Prediction of Drug–Polymer Miscibility through the use of Solubility Parameter based Flory–Huggins Interaction Parameter and the Experimental Validation: PEG as Model Polymer

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ABSTRACT: Important consideration for developing physically stable solid dispersion is miscibility of drug in carrier matrix. It is possible to predict thermodynamics of binary system through free energy calculations based on Flory–Huggins interaction parameter (χ_{dp}). In present study, PEG 6000 as model polymer and dataset comprising commonly used drugs/excipients was selected. The three-dimensional solubility parameter based on group contribution method was utilized for systemic calculation of χ_{dp} of the polymer with each compound in data set. On the basis of the values of χ_{dp}, it was possible to categorize all the compounds into three distinct categories, Types I and II: compounds predicted to be miscible and immiscible respectively with the polymer in all proportions and Type III: compounds expected to exhibit composition dependent miscibility behavior. The Bagley plot showed that majority of points for Type I fall in a region, which can approximately be delimited by a circle. Experimental verification through thermal analysis revealed that though it was possible to predict correctly miscibility behavior of Type II class compounds, distinction between Types I and III was less evident. Hence, solubility parameter based χ_{dp} may be used as an initial tool for fast screening of immiscible combination of polymer and drug. © 2013 Wiley Periodicals, Inc. and the American Pharmacists Association J Pharm Sci 102:2254–2263, 2013

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INTRODUCTION

Drug–polymer miscibility is considered to be an essential prerequisite for the successful formulation of a physically stable solid dispersion. The ultimate objective of the development of a drug–polymer miscible binary system is to provide an environment in which the crystallanity of the drug is so altered as to manipulate its solubility and solution rate. It is expected that in a drug–polymer miscible system, the local environment of the drug and eventually its physical stability are altered due to molecular level mixing of the drug with a polymer. Owing to the potential for the successful formulation of a poorly water-soluble drug, the study of miscibility of drug with polymer has increasingly become the topic of interest in both academic and industrial research.[1]

In terms of the classical thermodynamics, miscibility is defined as the level of molecular mixing adequate to yield macroscopic properties expected of single phase material, for example, a single glass transition.[2] On the contrary, statistical thermodynamics implies miscibility as homogeneity on a scale equivalent to the range of intermolecular forces (miscibility in this case is not necessarily defined by single glass transition) criteria. A single-phase binary system consisting of polymer as one component would on close scrutiny reveals areas rich in one component—a condition necessitated by the size of polymer molecules and the geometrical restraints imposed by covalent linking in the chain like macromolecules. In a truly miscible mixture, such regions would not grow in size even if given every incentive to do so; that is mixture would be stable up to reasonable time–temperature excursion. On the contrary, in an immiscible mixture, such regions would grow rapidly with time depending on ambient conditions.[3,4]

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On the basis of the concepts of statistical thermodynamics, Flory and Huggins separately and almost simultaneously proposed modifications in the original regular solution theory so as to make it applicable for a polymer–solvent binary system.[5,6] The lattice based Flory–Huggins theory of polymer solutions proposes an expression for the calculation of overall free energy of dissolution per mole of lattice site and has been quite successful in predicting behavior of polymer–solvent systems.[7] Recently there have been attempts to investigate applicability of the said theory, either in original form or with some modifications, for the prediction of behavior of drug–polymer binary system.[1,8–13] Flory–Huggins equation for the calculation of free energy of mixing of a drug–polymer binary system, that is, ΔG_m leads to the following expression:

$$\Delta G_m/RT = \underbrace{n_d ln\phi_d + n_p ln\phi_p}_{\text{Entropic contribution}} + \underbrace{n_d \phi_p \chi_{dp}}_{\text{Enthalpic contribution}} \quad (1)$$

where n_d and ϕ_d number of moles and volume fraction of drug, whereas n_p and ϕ_p are the number of moles and volume fraction of polymer respectively; χ_{dp} is Flory–Huggins interaction parameter between drug and the polymer. ΔG_m in the equation is normalized by gas constant R and absolute temperature T. Volume fraction, calculated as ratio of lattice site of the component to total number of lattice sites, was incorporated in the equation (in place of mole fraction in the regular solution theory) to make it possible to account for the comparatively larger volume occupied by a polymer chain in comparison with the second component of the binary system. While the first two terms in the equation describe the entropic contribution (combinatorial entropy), the last term represents the enthalpic contribution to the total free energy of mixing of the binary system. A necessary condition for miscibility is the total Gibbs free energy of mixing should be less than 0. As mixing is established to cause disorder and hence reduced entropy [with the value of volume fraction (ϕ) always being <1, ln ϕ a negative value always], the total entropic contribution is expected to facilitate mixing for all compositions. Hence, it is the enthalpic component of the free energy of mixing, which is going to determine whether $\Delta G_m \leq 0$ or not, hence whether mixing is going to occur or not.

In terms of enthalpic contribution to the total free energy of mixing, the determining factor in the mixing behavior is expected to be the Flory–Huggins interaction parameter between drug and polymer χ_{dp}. As is obvious from the equation, a negative or slightly positive value of χ_{dp} would lead to overall negative value of free energy of mixing and hence facilitate mixing. On the contrary, a high positive value of χ_{dp} is expected to offset the entropic gain due to mixing and indicate lack of mixing. A negative or slightly positive value of χ_{dp} is indicative of adhesive interaction between the drug and polymer and suggests mixing, whereas a positive value indicates strong cohesive forces either within drug or within polymer molecules and hence reduced tendency to undergo mixing. Thus the value of the interaction parameter is critical for understanding and predicting the behavior of drug–polymer binary system. Although initially χ_{dp} was expected to be a constant for a particular drug–polymer combination, it has now been shown to vary with temperature as per the following:

$$\chi_{dp} = A + B/T \quad (2)$$

where A and B are the constants for the particular binary systems.[14] As is evident from the Eq. 2, an increase in temperature is expected to causes corresponding decrease in χ_{dp}.

