Prediction of Poly(Ethylene) Glycol-Drug Eutectic Compositions Using an Index Based on the van't Hoff Equation

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Purpose. To define an index based on the van't Hoff equation that can be used as a screening tool for predicting poly(ethylene) glycol (PEG)-drug eutectic composition.

Methods. Phase diagrams of PEG with ritonavir, ibuprofen, fenofibrate, naproxen, and griseofulvin were constructed using differential scanning calorimetry, hot stage microscopy and powder X-ray diffractometry. Previously reported phase diagrams were also used to test the predictive capability of the index.

Results. This work shows that a modified van't Hoff equation can be used to model the drug liquidus line of these phase diagrams. The slope of the liquidus line depends on the melting point (T_d^f) and heat of fusion (ΔH_d^f) of the drug and describes the initial rate at which the eutectic or monotectic point is approached. Based on this finding, a dimensionless index I_c was defined. The index can be calculated from the melting points of the pure components and heat of fusion of the drug. In addition to the compounds listed above, the index was found to predict the eutectic composition for flurbiprofen, temazepam and indomethacin. These compounds range over 150°C in T_d^f, and from 25–65kJ/mole in ΔH_d^f.

Conclusion. Using I_c the approximate eutectic composition for eight different compounds was predicted. The index provides a useful screening tool for assessing the maximum drug loading in a drug-polymer eutectic/monotectic formulation.

KEY WORDS: solid dispersion; phase diagrams; eutectic; monotectic; poly(ethylene) glycol; van't Hoff equation.

INTRODUCTION

In the last four decades, there have been over 70 publications describing the preparation of eutectic or monotectic mixtures involving a poorly soluble drug and a water-soluble carrier. In these mixtures it is possible to produce an ultra-fine or colloidal dispersion of the drug with an improved dissolution rate, and thus the potential for improved bioavailability (1). For pharmaceutical applications the use of eutectic mixtures was first demonstrated by Sekiguchi and Obi (2), and monotectic phase diagrams were reported by Kauer *et al.* (3). These eutectic or monotectics have numerous advantages over other types of solid dispersion systems. The formulations are simple, and do not tend to segregate (4). Moreover, unlike solid dispersion systems that contain an amorphous phase, these formulations do not have physical stability issues because both the drug and the carrier are crystalline.

Despite these advantages, eutectics or monotectics have found limited application in pharmaceutics. The feasibility of developing a eutectic/monotectic system is dictated by the eutectic composition and the dose. Determining the eutectic composition requires construction of a phase diagram, which is not only time consuming and material intensive, but extremely laborious. At early stages of drug development the availability of the compound and resources are scarce, and it is nearly impossible to generate these phase diagrams.

A commonly used water-soluble carrier is the polymer poly(ethylene) glycol (PEG). Despite repeated attempts at preparing amorphous dispersions in PEGs (5) there are only a few examples of amorphous drug distributed in the crystalline PEG matrix (6,7). Most PEG-drug dispersions are either eutectic (8–11) or monotectic (3,12,13) with negligible solid solution regions. Based on solid state and solution phase interactions, Vasil'ev (14) classified binary phase diagrams for metallic systems into four different types. Following this nomenclature, the PEG-drug eutectic/monotectics belong to a category that exhibits complete miscibility in the liquid state and complete immiscibility in the solid state (14). In this category, the liquid phase interactions between unlike components are expected to be stronger than those between like components. The structural dissimilarity between PEG and most drugs results in the drug having minimal influence on the polymer melting. These concepts are graphically depicted in Fig. 1.

Based on the analysis of drug melting point depression a dimensionless index, I_c was defined. The integer value of the index I_c was calculated from the melting properties of the pure components, and was correlated with the eutectic composition (Fig. 1).

PEG-based solid dispersions with ritonavir, ibuprofen, naproxen, griseofulvin, indomethacin, temazepam, flurbiprofen and fenofibrate were used to demonstrate the utility of I_c. These examples are followed by a discussion of how the arguments developed here may be applied to other crystalline polymer carriers.

