ mol^{-1}	ΔH=–32.45 kJ mol^{-1}	ΔH^{-}=–18.99 kJ mol^{-1}

Table 5 Molar enthalpy of solution of crystalline and amorphous cefotaxime sodium (CET) at pH range 1–8 and fractions of various species

pH	f^+	$f^\pm$	f^-	10^3[SS] (M)	$\Delta_{sol}H_{crys}$/kJ mol^{-1}	$\Delta_{sol}H_{amor}$/kJ mol^{-1}
				0.838±0.0003	–6.34±0.048	–26.07±0.048
1.0	0.9261	0.0736	–	1.256±0.0005	–6.35±0.032	–26.08±0.032
				1.675±0.0007	–6.33±0.024	–26.06±0.024
				0.838±0.0003	–6.05±0.048	–25.83±0.048
1.5	0.7972	0.2003	0.0025	1.256±0.0005	–6.04±0.032	–25.81±0.032
				1.675±0.0007	–6.06±0.024	–25.82±0.024
				0.838±0.0003	–5.37±0.048	–24.98±0.048
2.0	0.5476	0.4350	0.0173	1.256±0.0005	–5.38±0.032	–24.99±0.032
				1.675±0.0007	–5.39±0.024	–24.98±0.024
				0.838±0.0003	–4.03±0.048	–22.40±0.048
2.5	0.2612	0.6562	0.0826	1.256±0.0005	–4.02±0.032	–22.41±0.032
				1.675±0.0007	–4.01±0.024	–22.42±0.024
				0.838±0.0003	–1.54±0.048	–20.62±0.048
3.0	0.0826	0.6561	0.2612	1.256±0.0005	–1.55±0.032	–20.60±0.032
				1.675±0.0007	–1.55±0.024	–20.61±0.024
				0.838±0.0003	1.98±0.048	–17.17±0.048
3.5	0.0173	0.4350	0.5476	1.256±0.0005	1.97±0.032	–17.18±0.032
				1.675±0.0007	1.99±0.024	–17.19±0.024
				2.094±0.0008	4.96±0.019	–14.12±0.019
4.0	0.0025	0.2002	0.7972	2.513±0.0010	4.94±0.016	–14.11±0.016
				2.932±0.0012	4.95±0.014	–14.10±0.014
				2.094±0.0008	7.07±0.019	–12.04±0.019
5.0	–	0.0245	0.9754	2.513±0.0010	7.06±0.016	–12.05±0.016
				2.932±0.0012	7.06±0.008	–12.06±0.014
				2.094±0.0008	7.32±0.019	–11.77±0.019
6.0	–	0.0025	0.9974	2.513±0.0010	7.33±0.016	–11.78±0.016
				2.932±0.0012	7.31±0.014	–11.78±0.014
				3.351±0.0013	7.35±0.012	–11.76±0.012
8.0	–	–	0.9999	3.770±0.0015	7.36±0.011	–11.75±0.011
				4.188±0.0017	7.34±0.010	–11.74±0.010

crystalline	$\Delta H^+ = -6.50$ kJ mol^{-1}	$\Delta H^\pm = -4.46$ kJ mol^{-1}	$\Delta H^- = 7.35$ kJ mol^{-1}
amorphous	$\Delta H^+ = -26.16$ kJ mol^{-1}	$\Delta H^\pm = -23.75$ kJ mol^{-1}	$\Delta H^- = -11.75$ kJ mol^{-1}

Table 6 Thermodynamic parameters of dissolution (pH 7.4) and ionization of drugs

		Cefazolin sodium		Cefoperazone sodium		Ceftriaxone sodium		Cefotaxime sodium	
		cryst.	amorph.	cryst.	amorph.	cryst.	amorph.	cryst.	amorph.
s/mol L^{-1}		0.525		0.924		0.529		1.452	
$\Delta_{sol}G$/kJ mol^{-1}		1.664		0.204		1.642		–0.962	
$\Delta_{sol}S$/J K^{-1} mol^{-1}		63.79		38.03		28.23		26.76	
ΔH_{ion}/kJ mol^{-1}	1st	5.53	6.35	5.80	6.20	4.52	5.44	2.036	2.42
	2nd	–	–	8.18	8.37	8.65	9.79	11.807	11.99
	3rd	–	–	–	–	11.65	13.46	–	–
ΔG_{ion}/kJ mol^{-1}	1st	12.47	12.47	15.44	15.44	16.04	16.03	12.47	12.47
	2nd	–	–	56.71	56.71	19.63	19.63	20.19	20.19
	3rd	–	–	–	–	24.35	24.35	–	–
ΔS_{ion}/J K^{-1} mol^{-1}	1st	–22.38	–19.73	–31.08	–29.72	–27.12	–34.15	–33.69	–32.40
	2nd	–	–	–156.48	–155.86	–35.31	–31.72	–37.03	–26.76
	3rd	–	–	–	–	–40.95	–35.11	–	–

cryst. – crystalline, amorph. – amorphous

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