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Phase equilibria and thermodynamic description of solid dispersions of 8-hydroxyquinoline – 4-chlorobenzoic acid drug system

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ABSTRACT

In present article 8-hydroxyquinoline (HQ)-4-chlorobenzoic acid (CBA) binary drug system has been undertaken to study phase diagram and thermodynamic contribution in the system in terms of partial and integral mixing and excess functions. The phase equilibria of the system undertaken shows the formation of 1:1 addition compound C and its eutectic E at 214º and199º c respectively. The negative value of molar free energy of mixing (ΔG^M) of solid dispersion at 0.810 and 0.895 mole fraction of CBA suggests that the mixing in these 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. The positive value of excess free energy (g^E) for all the eutectic and noneutectic solid dispersion suggests an association of weaker nature between unlike molecules and of stronger nature between like molecules. Gibbs-Duhem equation gives the graphical solution of partial molar heat of mixing (H_i-^{M}), activity and activity coefficient of a particular constituent in the binary mix. Interfacial roughness of the binary solid dispersion has also been explained.

Keywords: Binary drug dispersion, phase diagram, activity, activity coefficient, mixing and excess function.

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INTRODUCTION

The chemistry of drug materials has been the most active area of investigation due to their unusual anisotropic properties [1,2], enhanced solubility, bioavailability and dissolution rate, not normally shown by their parent components. The present substances have recently been attracting the attention in connection with searches of new drug for a number of therapeutic actions having concerning diseases. In addition these materials have considerably high nonlinearity, great possibility of varying the molecular structure, easier to engineer to fabricate instrument of high optical properties of the crystals, high resistance to high energy laser beams and are much cheaper than their inorganic counterparts. The eutectics, noneutectics and molecular solid dispersions have a remarkable commercial and technological importance in modern age. The idea behind single effort is to produce a drug material consists of very high strength but possibly brittle fibers embedded in a ductile matrix. In spite of great devotion to acquire the stronger and more reliable drug material to cater the ever growing need and diversified demand of modern civilization, the various studied on the binary drug dispersions are inadequate and incomplete as difficulty involved in their solidification. In recent past extensive study [3,4] has been developed for solidification of eutectic and noneutectic solid dispersions to produce materials of desired properties. Due to high biological activity, low transformation temperature, transparency, ease in purification and experimentation and wider choice of materials are the special features which have prompted the authors to select the binary drug system solidify as faceted growth. 8-hydroxyquinoline (HQ) and its complexes have been recognized as antiseptic, antifungal, disinfectant, pesticides and anti-cancer. 8-hydroxyquinoline (HQ)-4-cholorobenzoic acid (CBA) system has been taken for detailed physicochemical investigations, such as, phase diagram, activity, activity co-efficient, mixing and excess functions of binary organic crystals.

EXPERIMENTAL

Phase diagram study

The phase diagram of HQ-CBA system was determined by thaw-melt method [5,6]. Mixtures of different compositions were made in glass test tubes by repeated heating followed by

chilling in ice. The melting and thaw temperatures were determined in a Toshniwal melting point apparatus using a precision thermometer.

Materials and their purification

8-hydroxyquinoline (E. Merck, Bombay) was purified by fractional crystallization of ethanol and 4- chlorobenzoic acid (G.S. Chemical, New Delhi) was used directly as supplied. The purity of the compounds was confirmed by determining their melting points which were in good agreement with those quoted in reference literature.

Heat of fusion

Heats of fusions of pure components and their eutectic, noneutectic and 1:1 molecular solid dispersions were measured by DTA method [7] using a Stanton Redcroft STA-780 series unit.