THEORETICAL SECTION

The discussion in this section only applies to phase diagrams that exhibit complete liquid phase miscibility and are immiscible in the solid state. It is evident from Fig. 1 that monotectic systems may be considered as eutectics where the eutectic composition is close to the pure component. The liquidus line in binary phase diagrams represents the solubility of the drug in the carrier as a function of temperature, or alternatively the melting point depression of the drug caused by the carrier (15). In the absence of solid solution regions the initial melting point depression of the drug caused by the carrier may be described by the van't Hoff equation:

$$T_{mix} = T_d^f - x_p \frac{R(T_d^f)^2}{\Delta H_d^f} \quad (1)$$

where T_d^f is the melting point of the major component, χ_p is the mole fraction of the minor component, ΔH_d^f is the molar heat of fusion of the major component, R is the universal gas constant and T_{mix} is the temperature along the liquidus line as a function of X_p.

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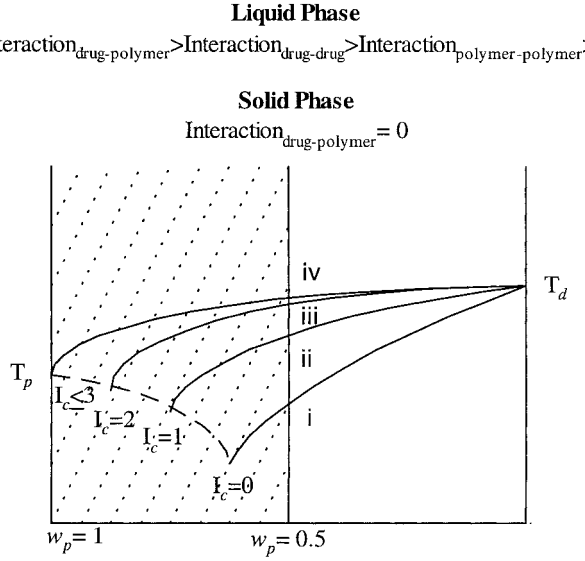

Fig. 1. The nature of PEG-drug phase diagrams and the proposed relationship between I_c and the eutectic point.

Calculation of thermodynamic parameters from equation (1) requires a molarity or molality based activity coefficient. Difficulties associated with defining polymer molecular weight, and the large difference in molar masses between a polymer and a small organic molecule, have led to the use of weight fraction based activity coefficient (16). These weight fraction based activity coefficients have been used to predict liquid-liquid equilibrium phase diagrams (17), vapor-liquid equilibrium diagrams (18), gas adsorption isotherms (19), and volatility of hydrocarbons (20). The weight fraction activity coefficient Ω_i, for the *i*th component in a mixture is defined as:

$$\Omega_i = \frac{\alpha_i}{w_i} \tag{2}$$

where α_i is the activity and w_i is the weight fraction based concentration. The standard state is defined to be the pure liquid at the temperature of interest.

To use the concept of weight fraction activity, equation (1) may be written as:

$$T_{mix} = T_d^f - w_p \frac{R(T_d^f)^2}{\Delta H_d^f} \tag{3}$$

This equation applies only when the polymer is the minor component on a weight fraction scale. (This region of the phase diagram in Fig. 1 is not shaded.) The lower melting component is the major component in a binary eutectic mixture (21), and for the polymer to be a carrier it is required to be the major component (22). This requirement imposes the constraint $T_p^f \leq T_d^f$. The thermodynamic arguments developed above cannot be extrapolated to describe the behavior to the shaded region in Fig. 1. An equation analogous to equation (3) describing the other half of the phase diagram requires knowledge of molar heat of fusion for the polymer and may not be useful because most drugs are expected to have negligible impact the polymer melting point depression curve. Therefore, an empirical relationship is developed to predict the eutectic composition.

