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Some Thermodynamic Studies on Paracetamol -Ascorbic Acid Binary Drug System

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ABSTRACT

The solid-liquid equilibrium study of binary drug system has been taken for providing the significant enhanced pharmaceutical properties as compared to the parent drug. The present communication aims at some thermodynamic and interfacial investigation of Paracetamol (PCM) and Ascorbic Acid (AA) binary drug dispersion. Partial and Integral thermodynamic quantities such as, excess Gibbs energy (g^E*), excess enthalpy (*h^E*), excess entropy (*s^E*) of eutectic and non-eutectic mixtures were also calculated using activity coefficient data. The value of excess Gibbs free energy indicates positive deviation from ideal behaviour which refers stronger association between like molecules during formation of binary mix. However, the negative value of mixing function, Gibbs free energy of mixing (*ΔG^M*) suggests the mixing for eutectic and non-eutectic is spontaneous. The interfacial properties such as entropy of fusion per unit volume (*ΔSv*), interfacial energy (*σ*), roughness parameter (*α*), grain boundary energy of parent components, eutectics and non-eutectics have been studied using enthalpy of fusion data. The size of critical nucleus at different undercooling in nanoscale may be a big challenge for pharmaceutical world.*

Keywords: Binary drug, Excess thermodynamic, mixing functions, Critical radius and Interfacial Energy.

INTRODUCTION

The recent development in the area of Pharmaceutical dosage of drugs [1-5] involves preliminary pre-formulation studies and requires detailed information about the physical, chemical and mechanical properties of the formulation constituents. Binary mixture of drug/excipients can boost the long term stability of the solid dosage form, as well as the drug bioavailability, therapeutic efficacy and safety profile. In addition, the interactions between drug and excipients can get sublimated quality of the mixture, including the binary form and crystallization profile of the drug and the formulation properties such as the solubility of the mixture, colour, odor and taste. Thermochemical and thermodynamics studies are useful for the analysis of drug/excipient interactions during the development of new binary formulation and related technique for classical solid dosage forms (e.g. powders, tablets and capsules). The physical properties, stability, compatibility and interaction between drugs and excipients can be investigated by the study of phase transformation, melting point and enthalpy changes. NSAID (Non-Steroidal Anti-inflammatory Drugs) drugs [6-10] are used in combination such as analgesic decongestant and anti-histaminic to ameliorate cough, pain and fever. It is important to evaluate the interaction and effect of drugs with excepients. Application in the study of compatibility between substances has gained great prominence because they allow predicting possible interaction and/or incompatibilities in the final product. Increased moistures content in commercial medicinal powders increases molecular mobility and chemical reactivity. Additionally, paracetamol containing the amid group which may be sensitive to hydrolytic degradation. Research on medicinal products [11-13] stored in different temperatures and humidity has shown that physical properties of paracetamol in the form of powder and solution remain unaffected for even as long as three months. It is different in the case of ascorbic acid's stability which decreases with increased temperature sun exposure and pH. It is welled tolerated and having of lacks of many side effects of aspirin, so it is commonly used for the relief of fever, headaches, minor aches, pains and severe pain. It also allows lower dose of additional non-steroidal anti-inflammatory drugs for minimizing overall side effect. Paracetamol is a widely used analgesic and antipyretic while ascorbic acid due to 2,3-endiol group in the molecule may act both as an antioxidant or pro-oxidant depending on the concentration. As a result of ascorbic acid oxidation to dehydroascorbic acid one hydrogen atom is removed and intermediate product is formed-the semi-hydroascorbic radical or two hydrogen atoms from the hydroxyl groups bonded to the 2nd and 3rd carbon atoms.