RESULTS AND DISCUSSION

Phase diagram

The phase diagram of HQ-CBA system determined by thaw-melt method is reported in the form of temperature-composition curve. The system shows the formation of an 1:1 molecular solid dispersions, C (214^{0}C) and one eutectic. The eutectic at the eutectic temperature a binary solution (L) is in equilibrium with two solid phases. The melting point of HQ is 73^{0}C and it increases with the addition of the second component CBA (235^{0}C) and attains maximum and then decreases to minimum. Eutectic alloy E 0.790 mole fraction of CBA is obtained at 199^{0}C. At the eutectic temperature phases namely a liquid phase L and two solid phases are in equilibrium and the system is invariant. In the region indicated by L a homogeneous binary liquid solution exists while the two solid phases exists below the horizontal line. In the case, in HQ+L region located on the extreme left side of the diagram a binary liquid and solid HQ exist while in a similar region located on the extreme right side of the diagram a binary liquid and the second component of the system co-exist. At maximum temperature at mole fraction of CBA an intermediate phase is a 1:1 molecular solid dispersions is formed which on decomposition gives

$$(HQ)_1\ (CBA)_1\ (L) \underset{\text{cooling}}{\rightleftharpoons} 1\ HQ\ (S) + 1\ CBA(S).$$

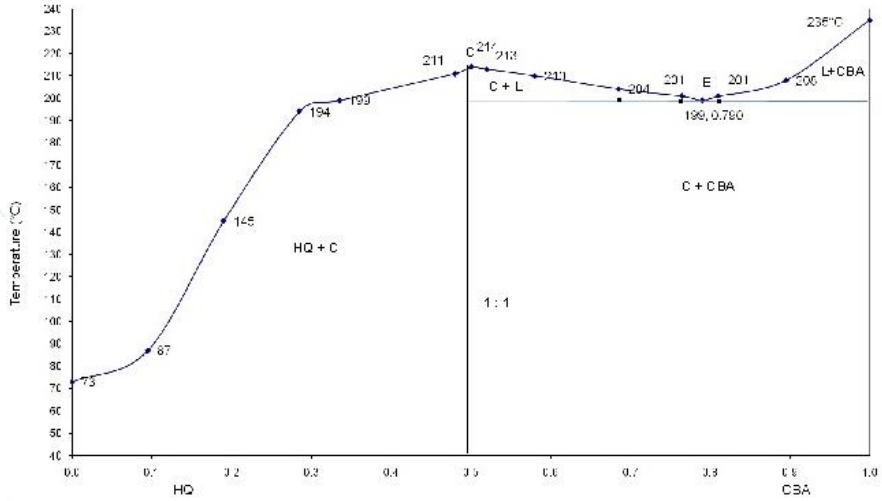

Figure 1: Phase diagram of 8-hydroxyquinoline (HQ) 4-chlorobenzoic acid (CBA) system.

The formation of molecular compound (1:1) with congruent melting point shows a characteristic maximum C. Near the C, the compound C with liquid CBA in the right region coexist. Below the horizon, at left hand side a mixture of two solids HQ and C and below horizon at right hand side mixture of CBA and C have been found. The system at eutectic temperature T_e has only one component and is consequently invariant. The better hump and sharp inclination in the intermediate region in the phase diagram infers the formation of a definite compound and possess the regarding stability of addition of CBA in HQ with eutectic solid dispersion.

Thermochemistry

The molecular complex is association of two or more molecules in definite stoichiometry and the association is somewhat stronger than Van der Wall's associations. The chemical interaction between electron donor and electron acceptor molecules leads to an association of molecules in definite proportions to form 1:1 molecular solid dispersions. In the formation of 1:1 molecular solid dispersions, physical as well as chemical forces are involved. Thermochemical studies unfold the nature of interactions between components forming the addition compound.

Heat of fusion

The values of heats of fusion of eutectic, noneutectic and 1:1 molecular solid dispersions are calculated by the mixture law using equation

$$(\Delta H)_e = x_1\ \Delta H_1 + x_2\ \Delta H_2 \qquad ...(1)$$

where 1 belongs for HQ and 2 belongs for CBA. x and ΔH are the mole fraction and heat of fusion of the component indicated by the subscript, respectively. The value of heat of fusion of binary solid dispersion $A_1 - A_{11}$, E and compound C($A_{1:1}$) is reported in Table1. The difference in experimental and calculate value of enthalpy of fusion of solid dispersion suggests the association characteristics between components.

Entropy of fusion

The entropy of fusion (ΔS) of pure components and the eutectic, noneutectic and 1:1 molecular solid dispersion can be calculated using the following equation

$$\Delta S = \frac{\Delta H}{T} \qquad ...(2)$$

where ΔH is the heat of fusion and T is the fusion temperature. The values for the entropy of fusion (Table1) are positive in all cases, these points to an increase in the randomness [8] of the system during melting and infer both factors namely energy and entropy favor the melting process of components, solid dispersion and compound.

