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Journal of Pharmaceutical and Biomedical Analysis 36 (2004) 295–307
JOURNAL OF PHARMACEUTICAL AND BIOMEDICAL ANALYSIS
www.elsevier.com/locate/jpba

Microcalorimetric evaluation of the in vitro compatibility of amoxicillin/clavulanic acid and ampicillin/sulbactam with ciprofloxacin

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Received 14 January 2004; received in revised form 27 April 2004; accepted 3 June 2004
Available online 30 July 2004

Abstract

Solution calorimetric technique has been used to determine the compatibility of binary and ternary systems of ampicillin trihydrate (AMP), sulbactam sodium (SS), amoxicillin trihydrate (AM), potassium clavulanate (PC) and ciprofloxacin hydrochloride (CP). The enthalpy of solution ($\Delta_{sol}H$) were obtained over a wide range of composition in the pH range 2–9. For all the pure drugs the $\Delta_{sol}H$ is endothermic in nature. The molar enthalpies of interaction of binary ($\Delta H^{E}_{bi.}$) and ternary ($\Delta H^{E}_{ter.}$) mixtures of the drugs in aqueous buffers have been determined. The $\Delta H^{E}_{bi.}$ for all binary systems is negative and pH dependent (maximum pH 6–8) indicating the interaction among charged species of the drugs. In case of binary systems with CP the magnitude of $\Delta H^{E}_{bi.}$ indicate strong interactions. The variation and magnitude of $\Delta H^{E}_{bi.}$ for the systems is discussed in terms of hydrogen bonding and van der Waal's interaction in the solution. The interaction parameter for ternary systems (A) is positive indicating repulsive interaction among the drugs. The coefficients h_i's calculated from Redlich–Kister equation for binary systems ($\Delta H^{E}_{bi.}$) and ternary interaction parameter (A) were used to predict the compatibility of the marketed formulations in pH range studied.

Keywords: Ampicillin trihydrate; Amoxicillin trihydrate; Ciprofloxacin hydrochloride; Enthalpy of solution; Potassium clavulanate; Solution calorimetry; Sulbactum sodium; Ternary interaction parameter

1. Introduction

Combination preparation of two or more active ingredients have attracted much interest because they can show synergistic curative effects and/or decreased side effects [1,2]. However, the existence of incompatibility between active ingredients or ingredients and excipients result in toxic or no clinical effects [3–5]. These drug interactions occurring outside the body may be categorized as physical or chemical and may occur during formulation, storage as well as while mixing ingredients. These are sometimes manifested by precipitation or color changes. Occasionally in vitro interactions occur without any observable change and can be determined quantitatively by determining their excess thermodynamic properties in solution [6,7].

Antibacterials accounts for between 3 and 25% of all prescriptions [8] and up to 50% of the drug budget in hospitals [9]. There is greater emphasis on achieving quality and cost-effective health care. One way of managing this, relevant to parenteral antibiotics, is to consider 'iv-to-oral' switch or sequential therapy [10]. Sequential therapy has been used to refer to conversion from intravenous to oral formulation of the same medication (maintaining equivalent potency). Examples of drugs that may be used for sequential therapy include metronidazole, ciprofloxacin, ofloxacin, co-amoxiclav and fluconazole [11]. The orally absorbed amoxicillin trihydrate/potassium clavulanate (AM/PC), the parenteral formulations of ampicillin sodium/sulbactam sodium (AMP/SS) and ticarcillin/potassium clavulanate (T/PC) [12] are marketed combinations. The pharmacodynamics, pharmacokinetics, safety, and efficacies of ampicillin–sulbactam and amoxicillin–clavulanic acid have been widely evaluated [13–16]. The binary mixture of amoxicillin trihydrate: potassium clavulanate combina-

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doi:10.1016/j.jpba.2004.06.003

tions (co-amoxiclav) and ciprofloxacin hydrochloride are prescribed in treatment of cancer patient with fever and neutropenia [5,6]. There are reports revealing the incompatibility of ciprofloxacin with co-amoxyclav and Unasyn preparations in solution [17–19].

Several methods, e.g. densitometric method, a liquid chromatographic method with electrochemical (EC) detection, capillary electrophoresis method and HPLC with beta-cyclodextrin stationary phase have been used for the quantitative determination of amoxicillin and clavulanic acid in pharmaceutical dosage forms [20–23]. A spectrophotometric method and capillary electrophoresis method have been used for ampicillin sodium and sulbactam sodium in pharmaceutical dosage forms [23,24]. Although methods are available for their simultaneous determination and quantitation in pharmaceutical dosage forms but not much information is revealed about their compatibility.

The use of microcalorimetry for excipients compatibility, product/container interaction studies, material source variation stability studies are likely to be major growth area in the pharmaceutical area [25]. In pervious work in our laboratory we have used solution calorimetry to study the compatibility of drugs by determining the excess thermodynamic parameters [6,7]. The use of immersion calorimetry to study interactions between additives (e.g. pigments, opacifers and talc) of hydroxypropyl methyl cellulose (HPMC) films has been reported [26]. Beside this not much published work exists relating to the use of microcalorimetry for interaction studies.

In order to quantify the specific or non-specific interactions between binary and ternary systems of the drugs in buffered aqueous solution, we have used the solution calorimetry. The molar enthalpy of interaction has been calculated to quantify the extent of interaction in binary and ternary systems. The present communication propose a method to study drug–drug interaction during the dissolution of their mixtures. As far as we know no direct calorimetric data have been reported for the above mentioned drugs and their mixtures.

2. Methods and materials

2.1. Chemicals

Amoxicllin trihydrate (AM) and potassium clavulanate (PC) (Osaka Pharmaceutical Ltd., India), ampicillin trihydrate (AMP) and sulbactum sodium (SS) (Morpen Laboratories Ltd., India), ciprofloxacin hydrochloride (CP) (Dr. Reddy's Laboratories Ltd., India) were procured as gift samples and used without further purification. All the drugs were sieved and fractions with particle size 80–150 μm were used throughout the study. Phosphate buffers were prepared using AR grade chemicals.

2.2. Buffers

In the present studies phosphate buffers were prepared by mixing solutions of appropriate sodium salts of phosphoric acid according to the given procedures [27]. The ionic strength of all phosphate buffers was 0.05 M. The pH values of various phosphate buffers were measured using pH meter (Elico, India) standardized with solution of pH 4.0, 7.0 and 9.2.

2.3. Solution calorimetry

The system used to determine the enthalpies of solution was isoperibol solution calorimeter (ISC) model 4300 (Calorimetry Science Corporation, Utah, USA). 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 enthalpy of solution measurements the individual drugs and their binary, ternary mixtures were filled into batch adapter of volume 0.9 ml sealed on both end with o-ring and glass ampoules. This was then inserted in to the Dewar flask containing solution (25 ± 0.01 ml), the batch adapter holding the drug isolated from the solution. The combined unit was then lowered in to the calorimeter water bath held at 37 °C. The glass stirrer was rotated at 100 revolution/min 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 by means of a plunger, releasing the drug into the solution and allowing dissolution. The ensuing heat changes was detected by a thermistor within the vessel enabling measurement of the enthalpy of solution.