Drug–polymer interactions, being solid–solid interactions, are usually quiescent in comparison with the normally turbulent liquid or gaseous interfaces and pose difficult to quantify.[15] One among the different approaches used for the estimation of the drug–polymer interaction parameter χ_{dp} is through the use of Hildebrand solubility parameter δ, which in turn is related to cohesive energy density (CED) as follows:

$$\delta = \sqrt{\text{CED}} = \sqrt{\frac{\Delta E^{\text{vap}}}{V}} \quad (3)$$

where ΔE^{vap} is energy of vaporization of the component and V is the molar volume. As per Hildebrand, enthalpy of mixing for a drug–polymer binary system can be given by:

$$\Delta H_m = V_{dp}\phi_d\phi_p\left([\delta]_d - \delta_p\right)^2 \quad (4)$$

where ϕ_d and ϕ_p are the volume fractions and δ_d and δ_p are the solubility parameters of drug and polymer respectively; V_{dp} is the volume of mixture. As per Flory–Huggins theory ΔH_m can be given by van Laar expression as:

$$\Delta H_m = \chi_{dp} RT\, n_d \phi_p \quad (5)$$

Hence, Flory–Huggins interaction parameter χ_{dp} can be estimated by comparison of Eqs. 4 and 5 as follows:

$$\chi_{dp} = V\frac{\left([\delta]_d - \delta_p\right)^2}{RT} \quad (6)$$

The above equation shows that two substances exhibiting similar numerical value of solubility parameter are expected to undergo mutual mixing, whereas higher difference between the values of δ_d and δ_p indicates decreased tendency to undergo mixing. The

solubility parameter δ of an organic compound, as proposed by Hansen, can be calculated as the sum of squares of the partial solubility parameters. Hence the three-dimensional solubility parameter includes δ_{di} accounting for nonpolar or dispersion effects, δ_{pi} for polar effects and δ_{hi} to express the hydrogen bonding nature of the species, that is,

$$\delta^2 = \mathrm{CED} = \delta_{di}^2 + \delta_{pi}^2 + \delta_{hi}^2 \quad (7)$$

The partial solubility parameters can in turn be calculated using group contribution method as follows:

$$\delta_{di} = \frac{\sum F_{di}}{V} \quad \delta_{pi} = \frac{\sqrt{\sum F_{pi}^2}}{V} \quad \delta_{hi} = \frac{\sqrt{\sum F_{hi}}}{V} \quad (8)$$

where F_{di}, F_{pi}, and E_{hi} are the group contributions at 25°C, as reported in literature, for the occasionally occurring structural components in organic molecules.[16–18] Theoretical estimation of the molar volume (V) can be carried out by employing group contribution values for different structural components as suggested by Fedor.

Given the group contribution values for structural components of an organic compound, it is possible to estimate solubility parameter and hence Flory–Huggins interaction parameter of the components of a pharmaceutical binary system. Once the interaction parameter is known, the same can be used for the construction of phase diagram of the binary system depicting total free energy of mixing for varying compositions of the components based on Flory–Huggins theory (Eq. 1). It is however to acknowledge the fact that the change from higher G state to lower G state may be sometimes kinetically hindered or may be occurring in the time scale too long. In such kinetically hindered transitions, phase diagrams are still useful tools in that they at least provide constraints and driving forces for phase transitions.[19]

Phase separation in a binary system is expected to occur when a system can lower its free energy by separating into two phases. In this case, the lever rule is helpful in the determining the relative proportion of two phases for a particular composition of the binary system by drawing a straight line connecting the corresponding points on the free energy curve. These tie lines represent the hypothetical free energy of the combinations of two phases for any overall composition that lies in between. In any mixture at a finite temperature, spontaneous small local fluctuations in concentration are expected, in a manner that there are small regions that have concentrations higher than average and small regions where it is smaller. It is expected that as long as ΔG_m curve is concave up, the straight line will lie above ΔG_m and therefore fluctuations and phase separation would actually increase the free energy of the system. Consequently these fluctuations would relax back to the original. Thus "concave up" gives criteria for stability of one-phase system. The reverse is applicable to the "concave down" free energy curve also.[4]

Review of recent literature reveals different attempts to estimate Flory–Huggins interaction parameter by solubility parameter method and to predict the phase diagram of a drug–polymer binary system.[10,11,13,20] The present study is focused on the prediction of miscibility of various drug–polymer binary systems using poly ethylene glygol (PEG) 6000 as the model polymer. Hence, the Flory–Huggins interaction parameters for different drugs/commonly used excipients with PEG 6000 were calculated and the predictions validated for randomly selected drug–polymer combinations by conducting thermal analysis of binary mixtures.

MATERIALS AND METHOD

Theoretical Estimations

A dataset comprising 83 drugs belonging to various categories and some of the commonly used excipients used in dosage formulation was extracted form literature. The dataset composed of drugs belonging to different therapeutic categories and possessing diverse chemical structures. Cambridge Structure Database (Conquest version 1.13)[21] was referred for the determination of true density values for all drugs/excipient powders and these values were divided by the respective molecular mass to determine the molar volume of each candidate in dataset (this was considered as reported molar volume for the present study). Group contribution values of different structural groups as suggested by Fedor were used for the estimation of calculated molar volume. Volume fraction of polymer and drug for each binary mixture was calculated by dividing lattice sites for each component by the total number of lattice sites (considering $N = 136$ for PEG 6000). Further, based on the listed F_{di}, F_{pi}, and E_{hi} values of different organic groups and employing Eqs. 7 and 8, three-dimensional solubility parameter was calculated for the polymer as well as for all the drugs/excipient in the dataset. These values were then utilized for the calculation of Flory–Huggins interaction parameter as per Eq. 6. The phase diagrams depicting total change in free energy upon mixing varying proportions of drug/excipient and polymer were constructed on the basis of the Flory–Huggins Eq. 1 for each combination of drugs/excipients with PEG 6000.