A plot of T_{mix} vs.w_p yields a straight line where the slope represents the rate at which the eutectic point is approached by the binary mixture. Because these binary systems do not interact in the solid state, the melting point of the eutectic is usually close to the melting point of the lower melting component. Therefore, the rate at which the eutectic point is approached, and the difference in melting temperatures between the drug and the polymer is used to define the index I_c:

$$I_c = \frac{T_d^f - T_p^f}{R(T_d^f)^2/\Delta H_d^f} \tag{4}$$

As stated above, for the polymer to be the carrier it is required that $T_p^f \leq T_d^f$, therefore $I_c$is always a positive number. The denominator in equation (4) represents the strength of polymer-drug interaction and this interaction determines the nature of the phase diagram. For drugs that have high solubility in PEG, the rate of melting point depression and therefore the denominator in equation (4) is large. In this case, the value of I_c is small and at the eutectic point the drug loading is high. However, the smaller the rate of melting point depression caused by the polymer, the smaller the denominator for equation (4), and larger the value of I_c. Monotectic systems represent the minimum drug loading and thus define the upper limit for I_c. Since the eutectic point lies on the $1 \geq w_p > 0.5$ segment, this segment is divided into four cases. The proposed relationship between $I_c$values and the approximate eutectic compositions are given in Table I and illustrated graphically in Fig. 1. Further explanation for the four cases has been provided below.

To reiterate, phase diagrams described by Figs. 1 and 2 are observed when there is no solid-state interaction, and the liquid state interactions between the two unlike components is stronger than that between like components. Stronger liquid-phase interactions between the unlike components gives greater rates of melting point depression and reduces the miscibility temperature at any w_p. In other words, stronger liquid phase interactions move the eutectic composition closer to the $w_p = 0.5$ line. Using equations (3) and (4), the I_c value at $w_p = 0.5$ can be rewritten as:

$$I_c = 0.5\left(1 + \frac{T_{mix}^{0.5} - T_p^f}{T_d^f - T_{mix}^{0.5}}\right) \tag{5}$$

where $T_{mix}^{0.5}$ is the melting temperature of the binary mixture at $w_p = 0.5$.

Case 1: If $(T_{mix}^{0.5} - T_p^f) < 0$, then I_c is a positive integer less than 0.5. In this case, the value of the index ranges from 0 to 0.5 or $I_c \approx 0$. The eutectic composition lies close to the $w_p = 0.5$ line and the liquidus line is described by curve (i) in Fig. 2.

Case 2: If $(T_{mix}^{0.5} - T_p^f) \cong 0$ then the eutectic composition moves away from the $w_p = 0.5$ line. Provided that there is

Table I. The Proposed Relationship between I_c and PEG-Drug Eutectic Composition

I_c value	w_p at the Eutectic Point	Percent (w/w) Drug in PEG at the Eutectic Point
$0 \leq I_c < 0.5$	$0.5 \leq w_p < 0.67$	~35
$0.5 \leq I_c < 1.5$	$0.67 \leq w_p < 0.82$	~25
$1.5 \leq I_c < 2.5$	$0.82 \leq w_p < 1$	~15
$2.5 < I_c$	Monotectic	Monotectic