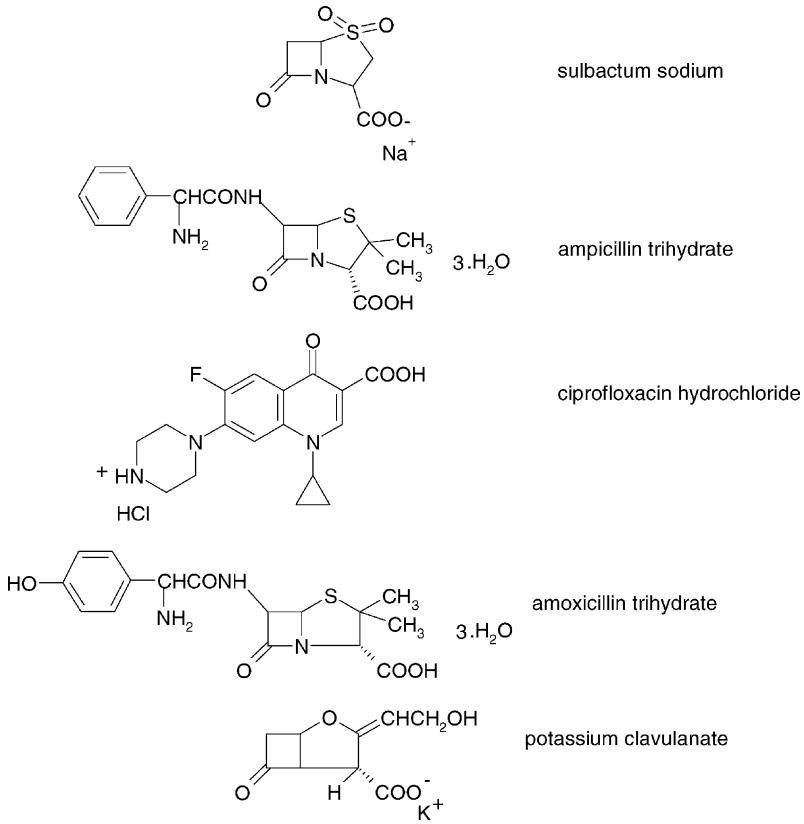
The performance of the system was checked using potassium chloride and tris (hydroxymethyl) aminomethane, both of which have known enthalpies of solution, a good agreement (±0.03 kJ mol^{-1}) was found with the published values. The precision of any individual measurement was better than 0.02 kJ mol^{-1} for three consecutive experiments and agreed with the standard value within ±0.03 kJ mol^{-1}.

The binary and ternary mixtures of the drugs have been prepared by mixing the weighed amounts of the drugs mechanically. Minimum weight of any one of the drugs in the mixture was 3.000 mg and maximum weight was 10.000 mg. The maximum uncertainty in weight is ±0.001 mg leading to an uncertainty ±0.0005 in mole fraction. For example mole fraction $x_1 = 0.5308$ was prepared by mixing 8.000 mg of AM and 4.000 mg of PC. In calculating the mole fraction we do not take into account water and other electrolytes present in aqueous buffers and call it apparent mole fraction. For each sample three replicate investigations were performed and results are quoted as mean values.

3. Results and discussion

3.1. Enthalpy of solutions

The structural formulae of the drugs for which the enthalpies of solution have been determined are given below.



The molar enthalpies of solution values of sulbactum sodium, ampicillin trihydrate, ciprofloxacin hydrochloride, amoxicillin trihydrate, and potassium clavulanate at different pH and concentrations are given in Tables 1–5. An endothermic behavior has been observed for all the drugs and the molar enthalpy of solution of the drugs is nearly independent of concentration (0.572–1.189 $\times$ 10^{-3} M). Therefore an average value has been taken for $\Delta_{sol}H$ of a drug at a particular pH within concentration range. The variation of $\Delta_{sol}H$ with pH is due to presence of different species of the drugs in varying amounts due to protonation or deprotonation. The corresponding fractions of the drug species determined from their pK_a's values are also reported (Tables 1–5). The pK_a values are taken from literature [28–31] and are given in Table 6. 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 constants and $\Delta_{sol}H_i$ represents its enthalpy of solution.

Values of $\Delta_{sol}H_i$ corresponding to various particular species of the drugs have been calculated by simultaneously solving Eq. (1) from the measured values of $\Delta_{sol}H$ at different pH. The values of $\Delta_{sol}H_i$ for different species give the enthalpy of ionization and combining these values with ionization constants a complete set of thermodynamic quantities for ionization of the drug have been calculated and are given in Table 6.

It may be mentioned that $\Delta_{sol}H$ for amoxicillin trihydrate and ampicillin trihydrate (pH 2, 5 and 7) are in agreement with the values reported in our previous study [6]. The endothermic behavior of enthalpies of solution indicates weak interaction between drugs and aqueous buffer. The values of molar free energy of solution (Tables 1–5) has been calculated using the following equation:

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

where s is the molar solubility of the drugs.

The values of s are available only at a few selected pH and temperature and have been taken from literature [29,32–34]. The molar entropy of solution of drugs calculated from the equation $\Delta S = (\Delta H - \Delta G)/T$ are also given in Tables 1–5. The positive values of entropy of solution indicate that the dissolution is largely entropically driven.

Table 1
Molar enthalpy of solution at different pH 2–7 (310.15 K) and fractions of various species of sulbactam sodium (SS) at the corresponding pH

pH	f^+	f^-	[SS] ($\times 10^3$ M)	$\Delta_{sol}H$ (kJ mol^{-1})	$\Delta_{sol}G$ (kJ mol^{-1})	$\Delta_{sol}S$ (J K^{-1} mol^{-1})
2.0	0.7992	0.2008	1.567	5.45 ± 0.025	–	–
			2.351	5.41 ± 0.017		
			3.134	5.43 ± 0.013		
3.0	0.2848	0.7153	1.567	7.59 ± 0.025	–	–
			2.351	7.58 ± 0.017		
			3.134	7.57 ± 0.013		
4.0	0.0383	0.9617	2.351	8.64 ± 0.017	–	–
			3.134	8.61 ± 0.013		
			3.918	8.61 ± 0.010		
5.0	0.0040	0.9960	2.351	8.73 ± 0.017	–	–
			3.134	8.77 ± 0.013		
			3.918	8.78 ± 0.010		
6.0	0.0004	0.9996	2.351	8.77 ± 0.017	–	–
			3.134	8.77 ± 0.013		
			3.918	8.77 ± 0.010		
7.0	–	0.9999	2.351	8.78 ± 0.017	14.29	17.77
			3.134	8.78 ± 0.013		
			3.918	8.78 ± 0.010		

$\Delta H_+ = 4.59$ kJ mol^{-1}, $\Delta H_- = 8.78$ kJ mol^{-1}.