Vitamin C or ascorbic acid a water-soluble vitamin is widely present in many biological systems and in multivitamin preparations. Ascorbic acid in commonly used to supplement inadequate dietary intake and as an antioxidant. The synergetic and protective effects during the use of paracetamol with vitamin C for therapeutic purposes have been studied. Other pharmacological and biologically active compounds can be included to intensify the main favorable effects of paracetamol in the function of liver. In past most of the scientific literature has been reported [14-16] about the major interferences between acetaminophen and/or vitamin C and a great number of chemical species in a variety of matrices. Keeping in view of better therapeutic response Paracetamol (PCM) and Ascorbic Acid (AA) binary system has been aimed for emphasizing thermodynamic and interfacial studies such as solid-liquid equilibrium, excess and mixing thermodynamic functions, activity and activity coefficient, interfacial energy, driving force of solidification and critical radius.

MATERIALS AND METHODS

Binary mixture were obtained by manual mixing of different ratios of drug (PCM) and excipients (AA) using a pestle and mortar. For measuring the solid-liquid equilibrium data of PCM-AA system, mixtures of different compositions of both were made in glass test tubes by repeated heating and followed by chilling in ice and melting temperatures of solid dispersions were determined by the thaw-melt method. The melting and thaw temperatures were determined in a Toshniwal melting point apparatus using a precision thermometer which could read correctly up to $\pm$ 0.1^{0}C. The heater was regulated to give above 1^{0}C increase in temperature in every 5 min. The literature value [17] of enthalpy of fusion of Paracetamol and Ascorbic Acid was used in determining the various thermodynamic parameters of the binary system.

RESULTS AND DISCUSSION

SLE Study: The solid liquid equilibrium (SLE) data of PCM-AA system determined by the thaw melt method is reported in table I. The system shows the formation of a eutectic (E)[l8] and non-eutectics solid dispersion (A1-A7). The melting point of PCM (M.P.-168.7^{0}C) decreases on the addition of second component AA (M.P. - 191^{0}C).

Table l : Phase Composition, melting temperature, values of entropy of fusion per unit volume (ΔS_V), heat of fusion (ΔH), interfacial energy (σ), grain boundary energy (σ_{gb}), Gibbs-Thomson coefficient (τ) and roughness parameter (α).

Alloy	χ_{PCM}	MP	ΔH (J/mol)	ΔS (J/mol/K)	α	$\sigma \times 10^2$ (J/m^2)	$\sigma_{gb} \times 10^2$ (J/m^2)	ΔS_V (kJ/m^3/K)	ΔH_V	$\tau \times 10^6$ Km
A1	0.1	187.5	36100	78.393	9.429	63.544	127.088	748.837	344.837	8.4856
A2	0.2	182.9	35100	76.990	9.260	61.523	123.046	730.239	332.916	8.4250
A3	0.3	179.5	34100	75.359	9.064	59.502	119.004	709.522	321.059	8.3862
A4	0.4	175.5	33100	73.801	8.876	57.481	114.962	689.571	309.273	8.3357
A5	0.5	174.0	32100	71.812	8.637	55.460	110.920	665.684	297.561	8.3312
E	0.72	151.8	29880	70.338	8.460	50.974	101.948	639.915	271.836	7.9657
A6	0.8	158.9	29100	67.376	8.103	49.397	98.794	608.696	262.896	8.1152
A7	0.9	164.3	28100	64.257	7.728	47.376	94.752	575.147	251.512	8.2371
PCM		168.7	27100	61.353	7.379	45.356	90.712	543.853	240.220	8.3397
AA		191.0	37100	79.956	9.617	65.565	131.130	69.021	356.826	8.5257

The values of heats of fusion of eutectic and non-eutectic are calculated by the mixture law. The value of heat of fusion of binary solid dispersions A1-A7 and E is reported in table 1. The activity coefficient and activity of components for the systems under investigation has been calculated from the equation [19] given below

$$-\ln\chi_i\gamma_i = \frac{\Delta H_i}{R}\left(\frac{1}{T_e} - \frac{1}{T_i}\right) \qquad (1)$$

where χ_j and γ_i is mole fraction .and activity coefficient of the component *i* in the liquid phase respectively. ΔH_i is the heat of fusion of component i at its melting point T_i and R is the gas constant. T_e is the melting temperature of alloy. Using the values of activity and activity coefficient of the components hi the binary product, the mixing and excess thermodynamic functions have been evaluated.