Table 1: Temperature-composition data, values of heat of fusion (ΔH), entropy of fusion(ΔS) and interfacial roughness (α) of HQ-CBA system.

Solid dispersion & Compound	Mole fraction of CBA	M.P (ºC)	ΔH (kJ/mol)	ΔS (J/mol/K)	α
A_1	0.095	87	19.27	53.53	6.44
A_2	0.190	145	19.84	47.46	5.71
A_3	0.285	194	20.41	43.70	5.26
A_4	0.335	199	20.71	43.88	5.28
A_5	0.480	211	21.58	44.59	5.36
$C(A_{1:1})$	0.500	214	21.70	44.56	5.36
A_6	0.520	213	21.82	44.90	5.40
A_7	0.580	210	22.18	45.92	5.52
A_8	0.685	204	22.81	47.82	5.75
A_9	0.765	201	23.29	49.13	5.91
E	0.790	199	23.44	49.66	5.97
A_{10}	0.810	201	23.56	49.70	5.98
A_{11}	0.895	208	24.07	50.04	6.02
CBA	1.000	235	24.70	48.62	5.85

Activity and activity coefficient

For ideal mixture, the composition and temperature of solid dispersion can be predicted the activity coefficient by solving the following equation

$$-\ln (x_1)_e = \frac{\Delta H_1}{R} \left(\frac{1}{T_e} - \frac{1}{T_1} \right) \quad \text{...(3)}$$

$$-\ln (x_2)_e = \frac{\Delta H_2}{R} \left(\frac{1}{T_e} - \frac{1}{T_2} \right) \quad \text{...(4)}$$

where T_e is the temperature of alloys and T_1 and T_2 are the melting points of components HQ and CBA, respectively. The activity coefficient of components HQ and CBA, for the systems under investigation may be calculated from the equation given below:

$$-\ln x_i^l \gamma_i^l = \frac{\Delta H_i}{R} \left(\frac{1}{T_e} - \frac{1}{T_i} \right) \quad \text{...(5)}$$

where x_i^l and γ_i^l are the 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 melting point T_i and R is the gas constant. The values of activity and activity coefficient of the components given Table 2.

Table 2: Values of activity and activity coefficient of components in binary melt of HQ-CBA system.

Solid dispersion	$\ln\gamma_1$	$\ln\gamma_2$	γ_1	γ_2	$\ln a_1$	$\ln a_2$	a_1	a_2	x_1/x_2
A_1	0.35	0.05	1.42	1.05	0.25	2.30	1.28	0.10	9.53
A_2	1.33	0.40	3.78	1.49	1.12	-1.27	3.06	0.28	4.26
A_3	2.02	0.74	7.54	2.10	1.68	-0.51	5.39	0.60	2.51
A_4	2.14	0.65	8.52	1.91	1.73	-0.45	5.66	0.64	1.98
A_5	2.51	0.45	12.27	1.56	1.85	-0.29	6.38	0.75	1.08
$C(A_{1:1})$	2.57	0.44	13.06	1.55	1.87	-0.26	6.53	0.77	1.00
A_6	2.61	0.39	13.60	1.48	1.88	-0.26	6.53	0.77	0.92
A_7	2.71	0.79	15.03	2.20	1.84	0.25	6.31	1.28	0.72
A_8	2.94	-0.00	18.91	1.00	1.78	-0.39	5.96	0.68	0.46
A_9	3.20	-0.15	24.53	0.86	1.75	-0.41	5.76	0.66	0.31
E	3.29	-0.21	26.84	0.81	1.73	-0.45	5.64	0.64	0.27
A_{10}	3.41	-0.21	30.26	0.81	1.75	-0.43	5.75	0.65	0.23
A_{11}	4.08	-0.19	59.14	0.83	1.83	-0.30	6.21	0.74	0.12