Materials

Phenylbutazone (PBZ), chloramphenicol, sucrose, and PEG 6000 were obtained from Sigma–Aldrich

Co., (St Louis, USA) All the chemicals were of analytical grade and were used as supplied.

Thermal Analysis

Thermal analysis of all the samples was performed using a DSC Q2000, TA System (USA) equipped with TA Universal Analysis software. The instrument was calibrated using Indium metal with a melting endotherm at 156.89°C.

Physical mixtures containing different proportions (0%, 20%, 40%, 60%, 80% and 100%, w/w) of drugs and polymers were prepared by geometric mixing. The samples (3–5 mg) were loaded into T-zero aluminum pans, crimped nonhermetically and loaded in sample furnace. All samples were heated at the rate of 10°C/min in an atmosphere of nitrogen gas (flow rate 60 mL/min). An empty aluminum pan was used as the reference pan. All samples were run in triplicate. The onset of the melting endotherm of each differential scanning calorimetry (DSC) thermogram was recorded.

RESULT AND DISCUSSIONS

Calculations for Molar Volume

The molar volume of various drugs/excipients was estimated using the reported density values and also calculated using the Fedor's group contribution method (Table 1). The scatter plot between the two values (Fig. 1) shows that the calculated molar values are appreciably correlated with the reported molar values ($r = 0.968$; $0.9 < r < 0.97$ appreciably correlated). The above indicates that Fedor's method for the determination of molar volume gives a reasonable estimation of the molar volume of a solid powder.

A review of the literature reveals comparison of experimental liquid molar volumes and Fedor's method based calculated molar volumes for a number of organic compounds that are known not to self-associate. A correlation coefficient of 0.999 has been reported in the particular study.[22] The slightly poorer correlation obtained in the present study may be attributed to self-associating groups such as alcohols, carboxylic acid, amide, or similar groups, which are abundantly present in molecular structures of drugs and excipients used in the present study.

Model Design

The Flory–Huggins interaction parameter between PEG 6000 and each of the candidate compounds in the selected dataset has been listed Table 1. The values of these parameters were used for construction of phase diagrams depicting total change in free energy upon mixing of the polymer with the varying proportion of drug/excipient. Retrofit analysis of the phase diagrams revealed that on the basis of the shape of free energy versus composition curve, it was possible to classify all the candidates in the dataset into three categories.

Type I: The drugs/excipients that showed negative value of total free energy of mixing for all the combinations of drug/excipient and polymer were classified as Type I (59% of the total dataset). Thus, the overall shape of the free energy versus composition curve is depicted to be concave up for all the compounds belonging to this category (Fig. 2). The small value positive enthalpic contribution in this case appears to be counterbalanced by the overall increase in entropy of the system and hence the system exhibits negative free energy of mixing for all proportions of drug and polymer. Drugs belonging to this category can be considered to be miscible with the polymer in all proportions. It is believed that the adhesive forces of interaction between the drug and polymer are stronger than the cohesive forces and hence facilitate mixing. The value of χ_{dp} with the compounds belonging to this class was found to be <0.98 in the present study. Some of the representative drugs belonging to this category include PBZ, griseofulvin, ibuprofen.

Type II: The compounds that showed a positive value of total free energy of mixing for all the combinations of drug/excipient and polymer were classified as Type II (13% of the compounds in the dataset). Thus the overall shape of the free energy versus composition curve in this case is found to be convex up (or concave down) for all the compounds belonging to this class (Fig. 3). (It is to acknowledge the fact at this point that if very low proportion of drug (i.e., almost pure polymer) or very high proportion of drug (i.e., almost pure drug) are considered, the free energy of mixing may attain a negative value, but these values are obtained with hypothetical concentrations (as low as 0.00001% or as high as 99.99999%) and hence are neglected for all practical purposes). These compounds can be considered to be immiscible with the polymer in all proportions. The high value of χ_{dp} (values between 5.19 and 28.27 in the present study) in this case lead to an overall increase in the value of enthalpic contribution and entropic gain obtained by mixing the drug with polymer may be believed to be insufficient. Some of the representative members of this class are sucrose, xylitol, ascorbic acid, hydroquinone.

Type III: All the compounds that exhibited a concave down followed by concave up free energy of mixing versus composition curve upon gradually increasing the volume fraction of polymer in the binary mixture (Fig. 4), were classified as Type III (26% of the compounds in the dataset). Thus, the total free energy of mixing for compositions containing low proportion of polymer was found to be positive, whereas upon increasing the polymer fraction, the system exhibited a negative value of free energy of mixing. The above

Table 1. Classification of Various Drugs and Excipients into Three Categories on the Basis of Flory–Huggins Interaction Parameter