Mixing Functions: The mixing characteristics of components in the system Integral molar free energy of mixing (ΔG^M), molar entropy of mixing (ΔS^M) and molar enthalpy of mixing (ΔH^M) and partial thermodynamic mixing functions of the binary solid dispersions were determined by using the following equations

$$\Delta G^M = RT(\chi_{PCM}\ \mathrm{Ina}_{PCM} + \chi_{AA}\ \mathrm{Ina}_{AA}) \qquad (2)$$

$$\Delta S^M = -R(\chi_{PCM}\ \mathrm{In}\chi_{PCM} + \chi_{AA}\ \mathrm{In}\chi_{AA}) \qquad (3)$$

$$\Delta H^M = RT(\chi_{PCM}\ \mathrm{In}\gamma_{PCM} + \chi_{AA}\ \mathrm{In}\gamma_{AA}) \qquad (4)$$

$$G^{-}{}_i{}^M = \mu^{-}{}_i{}^M = RT\ \mathrm{Ina}_i \qquad (5)$$

where $G^{-}{}_i{}^M$ ($\mu^{-}{}_i{}^M$) is the partial molar free energy of mixing of component i (mixing chemical potential) in binary mix and γ_i and a_i is the activity coefficient and activity of component respectively. The negative value [20] of molar free energy of mixing of alloys (Table 2) suggests that the mixing in all cases is spontaneous. The integral molar enthalpy of mixing value corresponds to the value of excess integral molar free energy of the system favors the regularity in the binary solutions.

Table 2: Value of partial and integral missing of Gibbs free energy (ΔG^M), enthalpy (ΔH^M) and entropy (ΔS^M) of PCM-AA system

Alloy	ΔG_{PCM}^{-M} J/mol	ΔG_{AA}^{-M} J/mol	ΔG^{-M} J/mol	ΔH_{PCM}^{-M} J/mol	ΔH_{AA}^{-M} J/mol	ΔH^{-M} J/mol	ΔS_{PCM}^{-M} J/mol/k	ΔS_{AA}^{-M} J/mol/k	ΔS^{-M} J/mol/k
Al	-2.297	-3.828	-3.675	8813.430	402.002	1243.144	19.143	0.875	2.701
A2	-2.274	-6.068	-5.309	6098.677	841.458	1892.901	13.380	1.855	4.160
A3	-0.376	-4.138	-3.009	4529.550	1339.302	2296.376	10.009	2.965	5.078
A4	-1.491	-3.728	-2.833	3415.607	1901.702	2507.264	7.618	74.247	5.595
A5	-1.858	-5.578	-3.718	2575.436	2571.719	2573.577	5.762	5.762	5.762
E	-2.684	-4.061	-3.067	1147.830	4517.155	2084.502	2.708	10.643	4.913
A6	-5.820	-5.820	-5.820	797.161	5774.033	1792.535	1.855	13.380	4.160
A7	-5.875	-5.875	-3.892	381.749	8365.773	1180.151	0.875	19.143	2.701

Excess Functions: For elucidating the nature of the interactions between the components forming the eutectic and non-eutectic solid dispersions., the excess thermodynamic functions such as integral excess integral free energy (g^E), excess integral entropy (s^E) and excess integral enthalpy (h^E) were calculated using the following equations

$$g^h = RT\,(\chi_{PCM}\,\mathrm{In}\gamma_{PCM} + \chi_{AA}\,\mathrm{In}\gamma_{AA}) \qquad (6)$$

$$s^E = -R\left(\chi_{PCM}\,\mathrm{In}\gamma_{PCM} + \chi_{AA}\,\mathrm{In}\gamma_{AA} + \chi_{PCM}\,T\,\frac{\delta\ \ln\gamma_{PCM}}{\delta T} + \chi_{AA}\,T\,\frac{\delta\ \ln\gamma_{AA}}{\delta T}\right) \qquad (7)$$

$$h^E = RT\left(\chi_{PCM}\,\frac{\delta\ \ln\gamma_{PCM}}{\delta\ T} + \chi_{AA}\,\frac{\delta\ \ln\gamma_{AA}}{\delta\ T}\right) \qquad (8)$$