Table 2
Molar enthalpy of solution at different pH 1–10 (310.15 K) and fractions of various species of ampicillin trihydrate (AMP) at the corresponding pH

pH	f^+	$f^\pm$	f^-	[AMP] ($\times 10^3$ M)	$\Delta_{sol}H$ (kJ mol^{-1})	$\Delta_{sol}G$ (kJ mol^{-1})	$\Delta_{sol}S$ (J K^{-1} mol^{-1})
1	0.9697	0.0307	–	0.892	12.80 ± 0.044	3.575	29.77
				0.991	12.82 ± 0.040		
				1.189	12.81 ± 0.033		
2	0.7598	0.2403	–	0.892	13.47 ± 0.044	4.726	28.09
				0.991	13.43 ± 0.040		
				1.189	13.42 ± 0.033		
3	0.2402	0.7597	–	0.892	15.02 ± 0.044	8.433	21.17
				0.991	14.99 ± 0.040		
				1.189	15.00 ± 0.033		
4	0.0306	0.9688	–	0.892	15.62 ± 0.044	9.131	21.01
				0.793	15.66 ± 0.050		
				0.743	15.67 ± 0.055		
5	0.0031	0.9906	0.0063	0.694	15.86 ± 0.055	9.221	21.37
				0.793	15.85 ± 0.050		
				0.892	15.87 ± 0.044		
6	–	0.9404	0.0593	0.694	16.98 ± 0.055	9.131	25.24
				0.743	16.95 ± 0.050		
				0.892	16.95 ± 0.044		
7	–	0.6131	0.3869	0.595	23.78 ± 0.067	8.877	47.95
				0.694	23.74 ± 0.055		
				0.793	23.73 ± 0.050		
8	–	0.1368	0.8632	0.595	33.60 ± 0.067	4.150	95.01
				0.694	33.63 ± 0.055		
				0.793	33.63 ± 0.050		
9	–	0.0156	0.9844	0.892	36.11 ± 0.055	–	–
				0.793	36.15 ± 0.050		
				0.743	36.16 ± 0.044		
10	–	0.0016	0.9984	0.892	36.43 ± 0.044	–	–
				0.991	36.44 ± 0.040		
				1.189	36.42 ± 0.033		

$\Delta H_+ = 12.71$ kJ mol^{-1}, $\Delta H_\pm = 15.73$ kJ mol^{-1}, $\Delta H_- = 36.46$ kJ mol^{-1}.

3.2. Interaction studies of binary mixtures

The enthalpy of solution ($\Delta_{sol}H_{bi.}$) per mole of the binary mixtures (AM:PC, AM:CP, PC:CP, AMP:SS, AMP:CP, and SS:CP) are given in Tables 7 and 8. The extent of molecular interaction between drugs in a binary system can be related to the molar enthalpy of interaction of binary mixtures. Thus the molar enthalpy of interaction ($\Delta H^E_{bi.}$) in the present study

Table 3
Molar enthalpy of solution at different pH 2–10 (310.15 K) and fractions of various species of ciprofloxacin hydrochloride (CP) at the corresponding pH

pH	f^+	$f^{\pm}$	f^-	[CP] ($\times 10^3$ M)	$\Delta_{sol}H$ (kJ mol^{-1})	$\Delta_{sol}G$ (kJ mol^{-1})	$\Delta_{sol}S$ (J K^{-1} mol^{-1})
2	0.9999	0.0001	–	0.882	37.69 ± 0.048	–	–
				0.934	37.72 ± 0.042		
				1.038	37.69 ± 0.038		
3	0.9990	0.0010	–	0.882	37.72 ± 0.048	–	–
				0.934	37.70 ± 0.042		
				1.038	37.68 ± 0.038		
4	0.9900	0.0100	–	0.830	37.75 ± 0.048	–	–
				0.882	37.77 ± 0.045		
				0.934	37.76 ± 0.042		
5	0.8632	0.1368	–	0.830	38.50 ± 0.048	10.655	89.85
				0.882	38.53 ± 0.045		
				0.934	38.53 ± 0.042		
6	0.3867	0.6129	–	0.830	41.41 ± 0.048	–	–
				0.882	41.36 ± 0.045		
				0.934	41.37 ± 0.042		
7	0.0588	0.9319	0.0093	0.674	43.47 ± 0.059	18.934	79.11
				0.726	43.46 ± 0.055		
				0.830	43.48 ± 0.048		
8	0.0057	0.9039	0.0904	0.674	44.99 ± 0.059	–	–
				0.726	44.97 ± 0.055		
				0.830	44.98 ± 0.048		
9	0.0003	0.4998	0.4998	0.830	51.04 ± 0.048	16.351	111.94
				0.882	51.08 ± 0.045		
				0.934	51.09 ± 0.042		
10	–	0.0909	0.9091	0.830	57.12 ± 0.048	–	–
				0.882	57.11 ± 0.045		
				0.934	57.13 ± 0.042		

$\Delta H_+ = 37.70\,\text{kJ mol}^{-1}$, $\Delta H_{\pm} = 43.68\,\text{kJ mol}^{-1}$, $\Delta H_- = 58.47\,\text{kJ mol}^{-1}$.

is defined by the equation:

$$\Delta H^{E}_{bi.} = \Delta_{sol}H_{bi.} - [x_1\Delta_{sol}H_1 + x_2\Delta_{sol}H_2] \quad (3)$$

where x_i is the apparent mole fraction of component 'i', $\Delta_{sol}H_i$ the molar enthalpy of solution of component 'i', $\Delta_{sol}H_{bi.}$ the molar enthalpy of interaction in binary mixtures.

It has been found that $\Delta H^{E}_{bi.}$ fits well with the Redlich–Kister equation [35] having two parameters for all the binary mixtures.

$$\Delta H^{E}_{bi.} = x_1x_2[h_1 + h_2(x_1 - x_2)] \quad (4)$$

The least squares method was used to determine the values of h_i's for different systems and their values are given in Table 9. The value of ($\Delta H^{E}_{bi.}$) can be calculated at any mole fractions using the coefficients given in Table 9. Fig. 1 shows the calculated molar enthalpy of interaction values for ampicillin and sulbactam sodium binary mixtures as solid curves and experimental values as points at different pH. Similar curves are obtained for other binary mixtures.

Tables 7 and 8 show that enthalpies of interaction ($\Delta H^{E}_{bi.}$) of all the binary systems are negative indicating stronger interaction of the drugs between themselves and little interaction with the solvent. It may be noted that the $\Delta H^{E}_{bi.}$ varies with the pH. The behavior can be explained in terms of varying interaction between different ionic species of each drug at a particular pH. The drugs such as amoxicillin, ampicillin and ciprofloxacin are amphoteric while sulbactum sodium

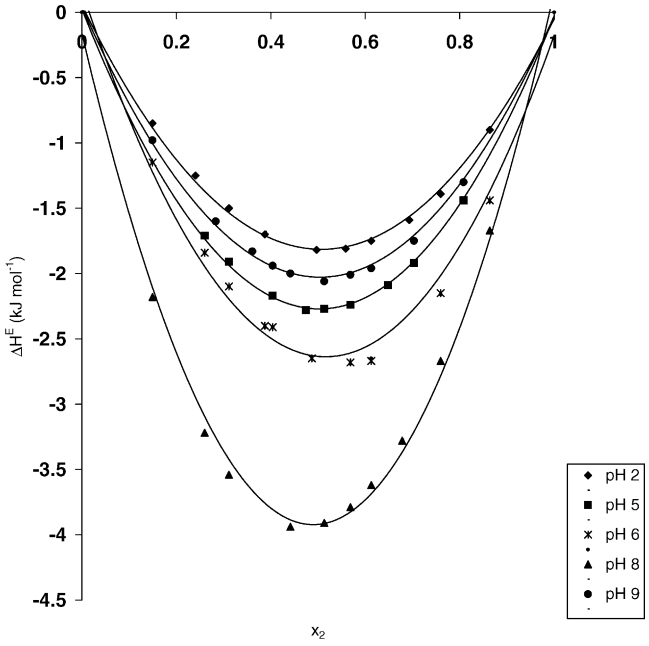


Fig. 1. Molar enthalpies of interaction ($\Delta H^{E}_{bi.}$) of binary mixtures of ampicillin trihydrate and sulbactam sodium at pH 2, 4, 6, 8, and 9. The solid lines were calculated using Eq. (4) and the experimental values represent points.