S. No.	Name	CSD code	ρ	V	δ_{di} $(J/cm^3)^{1/2}$	δ_{pi} $(J/cm^3)^{1/2}$	δ_{hi} $(J/cm^3)^{1/2}$	δ $(J/cm^3)^{1/2}$	χ	Type
1	PEG				17.78	11.11	9.13	22.9		
2	Phenyl butazone	BPYZDO20	1.223	243.2	20.48	9.16	7.58	23.69	0.06	I
3	Nifedipine	BICCIZ	1.378	251.9	19.6	5.84	8.59	22.19	0.05	I
4	Indomethacine	INDOMET	1.372	229.8	22.19	5.97	9.42	24.84	0.36	I
5	Phenobarbital	PHBARB	1.36	159.2	21.54	14.76	8.75	27.55	1.42	III
6	Acetophenone	ABACOX10	1.616	115.7	18.49	6.72	4.15	20.11	0.37	I
7	Aspirin	ACSALA	1.398	129	20.23	7.52	10.78	24.13	0.08	I
8	Paracetamol	COTZAN	0.821	111.2	21.13	8.53	15.02	27.29	0.88	I
9	Phenytoin	PYAHYON01	1.669	170.2	22.8	9.47	7.74	25.87	0.62	I
10	Nitrofurantoin	LABJON	1.652	135.5	20.44	16.5	12.62	29.25	2.26	III
11	Griseofulvin	GRISFL	1.466	226.1	21.14	10.19	8.52	24.94	0.39	I
12	Ibuprofen	COTYOA	1.023	195.5	17.95	2.22	7.15	19.45	0.96	I
13	Ketoprofen	KEMRUP	1.284	214.6	19.48	4.21	7.48	21.28	0.23	I
14	Ofloxacin	CUYCEF	1.414	232	22.77	11.15	11.37	26.97	1.59	III
15	Tolbutamide	ZZZPUS	1.264	238.5	19.53	6.97	9.13	22.61	0.01	I
16	Chloramphenicol	CLMPCL01	1.505	180.8	22.4	11.05	16.91	29.77	3.52	III
17	Prednisone	PRGDOL	1.315	190.4	23.37	13.22	15.54	31.03	5.19	II
18	Naproxen	COYRUD	1.266	157.3	19.26	3.68	9.09	21.62	0.11	I
19	Itraconazole	TEHZIP	1.36	457.51	21.66	10.94	10.64	26.5	2.45	III
20	Sulphathiazole	SUTHAZ	1.551	181.6	21.8	8.78	10.43	25.71	0.59	I
21	Ketoconazole	KCONAZ	1.4	353.5	21.55	9.63	10.2	25.72	1.16	III
22	Carbamazepine	CBMZPN01	1.347	168.8	20.38	6.58	9.55	23.45	0.02	I
23	Mebendazole	YULGIQ	1.446	191.6	21.55	6.73	10.27	24.81	0.29	I
24	Diazepam	DIZPAM10	1.373	195.7	22.56	7.56	7.96	23.92	0.08	I
25	Piroxicam	BIYSEH03	1.463	221.1	21.57	9.06	14.54	27.55	1.97	III
26	Phenacetin	PYRAZB	1.262	154.6	18.95	5.82	7.33	21.1	0.21	I
27	Mefanamic acid	XYANAC	1.268	185.8	21.9	2.66	8.39	23.61	0.39	I
28	Succinylsulfa-Thiazole	HEZNEF	1.357	238.4	21.56	8.29	11.1	25.62	0.73	I
29	Etodolac	DONSOO	1.253	219.5	20.18	2.81	8.65	22.1	0.05	I
30	Fenofibrate	TADLIU	1.285	275.2	19.84	4.21	6.71	21.36	0.27	I
31	Ritonavir	YIGPIO	1.279	512.9	20.26	4.97	10.38	23.2	0.02	I
32	Benzoic acid	BENZAC	1.315	99.9	19.62	4.35	10.01	20.1	0.32	I
33	Citric acid	CITRAC10	1.655	108.5	20.92	8.14	21.47	31.06	2.98	III
34	Fructose	FRUCTO11	1.602	90.3	22.71	13.15	33.78	42.78	14.73	II
35	Glucose	GLUSCA	1.566	92.9	21.64	12.78	33.3	41.72	13.58	II
36	Sucrose	SUCROS	1.587	159.5	23.45	9.87	32.55	41.31	22.31	II
37	Urea	UREAXX	1.319	49.2	17.28	15.65	19.55	30.43	1.15	-
38	Stearic acid	STARAC	1.041	319.5	16.5	1.3	5.59	17.46	3.90	III
39	Sorbic acid	LEZHUT	1.25	116	15.08	3.42	9.98	18.08	1.11	III
40	Lactose	LAKKEO01	1.618	237	19.6	26.2	23.2	39.9	28.27	II
41	Famotidine	FORVIG	1.55	222.6	20.97	12.39	16.47	29.40	3.88	III
42	Nabumetone	XOCXUI	1.228	193.8	18.73	4.48	5.08	19.92	0.71	I
43	Propranolol	IMITON	1.164	218.2	19.52	3.35	11.04	22.72	0.00	I
44	Theophylline	BAPLOT	1.491	138.2	17.80	12.85	12.65	25.33	0.34	I
45	Quinoline	EDAVUA	1.244	105.2	16.16	2.25	5.43	17.19	1.42	III
46	Allobarbital	DALLBA	1.282	154.4	19.75	15.20	8.89	26.47	0.81	I
47	Ascorbic acid	LASCACO1	1.699	88.7	20.86	15.95	27.07	37.71	8.03	II
48	Fumaric acid	FUMAAC	1.631	84	17.38	10.00	15.43	25.30	0.20	I
49	Lactic acid	YILLAG	1.385	71	17.46	9.19	20.55	28.50	0.92	I
50	Maleic acid	MALIAC	1.594	82.1	19.73	11.91	22.07	31.91	2.75	III
51	Tartaric acid	TARTAC	1.757	75	21.87	17.41	28.28	39.77	8.81	II
52	Mannitol	DMANTL	1.487	106.2	19.96	28.25	33.61	48.23	28.12	II
53	Hydroquinone	HYQUIN	1.381	62.4	27.08	16.12	25.32	40.43	7.91	II
54	Xylitol	XYLTOL	1.515	94.2	19.43	26.54	32.58	46.29	21.27	II
55	Ursodeoxycholic acid	FEBHUP	1.198	327.6	18.83	3.31	12.35	22.77	0.00	I
56	Quinidine	BOMDUC	1.234	244.2	20.72	5.37	11.97	24.52	0.26	I
57	Benzocaine	QQQAXG	1.205	139.2	18.89	3.61	10.52	21.92	0.06	I
58	Chlorpropamide	BEDMIG01	1.389	212.9	20.70	8.04	9.78	24.31	0.17	I
59	Salicylic acid	SALIAC	1.444	90.9	22.11	7.28	18.17	29.53	1.65	III
60	Sulfanilamide	SULAMD	1.479	141.8	20.87	9.61	14.19	27.00	0.98	I
61	Fenbufen	SAFNIW	1.265	176.3	22.12	5.13	8.25	24.16	0.12	I
62	Pyrazinacarbox-Amide	PYRZIN05	1.486	75	17.07	23.67	16.49	33.52	3.49	III
63	Diflusinal	FAFWIS	1.319	141.3	26.33	4.88	14.57	30.48	3.35	III