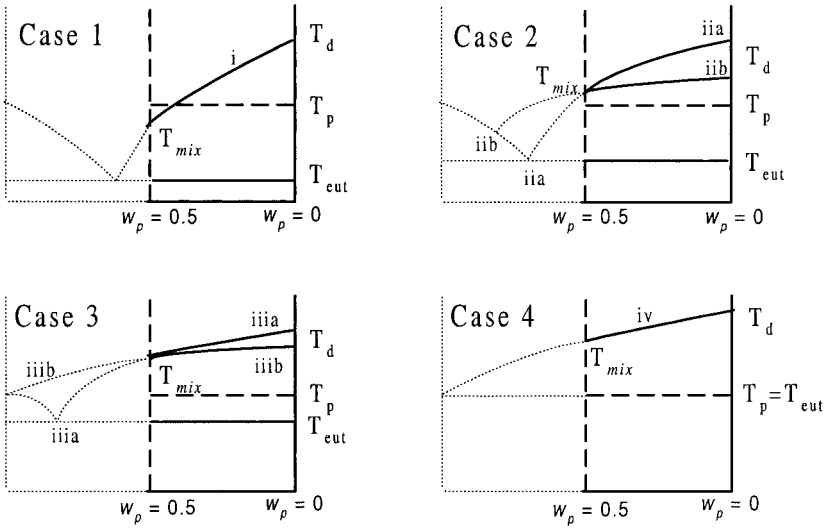

Fig. 2. The equations described in the text apply to the part of the phase diagram where $0.5 \leq w_p < 0$. Each integer value of I_c can be explained by the four cases. See text for details.

significant melting point depression caused by the polymer (i.e.$T^{0.5}_{mix} \neq T^f_d$) then $I_c \approx 1$ and the liquidus line follows curve (iia) in Fig. 2. Here the eutectic point lies around the midpoint of the line described by the segment $0.5 \leq w_p \leq 1$. On the other hand if the liquid phase interactions are weak then the denominator in equation (4) is small such that $T^{0.5}_{mix} \cong T^f_d$ in equation (5) then I_c increases from 1. When the integer value of I_c is 2 the liquidus line moves further away and follows curve (iib). However, at $(T^{0.5}_{mix} - T^f_p) \cong 0$ and $T^{0.5}_{mix} \cong T^f_d$ the system cannot be monotectic (14) because that would imply liquid phase immiscibility. Therefore $I_c > 2$ is not permissible for this case.

Case 3: If $(T^{0.5}_{mix} - T^f_p) \cong T^f_p$, then the eutectic composition moves even further away from the $w_p = 0.5$ line, and I_c becomes larger than 1. Again provided that $T^{0.5}_{mix} \neq T^f_d$ then $I_c \cong 2$, and the liquidus line follows curve (iiia). If the liquid phase interaction between the two unlike components is weak, then I_c is much larger than 2, and the system becomes monotectic and curve (iiib) represents the phase diagram.

Case 4: Anytime $(T^{0.5}_{mix} - T^f_p) >> T^f_p$, $I_c \geq 3$ and the system is monotectic.

The empirical rules described above hold only if the assumptions listed in the paragraph preceding equation (5) are not grossly violated. As the terms in equation (4) are easily accessible, this equation and not equation (5) will be used to calculate the index.

EXPERIMENTAL SECTION

Materials

Ibuprofen (Sigma Chemical, St. Loius, Missouri), naproxen (Sigma Chemical), griseofulvin (Sigma Chemical), fenofibrate (Sigma Chemical), ritonavir (Specialities Products Division, Abbott Laboratories), PEG 8000 (Carbowax, Union Carbide, Danbury, Connecticut), ethanol (McCormick Distilling Company, Weston, Missouri) and acetonitrile (EM Science, Gibbstown, New Jersey) were used in this study.

Solid Dispersion Preparation

Solid dispersions were prepared by fusion or fusion evaporation techniques (1,4). All other samples except ritonavir were aged at room temperature for a week. Ritonavir was annealed at 50ºC/75% RH for 24 h and then at 50ºC for an additional 24h. The samples were then ground, sifted, and particles between 149 and 250 μm were used for the study.

Differential Scanning Calorimetry (DSC)

The phase diagrams were constructed using DSC (DSC 30 using STAR^e software, Mettler Instrument, Hightstown, New Jersey). The samples (*ca.* 8 mg) were sealed in 40 μL aluminum pans (Mettler Instrument) with a single hole punched in the lid. An identical empty pan was used as a reference. The samples were scanned at 2.5°C/min with a 50 mL/min nitrogen purge. The temperature, time constant and the heat flow calibrations were performed using indium and zinc.