Table 4
Molar enthalpy of solution at different pH 1–10 (310.15 K) and fractions of various species of amoxicillin trihydrate (AM) at the corresponding pH

pH	f^+	$f^\pm$	f^-	f^{2-}	[AM] ($\times 10^3$ M)	$\Delta_{sol}H$ (kJ mol^{-1})	$\Delta_{sol}G$ (kJ mol^{-1})	$\Delta_{sol}S$ (J K^{-1} mol^{-1})
1	0.9771	0.0229	–	–	0.858	15.88 ± 0.046	4.283	37.42
					0.954	15.92 ± 0.041		
					1.144	15.87 ± 0.034		
2	0.8101	0.1899	–	–	0.858	16.32 ± 0.046	6.210	32.56
					0.954	16.30 ± 0.041		
					1.144	16.31 ± 0.034		
3	0.2852	0.6686	–	–	0.858	16.76 ± 0.046	10.090	21.54
					0.954	16.79 ± 0.041		
					1.144	16.76 ± 0.034		
4	0.0409	0.9585	–	–	0.667	18.20 ± 0.059	11.010	23.21
					0.763	18.24 ± 0.052		
					0.858	18.19 ± 0.046		
5	0.0042	0.9889	0.0069	–	0.667	18.47 ± 0.059	11.200	23.34
					0.763	18.42 ± 0.052		
					0.858	18.43 ± 0.046		
6	0.0004	0.9349	0.0647	–	0.667	19.57 ± 0.059	11.010	40.73
					0.763	19.58 ± 0.052		
					0.858	19.56 ± 0.046		
7	–	0.5904	0.4085	–	0.572	26.25 ± 0.069	9.960	52.41
					0.667	26.21 ± 0.059		
					0.763	26.20 ± 0.052		
8	–	0.1233	0.8527	0.0240	0.572	35.46 ± 0.069	6.510	93.36
					0.667	35.45 ± 0.059		
					0.763	35.49 ± 0.052		
9	–	0.0112	0.7714	0.2174	0.667	38.80 ± 0.059	–	–
					0.763	38.84 ± 0.052		
					0.858	38.85 ± 0.046		
10	–	0.0004	0.2618	0.7378	0.858	42.35 ± 0.046	–	–
					0.954	42.33 ± 0.041		
					1.144	42.34 ± 0.034		

$\Delta H_+ = 15.84\,\text{kJ mol}^{-1}$, $\Delta H_\pm = 18.32\,\text{kJ mol}^{-1}$, $\Delta H_- = 37.71\,\text{kJ mol}^{-1}$, $\Delta H_{2-} = 43.99\,\text{kJ mol}^{-1}$.

Table 5
Molar enthalpy of solution at different pH 1–6 (310.15 K) and fractions of various species of potassium clavulanate (PC) at the corresponding pH

pH	f^+	f^-	[PC] ($\times 10^3$ M)	$\Delta_{sol}H$ (kJ mol^{-1})	$\Delta_{sol}G$ (kJ mol^{-1})	$\Delta_{sol}S$ (J K^{-1} mol^{-1})
1.0	0.9617	0.0383	1.686	6.26 ± 0.024	−1.592	27.73
			2.529	6.25 ± 0.016		
			3.372	6.21 ± 0.012		
2.0	0.7152	0.2848	1.686	7.01 ± 0.024	−1.922	28.80
			2.529	7.02 ± 0.016		
			3.372	7.00 ± 0.012		
3.0	0.2008	0.7992	1.686	8.78 ± 0.024	−4.093	41.53
			2.529	8.79 ± 0.016		
			3.372	8.80 ± 0.012		
4.0	0.0245	0.9755	2.529	9.41 ± 0.016	−4.180	43.72
			3.372	9.36 ± 0.012		
			4.215	9.37 ± 0.010		
5.0	0.0025	0.9975	2.529	9.41 ± 0.016	−4.191	43.90
			3.372	9.45 ± 0.012		
			4.215	9.43 ± 0.010		
6.0	0.0002	0.9998	2.529	9.48 ± 0.016	−4.223	44.14
			3.372	9.47 ± 0.012		
			4.215	9.49 ± 0.010		

$\Delta H_+ = 6.14\,\text{kJ mol}^{-1}$, $\Delta H_\pm = 9.47\,\text{kJ mol}^{-1}$.

and potassium clavulanate are salts of moderately strong acids. Therefore the interaction of drugs with each other depends upon the dominant charged species present at the experimental pH.

In the system between ampicillin and sulbactum, at pH 2 the cationic form of the ampicillin is the major species where the amino group is protonated and carboxylic acid group is not dissociated. The exothermic interaction is attributed

Table 6
Protonation entropy and free energy of drugs at 310.15 K

Drug	pK	$\Delta_{ion}G$ (kJ mol^{-1})	$\Delta_{ion}H$ (kJ mol^{-1})	$\Delta_{ion}S$ (J K^{-1} mol^{-1})
SS	2.60	15.43	4.19	−36.24
PC	2.40	14.25	3.33	−35.21
AMP	2.50 (1st ion.)	14.85	3.02	−38.14
	7.20 (2nd ion.)	42.74	20.73	−70.97
AM	2.63 (1st ion.)	15.61	2.48	−42.33
	7.16 (2nd ion.)	42.50	19.39	−74.51
	9.55 (3rd ion.)	56.71	6.28	−162.59
CP	6.00 (1st ion.)	35.61	5.98	−95.53
	8.80 (2nd ion.)	52.23	14.79	−120.72

to the hydrogen bond between protonated amino group of AMP and ionized carboxylic acid group of sodium sulbactum. As the pH increases, the zwitterionic form of ampicillin predominates in the solution as well as de-protonation of carboxylic group of sulbactum is also complete, resulting in more negative $\Delta H^{E}_{bi.}$ (up to pH 8). After this stage there is the possibility that un-protonated amino group interact with sulbactum through hydrogen bonding with sulphoxide group but at the same time there may be repulsive interaction between both the negatively charged species.

In case of ampicillin and ciprofloxacin, at pH less than pK_{a_1} of ciprofloxacin hydrochloride i.e. at pH 2 both piperazinyl nitrogen and 3-carboxylic acid groups are protonated. Beside this there is an intra-molecular hydrogen bond formation between carboxylic acid group and neighboring keto function resulting in the stabilization of protonated species and avoiding hydrogen bonding with cationic form of ampicillin. However, there is possibility of hydrogen bond formation through the F and carboxyl functional groups of CP with cationic form of AMP. At pH 5, carboxylic acid group starts de-protonating resulting in zwitterionic form of ciprofloxacin which can interact with zwitterionic form of ampicillin, leading to more negative molar enthalpy of interaction for the system. The increase in the absolute value of the $\Delta H^{E}_{bi.}$ with further increase in pH (Table 7) can be explained by the fact the zwitterionic form of ciprofloxacin increases with pH and at pH 8, it is the predominant species.