(*Continued*).

Table 1. Continued.

S. No.	Name	CSD code	ρ	V	δ_{di} $(J/cm^3)^{1/2}$	δ_{pi} $(J/cm^3)^{1/2}$	δ_{hi} $(J/cm^3)^{1/2}$	δ $(J/cm^3)^{1/2}$	χ	Type
64	Tolfenamic acid	KAXXAI	1.454	176.3	23.26	4.19	8.75	25.20	0.38	I
65	Saccharine	SCCHRN	1.603	134.7	21.52	11.69	11.19	26.20	0.61	I
66	Sulfamerazine	SLFNMA	1.338	196	20.56	10.78	13.03	26.61	1.11	III
67	Primidone	EPHPMO	1.276	164.5	20.73	9.73	7.87	24.21	0.12	I
68	Flurbiprofen	FLUBIP	1.286	183.8	21.49	2.44	7.38	22.85	0.00	I
69	Flutamide	WEZCOT	1.524	195	19.13	6.87	5.82	21.14	0.25	I
70	Nimesulide	WINWUL	1.476	197.6	22.22	9.08	9.89	26.83	1.26	III
71	Sulfadimidine	SLFNMD10	1.423	210.5	20.52	10.03	12.57	26.07	0.87	I
72	Perfenazine	PERPAZ	1.323	281.7	21.65	8.92	11.21	25.96	1.09	III
73	Captopril	MCPRPL	1.332	170.2	18.39	6.97	9.99	22.06	0.05	I
74	Nizatidine	RAZDIF	1.324	253.9	19.22	6.35	8.35	21.89	0.11	I
75	Cimetidine	CIMETD	1.312	187.8	19.38	10.87	10.77	24.69	0.25	I
76	Clotrimazole	PUVRIH	1.316	252.5	21.15	5.07	6.42	22.68	0.01	I
77	Pyridoxine	BITZAF	1.383	101.6	22.44	16.73	22.59	37.73	9.22	II
78	Menadione	IVEJUO	1.355	134.5	20.07	11.48	5.45	23.76	0.04	I
79	Frusemide	FURSEM	1.634	212.5	23.76	7.49	13.13	28.16	2.43	III
80	Digoxin	DIGOXN	1.3	490	20.73	3.68	17.61	27.45	4.19	III
81	Ampicillin	AMCILL	1.382	224.3	21.98	6.69	11.70	25.78	0.77	I
82	Glibenclamide	DUNXAL	1.377	360.9	21.44	5.29	8.87	23.80	0.12	I
83	Hydrochlorthiazide	HCSBTZ	1.683	200.7	23.86	10.07	13.82	29.35	3.45	III
84	Aceclofenac	VUGCUV	1.512	274	19.63	4.78	8.73	22.01	0.79	I

Cambridge Structure Database (CSD) codes and the reported density values (ρ in gm/cm^3) are also included. [V: Fedor's molar volume (cm^3/mol).]

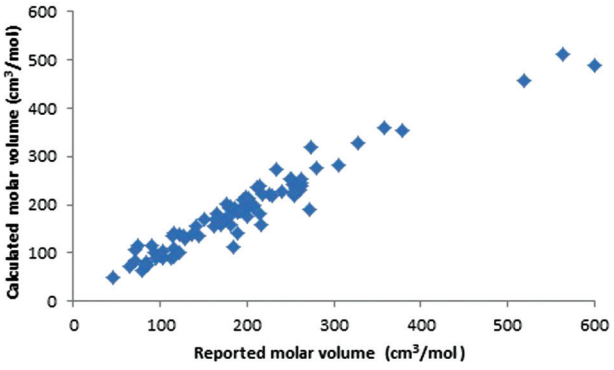

Figure 1. A plot showing the comparison of the reported molar volume and calculated molar volume (Table 1) of the compounds in the dataset.

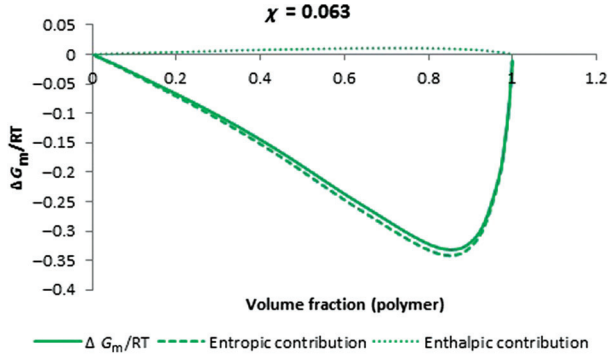

Figure 2. Composition dependence of entropic and enthalpic contribution and total free energy of mixing calculated for PEG 6000 and phenyl butazone ($\chi_{dp} = 0.063$).