Gibbs- Duhem equation

The partial molar quantity, activity and activity coefficient can also be determined by using Gibbs-Duhem equation

$$\sum x_i \, dz_i^{-} = 0$$

Or, $$x_1 \, dH_1^{-M} + x_2 \, dH_2^{-M} = 0 \qquad \ldots(6)$$

Or, $$dH_2^{-M} = \frac{x_1}{x_2} \, dH_1^{-M}$$

Or, $$[H_2^{-M}]_{x_2 = y} = \int_{x_2 = y}^{x_2 = 1} \frac{x_1}{x_2} \, dH_1^{-M} \qquad \ldots(7)$$

where 1 belongs for HQ and 2 belongs for CBA. Using eqn. (7) a graph (Fig.2) between x_1/x_2 and H_1^{-M} gives the solution of the partial molar heat of mixing of a particular constituent in the binary solid dispersion and plots between x_1/x_2 vs $\ln a_1$ and $\ln\gamma_1$ (Fig.3) determine the value of activity and activity coefficient of a specific component in binary solid dispersion respectively.

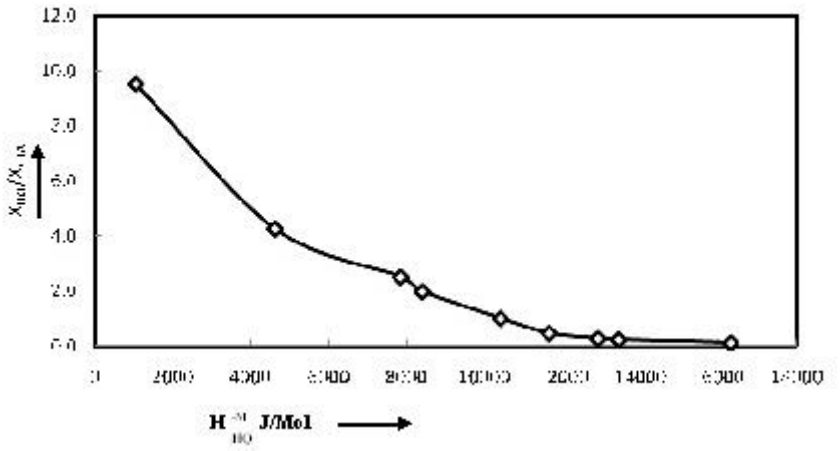

Figure 2: Graphical solution of partial molar heat of mixing of CBA in binary mixture.

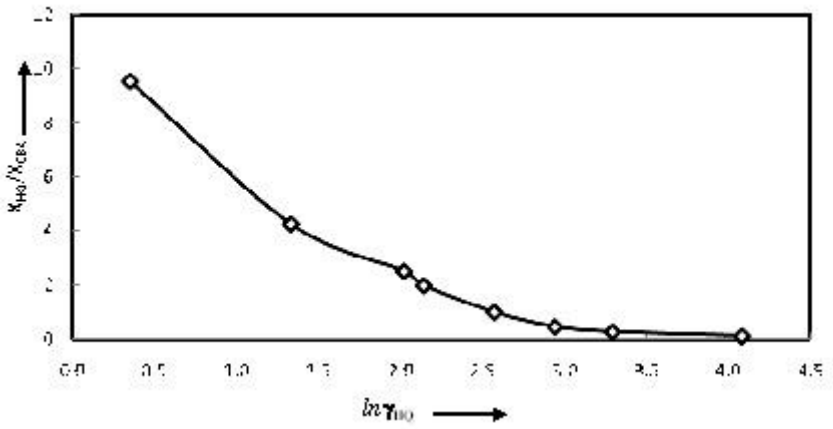

Figure 3: Graphical solution of activity coefficient of CBA in binary mixture.

Mixing functions

Intergral molar free energy of mixing (ΔG^M), molar entrophy of mixing (ΔS^M) and molar enthalpy of mixing (ΔH^M) and partial thermodynamic mixing functions of the binary solid dispersion when two components are mixed together were determined by using the following equations

$$\Delta G^M = RT\,(x_1 \ln a_1^{\,l} + x_2 \ln a_2^{\,l}) \quad ...(8)$$

$$\Delta S^M = -R\,(x_1 \ln x_1^{\,l} + x_2 \ln x_2^{\,l}) \quad ...(9)$$

$$\Delta H^M = RT\,(x_1 \ln \gamma_1^{\,l} + x_2 \ln \gamma_2^{\,l}) \quad ...(10)$$

$$G_i^{-M} = \mu_i^{-M} = RT \ln a_i^{\,l} \quad ...(11)$$

where G_i^{-M} (μ_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 the component, respectively. The negative value [9-11] of molar free energy of mixing of alloys A_{10} and A_{11} (Table 3) 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. The positive value of ΔS^M of all solid dispersion predicts the increase of randomness during mixing due to higher amplitude of phase distribution between the components forming the binary melt.