The results for the second set of binary system containing any two of amoxicillin trihydrate, potassium clavulanate and ciprofloxacin can be explained by assuming that at pH 7 the interaction is strong between predominant zwitterionic species of ciprofloxacin and with cationic and zwitterionic species of amoxicillin (present nearly in equal amounts). Interaction between both the drugs can also take place through hydrogen bond between phenolic group of amoxicillin and protonated piperazinyl nitrogen and keto group of ciprofloxacin. The decrease in absolute value of $\Delta H^{E}_{bi.}$ above pH 8 may be due to deprotonation of phenolic group. The OH and NH_2 groups may be involved in strong hydrogen bonding [36]. The high conformational flexibility of OH and the ability to form strong hydrogen bonding leads to the difference in the $\Delta H^{E}_{bi.}$ between amoxicillin and ampicillin with ciprofloxacin in binary systems.

In all the binary systems where ciprofloxacin is one of the components the interactions are highly exothermic indicating strong deviation from ideality. This is in agreement with the results reported on the visual non-compatibility of ciprofloxacin (2 mg/ml) with ampicillin/sulbactum sodium and amoxicillin/potassium clavulanate [19]. The results of these authors are based on the appearance of precipitate when ciprofloxacin in 5% dextrose solution was combined with the amoxicillin/potassium clavulanate. While in case of ampicillin trihydrate: sulbactum sodium there is change in pH by more than one unit. Similar results are reported on the incompatibility of ondesteron hydrochloride (1 mg/ml) with ampicillin sodium/sulbactam sodium (2 mg/ml) [37].

In the present study we have explored the possibility of relating compatibility with magnitude and sign of $\Delta H^{E}_{bi.}$. The results indicate that the binary mixtures: amoxicillin trihydrate and potassium clavulanate deviate from ideality at all the pH. The $\Delta H^{E}_{bi.}$ have been calculated using the values of h_i's (Table 9) to assess the interaction between two active ingredients in marketed tablet and injection dosages forms. The mole fraction of potassium clavulanate (x_2) in tablet dosages form of Augmentin 375® (250 + 125 mg) is 0.4693, in Augmentin 625 DUO® (500 + 125 mg) is 0.3067 and in Augmentin 1000 DUO® (875 + 125 mg) is 0.2017. The $\Delta H^{E}_{bi.}$ values calculated are −2.3340, −1.9072 and −1.4019 kJ mol^{-1} at pH 2 respectively. The oral suspension Co-Amoxiclav® (250 + 62.5 mg) has pH 5 (approx.) having mole fraction of potassium clavulanate ($x_2 = 0.3067$), the calculated value of $\Delta H^{E}_{bi.}$ at this pH is −2.659 kJ mol^{-1}. These values indicate that there is only physical interaction arising due to hydrogen bonding and van der Waal's interaction. Thus the interaction is not alarming for the Co-Amoxiclav® oral suspension and tablet dosage forms (Agumentin®). The ampicillin and sulbactam sodium are available in tablet and injection dosages forms. Unasyn® tablet and injection contain ampicillin:sulbactam in 2:1 ratio ampicillin (250 mg) and sulbactam sodium (125 mg). The calculated values of $\Delta H^{E}_{bi.}$ is −1.7682 and −3.937 kJ mol^{-1} at pH 2 and 8 respectively.

3.3. Interaction studies of ternary mixtures

The enthalpy of solution ($\Delta_{sol}H_{ter.}$) per mole of ternary mixtures (AM:PC:CP and AMP:SS:CP) were also determined at number of mole fractions (Tables 10 and 11). The molar enthalpy of interaction ($\Delta H^{E}_{ter.}$) of ternary system were obtained by the following equation:

$$\Delta H^{E}_{ter.} = \Delta_{sol}H_{ter.} - [x_1\Delta_{sol}H_1 + x_2\Delta_{sol}H_2 + x_3\Delta_{sol}H_3] \quad (5)$$

Table 7
Molar enthalpies of solution ($\Delta_{sol}H_{bi.}$) and excess molar enthalpies of solution ($\Delta H^{E}_{bi.}$) for the binary mixtures of drugs in buffers at different pH and 310.15 K

pH 2			pH 4			pH 6			pH 8			pH 9	
x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})
AMP (1) + SS (2)														
0.1494	11.39	−0.85	0.1494	13.50	−1.10	0.1494	14.59	−1.15	0.1494	27.73	−2.18	0.1494	31.09	−2.26
0.2402	10.27	−1.25	0.2600	12.16	−1.66	0.2600	12.99	−1.84	0.2600	23.94	−3.22	0.2833	26.79	−3.62
0.3112	9.45	−1.50	0.3112	11.61	−1.85	0.3112	12.31	−2.10	0.3112	22.35	−3.54	0.3609	24.44	−4.15
0.3874	8.64	−1.70	0.3874	10.89	−2.04	0.3874	11.39	−2.40	0.4415	18.71	−3.94	0.4039	23.15	−4.34
0.4970	7.64	−1.82	0.4415	10.42	−2.12	0.4868	10.32	−2.65	0.5131	16.96	−3.91	0.4415	22.07	−4.42
0.5585	7.15	−1.81	0.5131	9.88	−2.16	0.5685	9.62	−2.68	0.5685	15.71	−3.79	0.5131	20.04	−4.55
0.6126	8.59	−1.75	0.5585	9.61	−2.11	0.6126	9.27	−2.67	0.6126	14.78	−3.62	0.5685	18.58	−4.46
0.6931	6.30	−1.59	0.6126	9.33	−2.01	0.7034	8.79	−2.41	0.6782	13.49	−3.28	0.6126	17.42	−4.32
0.7597	5.96	−1.39	0.7597	8.77	−1.54	0.7597	8.59	−2.15	0.7597	12.08	−2.67	0.7034	15.15	−3.81
0.8635	5.62	−0.90	0.8259	8.63	−1.21	0.8635	8.45	−1.44	0.8635	10.50	−1.67	0.8083	12.73	−2.85
AMP (1) + CP (3)														
0.1975	16.77	−1.46	0.2073	18.08	−2.15	0.2073	19.21	−2.81	0.2073	32.49	−3.48	0.1975	35.23	−3.86
0.2950	18.71	−1.89	0.2746	19.15	−2.57	0.2585	20.01	−3.26	0.2585	32.50	−4.06	0.2585	35.35	−4.65
0.3434	19.58	−2.19	0.3856	21.16	−3.01	0.3434	21.55	−3.80	0.3434	32.77	−4.75	0.3434	35.79	−5.48
0.4108	21.24	−2.16	0.4657	22.84	−3.11	0.4000	22.70	−4.03	0.4000	33.09	−5.07	0.4108	36.40	−5.88
0.4657	22.54	−2.20	0.5112	23.86	−3.09	0.4396	23.57	−4.12	0.4396	33.41	−5.20	0.4657	37.04	−6.05
0.5112	23.81	−2.03	0.5115	23.84	−3.12	0.4566	24.05	−4.06	0.5112	34.17	−5.26	0.5112	37.71	−6.06
0.6107	26.19	−2.06	0.5666	25.13	−3.05	0.5112	25.29	−4.15	0.5666	34.90	−5.16	0.5666	38.65	−5.95
0.6766	27.98	−1.87	0.6355	26.88	−2.82	0.6655	29.46	−3.75	0.6655	35.98	−4.86	0.6107	39.50	−5.76
0.7234	29.29	−1.70	0.7233	29.32	−2.32	0.7234	31.36	−3.26	0.7234	37.65	−4.19	0.7583	43.03	−4.43
0.8075	31.73	−1.30	0.8075	31.68	−1.82	0.8075	34.17	−2.51	0.8075	39.54	−3.25	0.8075	44.44	−3.76
SS (2) + CP (3)														
0.1282	7.77	−1.80	0.1282	9.96	−2.40	0.1282	7.45	−5.50	0.1282	8.82	−4.60	0.1282	10.34	−3.85
0.2092	9.48	−2.70	0.2209	15.06	−3.85	0.2209	7.47	−8.50	0.2092	9.14	−7.00	0.2209	12.02	−6.09
0.3060	11.80	−3.50	0.3061	12.62	−4.92	0.3316	8.38	−11.20	0.3316	11.18	−9.60	0.3061	13.98	−7.74
0.3981	14.38	−3.90	0.3981	14.40	−5.82	0.3981	9.65	−12.10	0.3981	12.69	−10.50	0.3981	16.58	−9.03
0.4526	15.93	−4.10	0.4527	15.76	−6.05	0.4687	11.25	−12.80	0.4526	14.16	−11.00	0.4526	18.36	−9.55
0.4981	17.40	−4.10	0.4981	16.82	−6.31	0.5142	12.64	−12.90	0.4981	15.61	−11.20	0.4981	20.10	−9.74
0.5695	19.81	−4.00	0.5700	18.97	−6.26	0.5981	16.18	−12.40	0.5695	18.30	−11.10	0.6069	24.79	−9.65
0.6136	21.33	−3.90	0.6653	22.00	−6.01	0.6649	18.75	−11.70	0.6494	21.79	−10.50	0.6650	27.74	−9.16
0.6649	23.19	−3.70	0.7484	25.31	−5.12	0.7484	23.27	−9.90	0.6984	24.26	−9.80	0.7484	32.48	−7.95
0.7484	26.48	−3.10	0.8881	31.70	−2.80	0.8881	32.43	−5.30	0.7484	26.97	−8.90	0.8881	41.97	−4.37