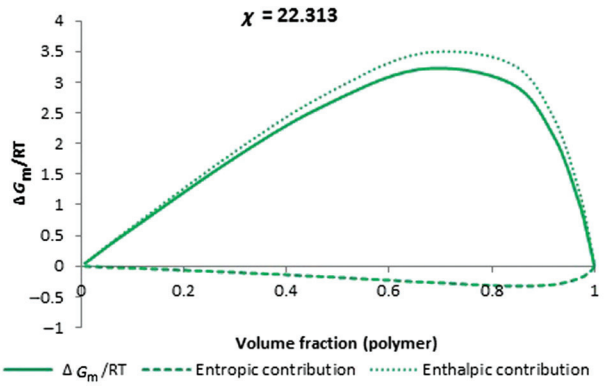

Figure 3. Composition dependence of entropic and enthalpic contribution and total free energy of mixing calculated for PEG 6000 and sucrose ($\chi_{dp} = 22.313$).

indicates that drugs/excipients have a tendency to form a biphasic system with low concentration of the polymer but the binary system is expected to exhibit single phase upon increasing the polymer fraction. This type of behavior was exhibited by drugs/excipients possessing χ_{dp} values 1.09–4.19 in the present study.

It is however to be realized that the solubility parameter based value of χ_{dp} are calculated at temperature 298 K. As at higher temperature the value of χ_{dp} is expected to reduce (Eq. 2), a system immiscible at lower temperature may attain miscibility at higher temperature. Alternatively, a single-phase binary system at higher temperature can be expected to exhibit phase separation when the temperature of the binary system is reduced.

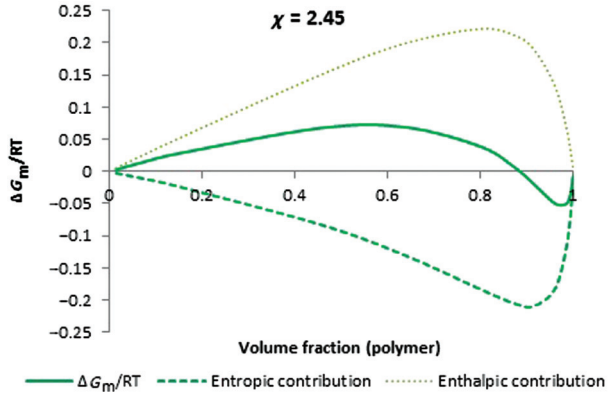

Figure 4. Composition dependence of entropic and enthalpic contribution and total free energy of mixing calculated for PEG 6000 and chloramphenicol ($\chi_{dp} = 2.45$).

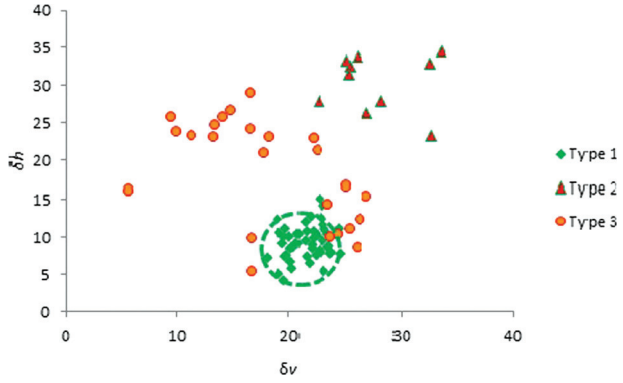

Figure 5. Position of substance-specific locations of drugs within Bagley diagram: Type I—predicted to be miscible; Type II—predicted to be immiscible; Type III—composition dependent miscibility.

Construction of Bagley's Plot

Based on thermodynamic considerations that δ_{di} and δ_{pi} show similar value, whereas effect of δ_{hi} is of quite different nature, Bagley et al. introduced combined solubility parameter δ_v, which is defined as:

$$\delta_v = \sqrt{\delta_{di}^2 + \delta_{pi}^2}$$

Bagley diagram, which demonstrates the relation between δ_v versus δ_{hi}, enables a projection of the three-dimensional solubility parameter into a two-dimensional plot.[23] Construction of such a diagram for the present data is presented as Figure 5. The plot shows majority of points for miscible substances fall in a single region, which can approximately be delimited by a circle with the center C, having coordinates as $\delta_v \approx 20.7$ $(J/cm^3)^{1/2}$ and $\delta_{hi} \approx 9.13$ $(J/cm^3)^{1/2}$ (Fig. 5). The circle is surrounded by substances exhibiting Type III behavior, whose location is widely spread over the Bagley diagram. In another typical region exhibiting higher values for δ_v and δ_{hi}, Type II (substances with immiscible behavior) are found to be located.

Bagley diagram depicts increased contribution of δ_{di}, δ_{pi}, and δ_{hi} parameters to the overall solubility parameter for a compound if its location is farther away from the origin. Localization of all Type II (immiscible) compounds in such a region of the Bagley's plot suggests increased cohesive energy for the compound, which may in turn account for the immiscible behavior with the polymer. The localization of all miscible compounds in a region in the vicinity of the origin in the plot suggests that miscibility with polymer is feasible only when the structure of drug molecules exhibits permissible degree of cohesiveness in the form of dispersion, polar and hydrogen bonding interactions.