and excess chemical potential or excess partial free energy of mixing;

$$\bar{g}_i^{M} = \bar{\mu}_i^{M} = RT\ \ln\gamma_I \qquad (9)$$

The values of $\delta\ln\gamma_i/\delta T$ can be determined by the slope of liquidus curve near the alloys. The values of the excess thermodynamic functions are given in table 3. The value of the excess free energy is a measure of the departure of the system from ideal behavior. The reported excess thermodynamic data substantiate the earlier conclusion of an appreciable interaction between the parent components during the formation of alloys. The positive g^E value [21,22] for all eutectic and non-eutectic solid dispersions infers stronger interaction between like molecules in binary mix. The excess entropy is a measure of the change in configurationally energy due to a change in potential energy and indicates an increase in randomness.

Table 3: Value of partial and integral excess Gibbs free energy (g^E), enthalpy (h^E) and entropy (s^E) of PCM-AA system

Alloy	g_{PCM}^{-E} J/mol	g_{AA}^{-E} J/mol	g^E J/mol	h_{PCM}^{-E} J/mol	h_{AA}^{-E} J/mol	h^E J/mol	s_{PCM}^{-E} J/mol/k	s_{AA}^{-E} J/mol/k	s^E J/mol/k
Al	8813.430	402.002	1243.144	149206.75	-17570.34	-892.631	304.871	-38.897	-4.520
A2	6098.677	841.458	1892.901	59288.42	-15499.71	-542.086	116.669	-35.843	-5.340
A3	4529.550	1339.302	2296.376	29644.60	-12780.68	-53.096	55.502	-31.204	-5.192
A4	3415.607	1901.702	2507.264	14709.41	-9226.98	347.547	25.181	-24.813	-4.815

A5	2575.436	2571.719	2573.577	6124.22	-3875.75	1124.233	7.939	-14.423	-3.242
E	1147.830	4517.155	2084.502	-6320.02	16866.40	125.801	-17.579	29.070	-4.610
A6	797.161	5774.033	1792.535	-7714.04	40431.27	1915.019	-19.706	80.243	0.283
A7	881.749	8365.773	1180.151	-9434.44	121881.49	3697.146	-22.4447	259.583	5.756

The Solid-Liquid Inter facial Energy (σ): The solid-liquid intertacial energy (σ) calculated by Singh and Glickman [23] from melting enthalpy change and values obtained are found in good agreement with the experimental values. Turnbull empirical relationship [24] between the interfacial energy and enthalpy change provides the clue to determine the interfacial energy value of binary solid dispersions and is expressed as:

$$\sigma = \frac{C\Delta H}{(N)^{1/3}(v_m)^{2/3}} \qquad (10)$$

where the coefficient *C* lies between 0.33 to 0.35 for nonmetallic system, v_m is molar volume and N is the Avogadro's constant. The value of the solid-liquid interfacial energy of Paracetamol and Ascorbic Acid was found to be 4.53×10^{-2} and 6.55×10^{-2} J m^{-2} respectively and σ value of the solid dispersions was given in table 1. The value of σ has also been determined by using the value of Gibbs-Thomson coefficient. The theoretical basis of determination oft was made for equal thermal conductivities of solid and liquid phases for some transparent materials.

Gibbs-Thomson Coefficient (τ): For a planar grain boundary on planar solid-liquid interface the Gibbs-Thomson coefficient (r) for the system can be calculated by the Gibbs-Thomson equation and is expressed as

$$\tau = r\Delta T = \frac{TV_m\sigma}{\Delta H} = \frac{\sigma}{\Delta S_V} \qquad (11)$$

Where τ is the Gibbs-Thomson coefficient, ΔT is the dispersion in equilibrium temperature and, r is the radius of grooves of interface. It was also determined by the help of Gunduz and Hunt numerical method [25] for materials having known grain boundary shape, temperature gradient in solid and the ratio of thermal conductivity of the equilibrated liquid phases to solid phase ($R = K_L/K_S$).The Gibbs-Thomson coefficient for PCM, AA and their solid dispersions are found in the range of 8.33 – 8.52 x 10^{-6} Km and is reported in table 1.