Table 8
Molar enthalpies of solution ($\Delta_{sol}H_{bi.}$) and excess molar enthalpies of solution ($\Delta H^{E}_{bi.}$) for the binary mixtures of drugs in buffers at different pH and 310.15 K

pH 2				pH 5			pH 7			pH 8			pH 9	
x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})	x_2	$\Delta_{sol}H_{bi.}$ (kJ mol^{-1})	$\Delta H^{E}_{bi.}$ (kJ mol^{-1})
AM (1) + PC (2)														
0.1810	13.347	−1.28	0.2017	14.698	−1.93	0.1586	9.466	−2.66	0.1710	28.735	−2.03	0.1810	32.027	−1.49
0.3065	11.549	−1.91	0.3065	13.022	−2.66	0.2612	9.902	−3.75	0.2613	25.947	−2.73	0.3065	27.592	−2.24
0.4142	10.218	−2.24	0.3708	12.112	−2.99	0.3612	11.149	−4.37	0.3708	22.430	−3.40	0.3356	26.608	−2.37
0.4692	9.616	−2.33	0.4692	10.904	−3.31	0.4299	12.098	−4.56	0.3987	21.564	−3.54	0.4144	24.004	−2.66
0.5148	9.152	−2.37	0.5701	9.934	−3.37	0.4751	12.847	−4.58	0.4692	19.531	−3.74	0.4692	22.275	−2.78
0.5701	8.648	−2.36	0.6388	9.434	−3.25	0.5308	13.850	−4.51	0.5249	18.013	−3.81	0.5148	20.876	−2.84
0.6388	8.099	−2.27	0.7262	9.015	−2.88	0.6013	11.674	−4.25	0.5708	16.840	−3.79	0.5701	19.263	−2.83
0.6627	5.666	−2.20	0.6797	9.195	−3.12	0.6292	15.898	−4.11	0.6388	15.222	−3.64	0.6627	16.724	−2.65
0.7022	7.699	−2.08	0.7796	8.874	−2.54	0.7387	18.552	−3.29	0.7388	13.131	−3.13	0.7022	15.694	−2.52
0.8414	7.115	−1.37	0.8761	8.893	−1.65	0.8190	20.717	−2.47	0.8414	11.374	−2.22	0.8414	12.447	−1.68
AM (1) + CP (3)														
0.2137	17.761	−3.12	0.2137	18.171	−3.74	0.2137	23.725	−6.18	0.2137	30.303	−7.20	0.2137	38.937	−2.51
0.3031	18.814	−3.98	0.3031	19.581	−4.94	0.3031	23.567	−7.88	0.3031	29.153	−9.20	0.3031	39.371	−3.17
0.3522	19.511	−4.33	0.3522	20.026	−5.50	0.3522	23.714	−8.58	0.3522	28.720	−10.10	0.3522	39.692	−3.45
0.4203	20.623	−4.68	0.4203	20.807	−6.07	0.4203	24.219	−9.25	0.4203	28.468	−11.00	0.4203	40.276	−3.70
0.4652	21.451	−4.81	0.4652	21.363	−6.35	0.4652	24.599	−9.54	0.4652	28.453	−11.30	0.4652	40.590	−3.78
0.5112	22.378	−4.87	0.5112	28.184	−6.52	0.5112	25.377	−9.66	0.5112	28.832	−11.50	0.5112	41.278	−3.81
0.6199	24.904	−4.67	0.6199	24.408	−6.48	0.6199	27.653	−9.26	0.6199	30.266	−11.10	0.6199	42.808	−3.61
0.6850	26.646	−4.31	0.6850	24.025	−6.11	0.6850	29.446	−8.59	0.6850	31.685	−10.30	0.6850	43.885	−3.33
0.7311	27.988	−3.96	0.7311	27.433	−5.69	0.7311	30.941	−7.89	0.7311	32.923	−9.50	0.7311	44.739	−3.04
0.8131	30.603	−3.10	0.8131	30.210	−4.56	0.8131	34.076	−6.17	0.8131	35.703	−7.50	0.8131	46.423	−2.36
PC (2)+ CP (3)														
0.1874	12.761	−2.56	0.1874	11.814	−3.19	0.1874	10.518	−5.45	0.1874	11.261	−4.99	0.1874	14.783	−2.61
0.2908	12.552	−3.38	0.2908	13.686	−4.20	0.2908	12.107	−7.25	0.2908	13.156	−6.64	0.2908	18.057	−3.51
0.3297	13.534	−3.59	0.3297	14.558	−4.46	0.3297	12.960	−7.72	0.3297	14.118	−7.06	0.3297	19.436	−3.75
0.3808	14.903	−3.79	0.3808	15.814	−4.69	0.3808	14.247	−8.17	0.3808	15.482	−7.51	0.3808	21.331	−3.98
0.4798	17.806	−3.93	0.4798	18.555	−4.83	0.4798	17.293	−8.49	0.4798	18.708	−7.80	0.4798	25.240	−4.19
0.6059	21.951	−3.66	0.6059	22.604	−4.45	0.6059	22.141	−7.93	0.6059	23.686	−7.30	0.6059	30.695	−3.98
0.6485	23.457	−3.45	0.6485	24.103	−4.19	0.6485	24.009	−7.51	0.6485	25.618	−6.88	0.6485	32.668	−3.78
0.6828	24.708	−3.26	0.6828	25.341	−3.95	0.6828	25.595	−7.09	0.6828	27.216	−6.50	0.6828	34.284	−3.59
0.7546	27.430	−2.74	0.7546	28.080	−3.30	0.7546	29.146	−5.98	0.7546	30.786	−5.48	0.7546	37.811	−3.05
0.7999	29.217	−2.34	0.7999	29.888	−2.81	0.7999	31.147	−5.12	0.7999	33.184	−4.69	0.7999	40.116	−2.63