Thermal Analysis

Out of the three categories developed for the selected dataset in the present study, one representative member was selected from each of the category. The physical mixtures containing varying proportion of drug and polymer were prepared and DSC thermograms of the mixtures were recorded. The purpose of carrying out thermal analysis was to look for depression in melting point of the drug as these measurements have been widely used to investigate polymer-polymer mixing thermodynamics.[24,25]

Phenylbutazone was selected as the member from Type I category and an overlay depicting thermograms of mixtures containing different proportions of PBZ and PEG 6000 is presented as Figure 6. PEG 6000 is characterized by a melting endotherm at 61.36°C and the corresponding endotherm for PBZ occurs at 107.17°C. Physical mixtures containing 20% and 40% of the drug content show the absence of melting endotherm for the drug. The results are in agreement with a recent study where analysis of samples containing 20%–40% (w/w) drug content for PBZ in the presence of PEG 8000 showed only a single peak corresponding to the melting of the polymer.[26] The lack of endotherm of the drug has been attributed to the melting and eventual solublization of the drug within the molten carrier during heating the sample. It has been proposed that during the process of heating for analysis of thermogram of the physical mixture, the molten carrier (which has nearly half the melting temperature as compared with the drug) begins to solubilize the drug, thereby dispersing it within its matrix with the consequence that the endotherm for the drug disappears completely. Upon increasing the proportion of PBZ in the mixture to 60% (w/w) and above, the depression in onset of melting point of the drug is found to be quite evident in the

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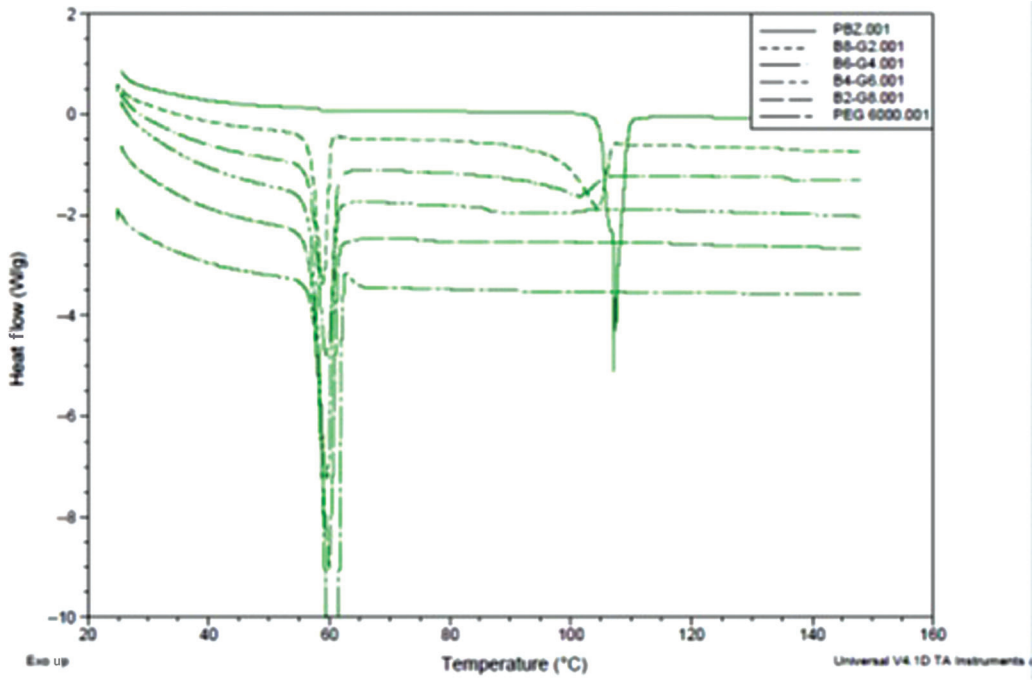

Figure 6. Overlay depicting DSC thermograms of physical mixtures of PEG 6000 and phenylbutazone (G: PEG 6000; B: phenylbutazone).

thermogram. The same is indicative of miscibility of drug in the polymer.

Sucrose was selected as the representative member belonging to Type II, compounds in the data set predicted to be immiscible with PEG. An overlay depicting thermograms of physical mixtures containing different proportions of sucrose and PEG 6000 are presented as Figure 7. Sucrose depicted a melting endotherm at 191.07°C. The figure shows that for the thermograms of physical mixtures containing lower proportion of polymer, there is no evidence of depression in melting point of the sucrose. Similarly the

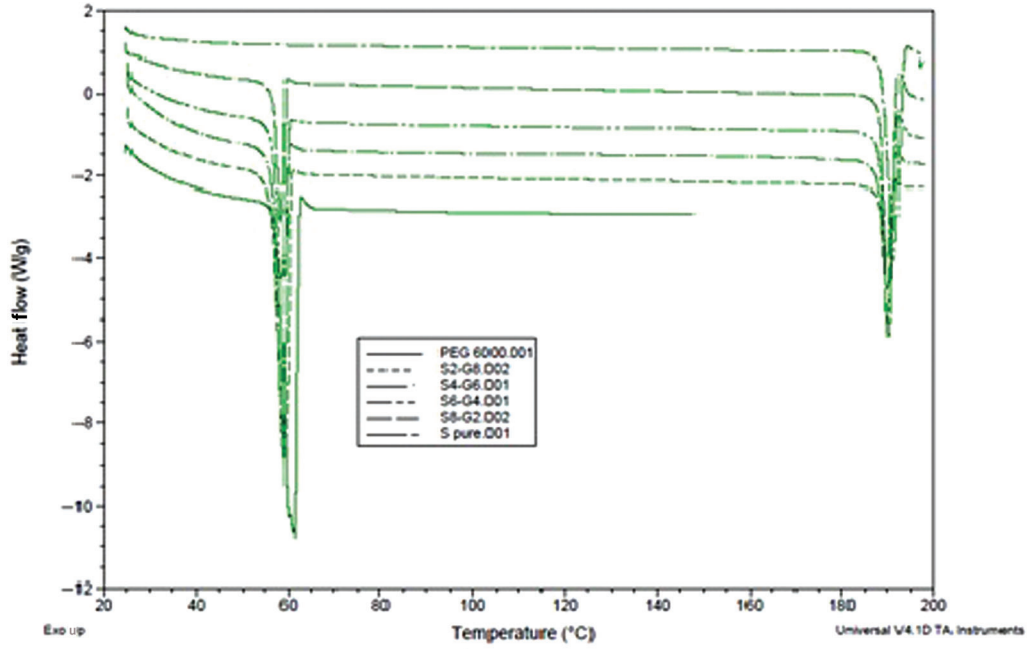

Figure 7. Overlay depicting DSC thermograms of physical mixtures of PEG 6000 and sucrose (G: PEG 6000; S: sucrose).