Hot Stage Microscopy (HSM)

Thermal transitions around the eutectic point were confirmed using a polarizing microscope (Optiphot, Nikon, Melville, New Jersey) equipped with a hot stage (FP82HT stage and FP90 processor, Mettler Instruments, Hightstown, New Jersey). The hot stage was calibrated using benzophenone and benzoic acid. The samples were placed on an appropriate microscope slide and heated at 2°C/minute.

Powder X-Ray Diffraction (PXRD)

The diffractometer (XDS 2000, Scintag, Sunnyvale, California) consisted of a 2 kW generator (voltage 45 kV and current 40 mA) with Cu anode tube and either a liquid nitrogen cooled Ge detector (GLP-10195/07-S, EG&G ORTEC, Oak Ridge, Tennessee), or a peltier cooled Ge detector (4-S-TE, Scintag). The samples were placed on a quartz plate and scanned at a rate of 10° 2θ per min. The data were analyzed using DMSNT Data Analysis version 1.37 (Scintag).

RESULTS AND DISCUSSION

Phase Diagrams

The phase diagrams for fenofibrate and ibuprofen in Fig. 3 were constructed using the fusion technique. For naproxen

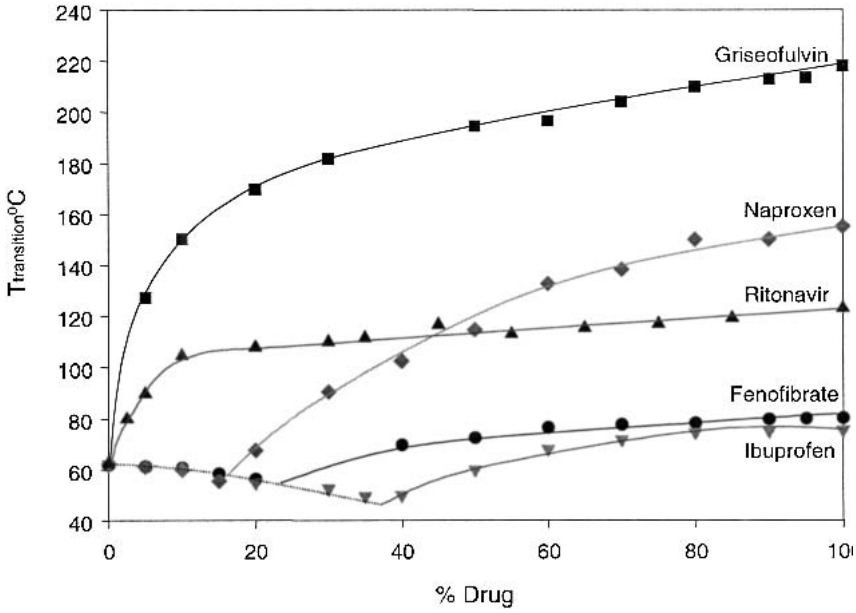

Fig. 3. PEG 8000-drug phase diagrams. HSM and DSC were used to generate the phase diagram.

fusion the evaporation method was used because naproxen was found to form a racemic mixture at elevated temperatures. Because of the limited solubility of ritonavir and griseofulvin in molten PEG, these phase diagrams were also prepared by the fusion evaporation method. For each of the mixtures analyzed in Fig. 3 the presence of crystalline drug at room temperature was confirmed by PXRD. Based on DSC, HSM and PXRD results it was concluded that all five compounds formed eutectic/monotectic mixtures with PEG 8000. Table II provides a list of drugs, the type of PEG, the eutectic composition, and the literature reference. Except for ibuprofen and ritonavir, all other compounds have been previously used to prepare solid dispersions with PEG.

The utility of a eutectic/monotectic formulation depends on the nature of the phase diagram and the dose. Griseofulvin, which has a daily dose of 125–150mg, forms a monotectic system with PEG and is marketed as a dispersion containing 5%(w/w) drug in PEG. Ritonavir, which also forms a monotectic phase diagram with PEG, has a daily dose of 1200mg and thus a crystalline solid dispersion in PEG is not practical.