Table 9
Parameters (h_i's) of Redlich–Kister equation for the binary systems of drugs in buffers of different pH

pH	AMP + SUL		AMP + CP		SS + CP	
	h_1	h_2	h_1	h_2	h_1	h_2
2	−7.2486	0.6610	−8.7962	−0.6873	−16.4233	0.1746
4	−8.5642	−0.1932	−12.4286	−1.2189	−25.0597	4.6817
6	−10.6474	2.2514	−16.6457	−0.5739	−51.3288	2.8802
8	−15.7272	−2.0814	−21.1488	0.0709	−44.7900	4.5454
9	−8.1446	0.5543	−24.2597	−0.1274	−39.0292	6.4293
pH	AM + PC		AM +CP		PC + CP	
	h_1	h_2	h_1	h_2	h_1	h_2
2	−9.4501	1.2456	−19.4413	1.5194	−15.6728	−1.7356
5	−13.4309	2.3906	−25.9569	6.4415	−19.2267	−2.7665
7	−18.2481	2.4903	−38.5694	3.2606	−33.8745	−3.1118
8	−15.1642	2.1980	−45.8494	5.3800	−31.0715	−2.8248
9	−11.2773	1.9056	−15.2345	0.4877	−16.7693	−0.5701

where $\Delta_{sol}H_1$, $\Delta_{sol}H_2$, $\Delta_{sol}H_3$ represent the molar enthalpy of solution of pure components in the respective ternary mixtures and $\Delta_{sol}H_{ter.}$ the molar enthalpy of solution of ternary mixtures.

We assume that interactions in a ternary system are due to binary interactions and calculated their molar enthalpies of interaction ($\Delta H^{E}_{cal.\ (binary\ contribution)}$) from those of constituent binary mixtures. If the apparent mole fraction of the components 1, 2 and 3 are x_1, x_2 and x_3 in the ternary mixtures then the number of moles of binary mixture e.g. is $(x_i + x_j)$ and the mole fraction used for binary interaction in Redlich–Kister equation should be $x'_i = x_i/(x_i + x_j)$. Thus the contribution of the binary interaction between components 'i' and 'j' in the ternary mixtures is given by the equation:

$$\Delta H^{E}_{ij} = (x_i + x_j)\{x'_i x'_j[h^{ij}_1 + h^{ij}_2(x'_i - x'_j)]\},$$

$$\Delta H^{E}_{ij} = \frac{x_i x_j}{x_i + x_j}\left[h^{ij}_1 + h^{ij}_2\left(\frac{x_i - x_j}{x_i + x_j}\right)\right] \quad (6)$$

Thus if only binary interaction are taken into account the calculated $\Delta H^{E}_{cal.\ (binary\ contribution)}$ for the ternary system is given by

$$\Delta H^{E}_{cal.\ (binary\ contribution)} = \sum_{i<j=1}^{3}(x_i + x_j)[x'_i x'_j(h^{ij}_1 + h^{ij}_2(x'_i - x'_j)] \quad (7)$$

or

$$\Delta H^{E}_{cal.\ (binary\ contribution)} = \sum_{i<j=1}^{3}\frac{x_i x_j}{x_i + x_j}\left[h^{ij}_1 + h^{ij}_2\left(\frac{x_i - x_j}{x_i + x_j}\right)\right] \quad (8)$$

Table 10
Experimental and calculated (Eqs. (9) and (10)) values of excess enthalpies for ternary mixtures at different pH for the ampicillin trihydrate, sulbactum sodium and ciprofloxacin hydrochloride

x_1	x_2	x_3	$\Delta_{sol}H_{ter.}$ (kJ mol^{-1})	$\Delta H^{E}_{ter.}$ (kJ mol^{-1})	$\Delta H^{E}_{cal\ (binary\ contribution)}$ (kJ mol^{-1})	$\Delta H^{E}_{cal\ (binary\ contribution)}$ (kJ mol^{-1})
pH 2 ($A = 22.87$)						
0.2337	0.5122	0.2542	11.21	−4.29	−5.05	4.35
0.2342	0.2566	0.5092	19.27	−4.46	−5.07	4.37
0.3792	0.3116	0.3110	14.02	−4.49	−5.31	4.47
0.4781	0.2619	0.2599	13.57	−4.07	−4.86	4.12
pH 4 ($A = 38.28$)						
0.2410	0.2548	0.5048	18.11	−6.40	−7.52	6.33
0.2414	0.4960	0.2626	12.08	−5.88	−6.99	5.78
0.3501	0.3453	0.3046	13.44	−6.15	−7.54	6.13
0.4781	0.2619	0.2599	13.85	−5.44	−6.87	5.62
pH 6 ($A = 46.81$)						
0.2202	0.2611	0.5187	16.58	−10.91	−12.31	10.91
0.2537	0.4812	0.2651	8.30	−11.19	−12.65	11.13
0.3755	0.2968	0.3278	11.52	−11.01	−12.65	10.94
0.5019	0.2645	0.2336	11.31	−9.18	−10.74	9.29
pH 8 ($A = 41.91$)						
0.2138	0.2635	0.5228	21.77	−11.24	−12.57	11.33
0.2497	0.4788	0.2715	13.18	−11.63	−12.93	11.56
0.3418	0.3606	0.2979	16.19	−11.86	−13.41	11.87
0.4923	0.2697	0.2379	19.84	−9.78	−11.05	9.72
pH 9 ($A = 31.58$)						
0.2338	0.2770	0.4893	24.85	−11.02	−12.09	11.09
0.2536	0.4812	0.2651	17.00	−9.92	−10.87	9.85
0.3119	0.2959	0.3920	22.93	−10.96	−12.18	11.03
0.4725	0.2801	0.2474	22.72	−9.45	−10.42	9.38