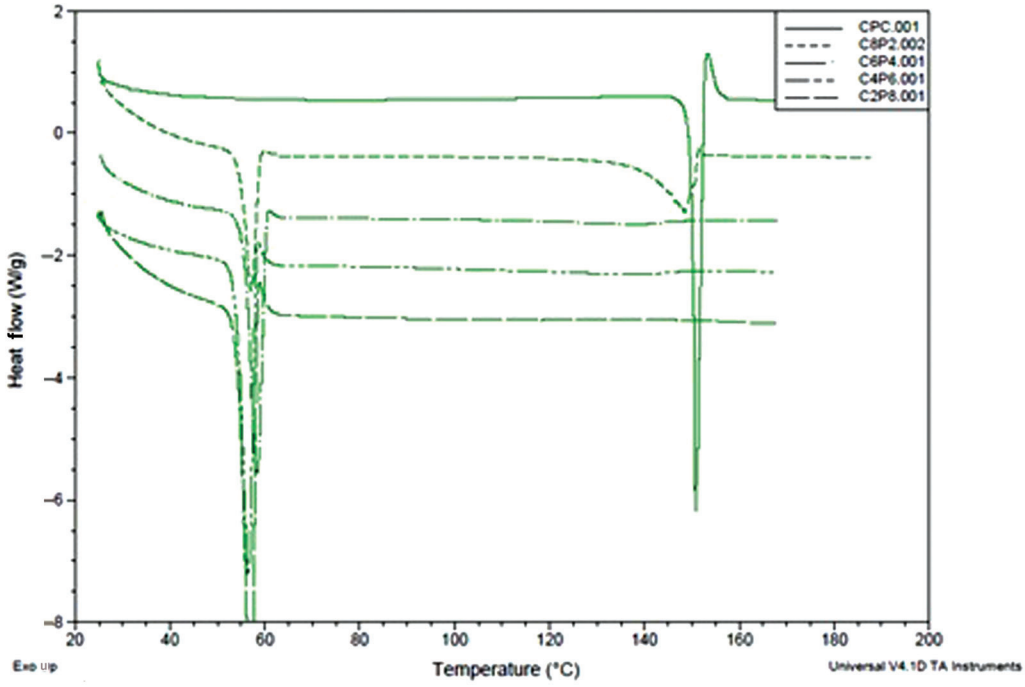

Figure 8. Overlay depicting DSC thermograms of physical mixtures of PEG 6000 and chloramphenicol (P: PEG 6000; C: chloramphenicol).

thermograms of mixtures containing higher proportion of polymer also demonstrated the distinct melting endotherms both for the polymer as well as for sucrose. The absence of any depression in the onset of melting endotherm for sucrose in the presence of molten PEG can be considered as indicative of immiscibility of sucrose with PEG. The particular behavior may be attributed to strong hydrogen bonding induced cohesive interactions among sucrose molecules, as is evident from the higher value for δ_{hi} and hence higher value of δ in the present case.

Chloramphenicol was selected as the representative drug for Type III category, that is, drugs which exhibited composition dependent behavior. An overlay representing thermograms of the drug, PEG 6000 and their physical mixtures in varying proportions is presented as Figure 8. The melting endotherm for the drug was found to be at 150.79°C. The overlay shows the absence of melting endotherm for the drug when the physical mixture contained higher proportion of polymer. On the contrary, in the thermograms of the physical mixtures containing lower proportion of polymer, the depression in the onset of melting point of the drug is also quite evident.

As per the phase diagram constructed on the basis of Flory–Huggins theory, it was expected that the drug would exhibit immiscibility with lower proportion of polymer, which should have been manifested as distinct melting endotherm with 20% polymer content. On the contrary, the thermal behavior of PEG–chloramphenicol binary mixture appears to be quite similar to the one exhibited by PBZ–PEG mixtures. Although chloramphenicol was estimated to be type III class drug, that is, drugs exhibiting immiscibility with lower polymer fraction but showing miscibility with higher polymeric content, the difference apparently could not be translated into the difference in the thermal behavior of drug–polymer binary mixtures.

The results reveal that although the thermal behavior of candidate compounds from the Types I and III in the presence of PEG was not distinguishable, the prediction of immiscibility of sucrose was in fact manifested as its unaltered melting endotherms in the presence of PEG. The above indicates that with the help of similar approach, it may be possible to screen out candidate drug/excipients for which PEG may not be suggestive polymer for the possible development of stable binary mixtures. Strategies along these lines can be developed for the other common pharmaceutical polymers for their ability to yield a stable pharmaceutical system and as an initial tool for fast screening of immiscible combination of a polymer and drug.

CONCLUSION

The present study investigates theoretical estimation of Flory–Huggins interaction parameter for a number of drug/excipients with PEG 6000 as the model polymer. The study revealed that Fedor's group contribution method for the calculation of molar volume

gave reasonable good estimation of molar volume. Using group contribution method for the estimation of solubility parameter and Flory–Huggins interaction parameter, it is possible to predict free energy phase diagram of the system for varying proportions of drug and polymer in the binary mixture. Bagley's plot provided reasonable good approximation of behavior on the basis of the location of the compound on the plot. The results revealed that though it was possible to differentiate between polymer immiscible drugs using the approach, the behavior of drugs showing complete miscibility and composition dependence miscibility could not be clearly distinguished. To conclude, the development of similar models for different pharmaceutical polymers could be helpful in initial screening of polymers that may yield a stable binary mixture with a particular drug based on the knowledge of the interaction parameter between the two.

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