Table 3: Values of partial and integral thermodynamic mixing functions of HQ-CBA system.

Solid dispersion & Compound	G_1^{-M} (J/mol)	G_2^{-M} (J/mol)	ΔG^M (J/mol)	S_1^{-M} (J/mol/K)	S_2^{-M} (J/mol/K)	ΔS^M (J/mol/K)	H_1^{-M} (J/mol)	H_2^{-M} (J/mol)	ΔH^M (J/mol)
A_1	739.28	-6889.98	14.50	0.83	19.57	2.61	1038.08	155.22	962.26
A_2	3885.33	-4423.99	2306.56	1.75	13.81	4.04	4616.83	1348.59	4008.01
A_3	6538.36	-1984.03	4109.48	2.79	10.44	4.97	7841.29	2891.45	6426.54
A_4	6800.65	-1750.20	3936.12	3.39	9.09	5.30	8400.73	2540.28	6439.04
A_5	7456.43	-1158.90	3321.07	5.44	6.10	5.76	10089.39	1793.50	6121.27
C ($A_{1:1}$)	7595.77	-1056.77	3269.50	5.76	5.76	5.76	10400.89	1748.35	6074.62
A_6	7596.33	-1050.56	3099.95	6.10	5.44	5.76	10560.93	1593.28	5881.50
A_7	7396.85	991.87	3681.96	7.21	4.53	5.66	10879.28	3179.86	6410.60
A_8	7078.91	-1530.79	1181.27	9.60	3.14	5.17	11658.11	-33.01	3667.27
A_9	6896.46	-1615.74	384.63	12.04	2.23	4.53	12603.42	-558.72	2511.30
E	6788.88	-1750.20	43.01	12.97	1.96	4.27	12910.72	-825.08	2060.21
A_{10}	6896.46	-1694.56	-62.26	13.81	1.75	4.04	13442.40	-865.06	1882.93
A_{11}	7302.24	-1203.71	-310.58	18.74	0.92	2.79	16316.18	-761.19	1033.15

Excess thermodynamic functions

In order to unfold the nature of the molecular interactions between the components forming the eutectic, noneutectic solid dispersion and 1:1 molecular solid dispersion, the excess thermodynamic functions, such as, excess integral free energy (g^E), excess integral entropy (s^E) and excess integral enthalpy (h^E) were calculated using the following equations

$$g^E = RT\,(x_1 \ln \gamma_1^{\,l} + x_2 \ln \gamma_2^{\,l}) \quad ...(12)$$

$$s^E = -R\,(x_1 \ln \gamma_1^{\,l} + x_2 \ln \gamma_2^{\,l} + x_1 T \frac{\delta \ln \gamma_1^{\,l}}{\delta T} + x_2 T \frac{\delta \ln \gamma_2^{\,l}}{\delta T}) \quad ...(13)$$

$$h^E = -RT^2 (x_1 \frac{\delta \ln \gamma_1^{\,l}}{\delta T} + x_2 \frac{\delta \ln \gamma_2^{\,l}}{\delta T}) \quad ...(14)$$

and excess chemical potential or excess partial free energy of mixing

$$g_i^{-E} = \mu_i^{-E} = RT \ln \gamma_i^{l} \quad ...(15)$$

The values of $\delta \ln \gamma_i^{\,l} / \delta T$ can be determined by the slope of the liquidus curve near the alloys from in the phase diagram. The values of excess thermodynamic functions are given in Table 4. 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 [12,13] between the parent components during the formation of solid dispersion. The positive values in the present system suggest an association of weaker nature between unlike molecules and of stronger nature between like molecules. However, its sign provides information regarding a change in density of the solid dispersion during the phase transformation. The positive value of excess entropy is a measure of the change in configurational energy due to a change in potential energy and indicates an increase in randomness.