Table 11
Experimental and calculated (Eqs. (9) and (10)) values of excess enthalpies for ternary mixtures at different pH for amoxicillin trihydrate, potassium clavulanate and ciprofloxacin hydrochloride

x_1	x_2	x_3	$\Delta_{sol}H_{ter.}$ (kJ mol^{-1})	$\Delta H^E_{ter.}$ (kJ mol^{-1})	$\Delta H^E_{cal\ (binary\ contribution)}$ (kJ mol^{-1})	$\Delta H^E_{cal\ (binary\ contribution)}$ (kJ mol^{-1})
pH 2 (A = 53.64)						
0.1990	0.2618	0.5195	19.586	−5.221	−6.739	−5.177
0.2444	0.4898	0.2658	12.312	−5.128	−6.744	−5.037
0.3132	0.3462	0.3406	14.798	−5.578	−7.440	−5.459
0.4896	0.2886	0.2218	16.641	−4.730	−6.649	−4.967
pH 5 (A= 83.32)						
0.1823	0.3223	0.4954	18.535	−6.963	−9.137	−6.711
0.2444	0.4898	0.2658	13.969	−5.342	−8.164	−5.510
0.3132	0.3462	0.3406	15.648	−6.551	−9.770	−6.693
0.4668	0.3302	0.2030	13.832	−5.741	−8.331	−5.730
pH 7 (A =123.04)						
0.1907	0.2178	0.5358	21.567	−10.062	−12.5567	−9.819
0.2594	0.4586	0.2820	12.329	−10.258	−14.4126	−10.284
0.3365	0.2975	0.3659	16.960	−10.266	−15.1476	−10.641
0.4770	0.2636	0.2594	16.820	−9.7170	−13.7274	−9.714
pH 8 (A = 91.46)						
0.1990	0.2618	0.5195	20.825	−11.689	−14.2771	−11.613
0.2444	0.4898	0.2658	10.868	−10.394	−13.9569	−11.040
0.3132	0.3462	0.3406	16.830	−12.168	−15.3680	−11.990
0.4896	0.2886	0.2218	19.518	−9.962	−13.2836	−10.420
pH 9 (A = 26.16)						
0.1990	0.2618	0.5195	27.146	−5.940	−6.6707	−5.908
0.2444	0.4898	0.2658	22.019	−5.690	−6.8035	−5.971
0.3132	0.3462	0.3406	26.580	−6.264	−7.2390	−6.272
0.4896	0.2886	0.2218	32.224	−5.706	−6.3685	−5.548

or

$$\Delta H^E_{cal.\ (binary\ contribution)} = \frac{x_1x_2}{x_1+x_2}\left[h_1^{12}+h_2^{12}\left(\frac{x_1-x_2}{x_1+x_2}\right)\right]+\frac{x_2x_3}{x_2+x_3}\times\left[h_1^{23}+h_2^{23}\left(\frac{x_2-x_3}{x_2+x_3}\right)\right]+\frac{x_1x_3}{x_1+x_3}\times\left[h_1^{13}+h_2^{13}\left(\frac{x_1-x_3}{x_1+x_3}\right)\right] \quad (9)$$

The values of the parameters h_1^{ij} and h_1^{ij} have been taken from Table 9. Results for the enthalpy of solution for the ternary mixture ($\Delta_{sol}H_{ter.}$) are reported along with experimental $\Delta H^E_{ter.}$ and calculated molar enthalpy of interaction ($\Delta H^E_{cal.\ (binary\ contribution)}$) values (Tables 10 and 11). It can be seen that the calculated values of molar enthalpy of interaction ($\Delta H^E_{cal.\ (binary\ contribution)}$) (Table 10) for ternary system taking into account only binary interactions are lower (more negative) than the experimental values ($\Delta H^E_{ter.}$) in all cases although the deviations are not large suggesting that binary interactions are most dominant. However, a ternary contribution ($Ax_1x_2x_3$) can be included so that the difference between our experimental values and that predicted from binary mixtures be minimized. We have used the following equation for this purpose:

$$\Delta H^E_{cal.\ (ternary\ contribution)} = \frac{x_1x_2}{x_1+x_2}\left[h_1^{12}+h_2^{12}\left(\frac{x_1-x_2}{x_1+x_2}\right)\right]+\frac{x_2x_3}{x_2+x_3}\times\left[h_1^{23}+h_2^{23}\left(\frac{x_2-x_3}{x_2+x_3}\right)\right]+\frac{x_1x_3}{x_1+x_3}\times\left[h_1^{13}+h_2^{13}\left(\frac{x_1-x_3}{x_1+x_3}\right)\right]+Ax_1x_2x_3 \quad (10)$$

where A is the ternary interaction parameter.

The values of interaction enthalpy ($\Delta H^E_{cal.(ternary\ contribution)}$) using Eq. (10) are given in the last column of Tables 10 and 11. It can be seen that there is an excellent agreement with the experimental values ($\Delta H^E_{ter.}$) (within ±0.08 kJ mol^{-1}) for all mole fractions.

Interaction between the drugs in ternary systems is interpreted by the sign and magnitude of the ternary interaction parameter (A) calculated from Eq. (10). The calculated value of A have found to be positive for all the systems. This indicates that ternary system deviates less from ideality as compared to constituents binary system. This type of behavior suggests repulsive interactions between drugs. The reason for this is that in ternary systems there is competition between the drugs and also there is steric hindrance while forming hydrogen bond. The present study shows that when the ciprofloxacin is combined with amoxicillin/potassium

clavulanate and ampicillin/sulbactum in ternary systems, the interaction between drugs is less as compared to binary systems of ciprofloxacin with the other drugs.

We have used the ternary interaction parameter to determine interaction of drugs in an empirical therapy with oral ciprofloxacin and amoxicillin/potassium clavulanate, which have been reported to be safe and effective for hospitalized low risk patients having fever and neutropenia during cancer chemotherapy [1]. Above-mentioned oral empirical therapy consisted of 30 mg of ciprofloxacin/kg of body weight ($x_3 = 0.4550$) plus 40 mg of amoxicillin/clavulanate (Agumentin: $x_1 = 0.4460$; $x_2 = 0.0992$). The molar enthalpy of interaction ($\Delta H^{E}_{\text{cal. (ternary contribution)}}$) for using these mole fractions is $-5.3938\,\text{kJ mol}^{-1}$ at pH 2.

This calculated value of molar enthalpy of interaction for ternary systems further increases with increase in pH ($-12.676\,\text{kJ mol}^{-1}$ at pH 7, $-12.569\,\text{kJ mol}^{-1}$ at pH 8 for ternary AM:PC:CP and AMP:SS:CP respectively). This is explained on basis that binary interactions with ciprofloxacin as one of components are found to be most dominant in ternary systems. Thus the combination of ciprofloxacin hydrochloride with above-mentioned drugs should be avoided in parenteral solutions. The technique of solution calorimetry can be adopted for the routine analysis of pharmaceuticals. The technique can be useful for the compatibility of drugs in solution state in pharmaceutical industry with valuable results and serves as excellent alternative to HPLC technique [38].

4. Conclusion

The solution calorimetry has been used to characterize the drugs by determining thermodynamic parameters accompanying their dissolution. These parameters are independent of concentration but found to be pH dependent. The dissolution process is entropically favoured. Enthalpy of solution of binary and ternary mixtures of drugs have been determined and molar enthalpy of interaction have been calculated. The molar enthalpy of interaction of marketed formulation of ampicillin trihydrate/sulbactam sodium and amoxicillin trihydrate/potassium clavulanate indicated compatibility in pH range studied. The oral combination with ciprofloxacin hydrochloride is also found to be compatible but should be avoided in parenteral solution. However, quantitative basis for calorimetrically determined molar enthalpy of interaction and compatibility have yet to be established.

Acknowledgements

We are grateful to Council for Scientific and Industrial Research (CSIR), New Delhi, India for the financial assistance (scheme no. 01(1715)/01/EMR-II).

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