Table II. The Eutectic Compositions for Various PEG-Drug Systems

Drug	PEG	Percent (w/w) Drug in PEG at the Eutectic Point	Reference
Ibuprofen	8000	~35	This work
Fenofibrate	8000	~25	8,9
Flurbiprofen	6000	~25	23
	4000	~25	23
Naproxen	4000	Monotectic	12
	6000	Monotectic	12
	8000	~15	This work
	20000	Monotectic	12
Indomethacin	6000	~15	10
Temazepam	6000	~15	25
Griseofulvin	2000	Monotectic	3
	8000	Monotectic	This work
Ritonavir	8000	Monotectic	This work

The selection of ibuprofen was based on the structural similarity of ibuprofen and naproxen. In addition they belong to the same class of compounds, i.e., they are NSAIDs. The phase diagram of ibuprofen (Fig. 3) shows that the eutectic composition is ~35% (w/w) drug in PEG. Naproxen has been reported to be a monotectic system (12) however, Fig. 3 shows that it is in fact a eutectic system with ~15% (w/w) naproxen at the eutectic point. Although structurally similar, ibuprofen and naproxen have very different phase diagrams.

There are several possible reasons for the difference between the previously reported naproxen phase diagram (12) and the one reported in this work. First during the preparation of a phase diagram it is usually necessary to refine the phase boundaries through a process of iteration. In other words, a larger number of samples around the anticipated eutectic composition need to be tested to accurately define the eutectic point. Also during thermal analysis the temperature gradient through the sample must be minimized by controlling sample particle size distribution, using a slow heating rate, etc. In this work the PEG-naproxen samples were carefully prepared to prevent naproxen from racemizing, compositions between 10–20%(w/w) naproxen were tested, sample particle size was carefully controlled, and a slow heating rate was used to generate the phase diagram. This description for constructing drug-PEG phase diagrams exemplifies how tedious it is to obtain an accurate phase diagram.

A survey of the literature shows that the PEG-drug phase diagrams are not sensitive to the PEG molecular weight (12,23). For example griseofulvin, forms a monotectic system with both PEG 2000 (3) and PEG 8000 (Fig. 3). Griseofulvin is not unique (*cf.* Table II), therefore attention was directed to the physicochemical properties of the drugs summarized in Table III. On the basis of molecular weight, seven out of eight compounds are similar. As a first approximation, T_d^f may be taken to represent the crystal energy of a compound, however, the true lattice energy is represented by ΔH_d^f. The entropy of fusion (ΔS_d^f) represents the crystal packing efficiency (24). Although the melting point ranged over 150°C and ΔH_d^f

Table III. The Molecular Weight, Experimental and Predicted T_d^f (K) and ΔH_d^f (KJ/mole) values, the Calculated ΔS_d^f (J/mole-K) and I_c Values, and Predicted and True Eutectic Compositions for Drug-PEG Systems

Drug	Molecular weight	T_d^f	ΔH_d^f	ΔS_d^f	Predicted T_d^f	Predicted ΔH_d^f	I_c	Eutectic point	Predicted point
Ibuprofen	206	348	25	72	351	20	0	~35%	~35%
Fenofibrate	361	353	33	94	355	35	1	~25%	~25%
Flurbiprofen	244	386	26	67	ND	ND	1	~25%	~25%
Naproxen	230	429	28	65	428	22	2	~15%	~15%
Indomethacin	358	421	31	74	ND	ND	2	~15%	~15%
Temazepam	301	427	36	84	ND	ND	2	~15%	~15%
Griseofulvin	352	493	41	83	491	41	3	~0%	~0%
Ritonavir	720	397	65	164	395	64	3	~0%	~0%

ND is not determined.

varied from 25–65 kJ/mole, there is no obvious correlation between the thermal properties and the PEG-drug eutectic composition. However, ibuprofen with the lowest T_d^f, and the smallest ΔH_d^f, forms a eutectic mixture with a much higher drug load at the eutectic point than naproxen, which has a higher T_d^f, and a larger ΔH_d^f. Therefore, it appeared that the crystal energy of the drug played an important role in defining the eutectic composition for the PEG-drug systems.