Interfacial Grain Boundary Energy (σ_{gb}): Grain boundary can be understood in a very similar way to nucleation on surfaces in liquid-solid transformation. In past, a numerical method [26] is applied to observe the interfacial grain boundary energy (σ_{gb}) without applying the temperature gradient for the grain boundary groove shape. A considerable force is employed at the grain boundary groove in anisotropic interface. The grain boundary energy can be obtained by the equation:

$$\sigma_{gb} = 2\sigma\cos\theta \qquad (12)$$

where θ is equilibrium contact angle precipitates at solid-liquid interface of grain boundary. The grain boundary energy could be twice the solid-liquid interfacial energy in the case where the contact angle tends to zero. The value of σ_{gb} for solid PCM and AA was found to be 9.07×10^{-2} and 13.11×10^{-2} Jm^{-2} respectively and the value for all solid dispersions is given in table 1.

The Effective Entropy Change (ΔS_V): The effective entropy change and the volume fraction of phases in the alloy are inter-related to decide the interface morphology during solidification and the volume fraction of the two phases depends on the ratio of effective entropy change of the phases. The entropy effusion ($\Delta S = \Delta H/T$) value (Table 1) of alloys is calculated by heat of fusion values of the materials. The effective entropy change per unit volume (ΔS_V) is given by

$$\Delta S_V = \frac{\Delta H}{T} \cdot \frac{1}{v_m} \qquad (13)$$

where ΔH is the enthalpy change, T is the melting temperature and v_m is the molar volume of solid phase. The entropy of fusion per unit volume (ΔS_V) for PCM and AA was found 543 and 769 $kJK^{-1}m^{-3}$ respectively. Values of ΔS_V for alloys are reported in table 1.

The Driving Force of Nucleation (ΔG_V): During growth of crystalline solid there is change in enthalpy, entropy and specific volume and non-equilibrium leads the Gibb's energy. Thermodynamically metastable phase occurs in a supersaturated or super-cooled liquid. The driving force for liquid-solid transition is the difference in Gibb's energy between the two phases. The theories of solidification process in past have been discussed on the basis of diffusion model, kinetic characteristics of nucleation and on thermodynamic features. The lateral motion of rudimentary steps in liquid advances stepwise with non-uniform surface at low driving force while continuous and uniform surface advances at sufficiently high driving force. The driving force of nucleation from liquid to solid during solidification (ΔG_V) can be determined at different undercoolings (ΔT) by using the following equation [27]

$$\Delta Gv = \Delta S_V \, \Delta T \qquad (14)$$

It is opposed by the increase in surface free energy due to creation of a new solid-liquid interface. By assuming that solid phase nucleates as small spherical cluster of radius arising due to random motion of atoms within liquid. The value of ΔG_V for each solid dispersions and pure components are shown in the table 4.

Table 4: Value of volume free energy change (ΔG_v) during solidification for PCM-AA system of different undercoolings (ΔT)

Alloy	ΔG_v (J/cm^3)					
$\Delta T \rightarrow$	1.0	1.5	2.0	2.5	3.0	3.5
Al	0.749	1.123	1.498	1.872	2.247	2.621
A2	0.730	1.095	1.460	1.825	2.190	2.555
A3	0.709	1.063	1.418	1.772	2.127	2.481
A4	0.689	1.033	1.378	1.722	2.067	2.411
A5	0.665	0.997	1.330	1.662	1.995	2.327
E	0.640	0.960	1.280	1.600	1.920	2.240
A6	0.608	0.912	1.216	1.520	1.824	2.128
A7	0.575	0.862	1.150	1.437	1.725	2.012
PCM	0.544	0.816	1.088	1.360	1.632	1.904
AA	0.769	1.153	1.538	1.922	2.307	2.691