Table 4: Values of excess partial and integral thermodynamic functions of HQ-CBA system.

Solid dispersion & Compound	g_1^{-E} (J/mol)	g_2^{-E} (J/mol)	g^E (J/mol)	s_1^{-E} (J/mol/K)	s_2^{-E} (J/mol/K)	s^E (J/mol/K)	h_1^{-E} (kJ/mol)	h_2^{-E} (kJ/mol)	h^E (kJ/mol)
A_1	1047.56	149.65	962.26	-38.33	-6.40	-35.75	-12.93	-2.15	-11.91
A_2	4622.08	1390.10	4008.01	-47.20	-25.91	-43.15	-15.11	-9.44	-14.03
A_3	7842.93	2873.15	6426.54	-43.97	75.38	-9.96	-12.69	38.08	1.78
A_4	8397.80	2550.73	6439.04	1.83	57.38	20.24	9.26	29.63	15.99
A_5	10100.18	1810.79	6121.27	19.37	28.45	23.73	19.48	15.58	17.61
C ($A_{1:1}$)	10405.72	1781.52	6093.62	21.15	-13.78	3.68	20.70	-4.93	7.89
A_6	10545.98	1575.83	5881.50	107.60	108.81	104.59	62.84	51.06	56.71
A_7	10882.44	3172.37	6410.60	33.69	11.50	20.82	27.15	8.73	16.47
A_8	11659.39	-7.93	3667.27	62.80	5.96	23.87	41.62	2.84	15.05
A_9	12610.67	-591.12	2511.30	268.96	24.89	81.36	140.10	11.21	41.08
E	12910.64	-824.08	2060.21	116.60	-2.18	23.02	68.53	-1.85	12.93
A_{10}	13438.25	-827.56	1882.93	141.10	21.45	44.18	80.32	9.34	22.83
A_{11}	16316.06	-759.82	1033.15	304.67	-26.30	8.45	163.50	-13.46	5.12

Interfacial Roughness

The microstructure of a material has been found to be significant in deciding its mechanical, electrical, magnetic and optical properties. The growth morphology of organic binary solid dispersion during solidification depends on the growth characteristics of individual constituent phases which solidify with either faceted (nonmetallic) or nonfaceted (metallic) interfaces. This behaviour is related to the nature of the solid-liquid interface and can be predicted from the value of the entropy of fusion. According to Hunt and Jackson [14] the type of growth from eutectic melt depends upon a factor α, defines as,

$$\alpha = \xi \frac{\Delta H}{RT} = \xi \frac{\Delta S}{R} \quad ...(16)$$

where ξ is a crystallographic factor depending upon the geometry of the molecules and has a value less than or equal to one. ΔS / R (α) is known as Jackson's roughness parameter and R is the gas constant. When α is greater than two, the solid-liquid interface is a atomically smooth and exhibits faceted growth [15,16]. When α is less than two the solid-liquid interface is atomically rough and leads nonfaceted growth. The value of α (Table1) of all the solid dispersion under investigation are greater than two indicate that they exhibit faceted growth. Further a prediction of microstructure of eutectic can be made from Spengler's equation [10]

$$\theta = \frac{T_1 - T_e}{T_2 - T_e} \quad ...(17)$$

where T_1 and T_2 are the melting temperature of low melting and high melting component, respectively and T_e is the eutectic temperature. The normal eutectics are formed when θ lies between 0.1 and 1.0 but it lies between 0.01 to 0.1, so anomalous structure is obtained. The microstructure of the simple eutectic of HQ-CBA system containing mole fraction of CBA at 0.790 appears with normal faceted growth.

CONCLUSION

The phase diagram of the HQ-CBA system shows the formation of 1:1 molecular solid dispersion with only one eutectic. The experimental observation of solid dispersion growth indicates that a binary melt solidifies spontaneously only below its equilibrium temperature. The Gibbs-Duhem equation gives the solution of partial molar enthalpy of mixing, activity and activity coefficient of a component in binary mix. The value of surface roughness is greater than two gives indication about faceted growth in the solid dispersion.

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