The Critical Radius (r*): Embryos are rapidly dispersed in unsaturated liquid and on undercooling liquid becomes saturated and provides stable embryo of a critical size with radius r* for nucleation which can be determined by the Chadwick relation [28]

$$r^* = \frac{2\sigma}{\Delta G_v} = \frac{2\sigma\, T}{\Delta H_V\, \Delta T} \tag{15}$$

where σ is the interfacial energy and ΔH_V is the enthalpy of fusion of the compound per unit volume, respectively. The critical size of the nucleus for the components and alloys was calculated at different undercoolings and values are presented in table 5. It can be inferred from table that the size of the critical nucleus decreases with increase in the undercooling of the melt. The existence of embryo and a range of embryo size can be expected in the liquid at any temperature. The value of r* for pure components (PCM and AA) and solid dispersions lies between 45 to 170 nm at undercooling 1 – 3.5^0C.

Table 5: Critical size of nucleus (r*) at different undercoolings (ΔT)

Alloy	r* (nm)					
ΔT	→ 1.0	1.5	2.0	2.5	3.0	3.5
Al	169.70	113.13	84.85	67.88	56.56	48.48
A2	168.50	112.33	84.25	67.40	56.16	48.14
A3	167.72	111.81	83.86	67.08	55.90	47.92
A4	166.70	111.13	83.35	66.68	55.56	47.62
A5	166.62	111.08	83.31	66.64	55.54	47.60
E	159.30	106.20	79.65	63.72	53.10	45.51
A6	162.30	108.20	81.15	64.92	54.10	46.37
A7	164.74	109.82	82.37	65.89	54.91	47.06
PCM	166.78	111.18	83.39	66.71	55.59	47.65
AA	170.50	113.66	85.25	68.20	56.83	48.71

Critical Free Energy of Nueleation (ΔG*): To form critical nucleus, it requires a localized activation/critical free energy of nucleation (ΔG*) which is evaluated[29] as

$$\Delta G^* = \frac{16\pi\sigma^3}{3\Delta G_V^2} \tag{16}$$

The value of ΔG* for alloys and pure components has been found in the range of 10^{-15} to 10^{-16} J per molecule at different undercoolings, and has been reported in table 6.

Table 6: Value of critical free energy of nucleation (ΔG*) for alloys of PCM-AA system at different undercoolings (ΔT)

Alloy	$\Delta G^* \times 10^{16}$ (J)					
ΔT	→ 1.0	1.5	2.0	2.5	3.0	3.5
Al	76.665	34.073	19.166	12.266	8.518	6.258
A2	73.169	32.519	18.229	11.707	8.129	5.973
A3	70.115	31.162	17.528	11.218	7.790	5.723
A4	66.921	29.742	16.730	10.707	7.435	5.462
A5	64.498	28.666	16.124	10.319	7.166	5.265
E	54.193	24.086	13.548	8.671	6.021	4.223

Interface Morphology: Growth during phase transformation is based on the ground of thermodynamics, kinetics, fluid dynamics, crystal structures and interfacial sciences. The solid-liquid interface morphology can be predicted from the value of the entropy effusion. According to Hunt and Jackson [30], the type of growth from a binary melt depends upon a factor a, defined as:

$$\boldsymbol{\alpha} = \xi \frac{\Delta H}{RT} = \xi \frac{\Delta S}{R} \qquad (17)$$

where ξ is a crystallographic factor depending upon the geometry of the molecules and has a value Jess than or equal to one. $\Delta S/R$ (also known as Jackson's roughness parameterα) is the entropy of fusion (dimensionless) and R is the gas constant. When R is less than two the solid-liquid interface is atomically rough and exhibits non-faceted growth. The value of Jackson's roughness parameter (α) is given in Table 1. For the entire solid dispersions the σ value was found greater than 2 which indicate the faceted [31] growth proceeds in all the cases.

CONCLUSIONS

The solid-liquid equilibrium phase diagram of PCM-AA system shows the formation of simple eutectic alloy. The activity and activity coefficient values are very useful in computing thermodynamic mixing and excess functions. Thermodynamic excess and mixing functions g^E and ΔG^M values for eutectic and non-eutectics are being found positive and negative respectively which suggest the stronger association between like molecules and there is spontaneous mixing in all the binary drugs.

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