Modified van't Hoff Plots and I_c

Since the slope and intercept of equation (3) are functions of T_d^f and ΔH_d^f, the utility of this equation for describing PEG-drug systems was evaluated. Applying equation (3) to construct the modified van't Hoff plots (Fig. 4) is far more difficult than generating the phase diagrams, therefore only five compounds were used to illustrate that this equation can be used to describe the melting point depression of the drug caused by the carrier. The five compounds were ibuprofen which has a eutectic composition of ~35% (w/w), fenofibrate with ~25% (w/w) (8,9), naproxen with ~15% (w/w), griseofulvin ~0% (w/w) (3) and ritonavir ~0% (w/w) in PEG. In all five cases, the melting point depression caused by PEG followed the modified van't Hoff relationship and linearly decreased as the weight fraction of PEG is increased (Fig. 4). The intercept of the fitted line is the predicted T_d^f, and ΔH_d^f can be calculated from the slope. The predicted and experimental T_d^f and ΔH_d^f values in Table III are in agreement. The liquidus line in a binary phase diagram represents the solubility of the drug in the carrier as a function of temperature, or alternatively the melting point depression of the drug caused by the carrier (15) therefore, the lines in Fig. 4 are not sensitive to the solid state properties of the polymer. Differences between experimental and predicted ΔH_d^f values are less than 10% for fenofibrate, griseofulvin and ritonavir. Ibuprofen and naproxen show a considerable difference in the experimental and predicted ΔH_d^f. For ibuprofen this difference is attributed to the lack of proper resolution of the eutectic and ibuprofen melting endotherms. In the case of naproxen, racemization of the compound at elevated temperatures precluded preparation by the fusion technique. The solvent evaporation-fusion technique allowed a lower preparation temperature (70°C) however, some racemization is possible and this could have led to the error in the predicted

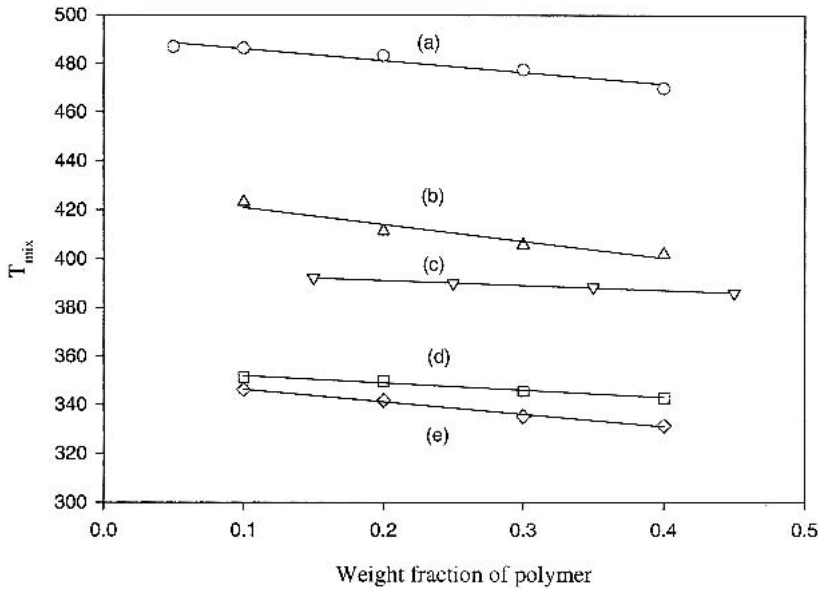

Fig. 4. The melting point depression caused by PEG: (a)Griseofulvin: y = -48.5x + 491, R^2 = 0.95, (b) Naproxen: y = -68.7x + 428, R^2 = 0.93, (c) Fenofibrate: y = -29.4x + 355, R^2 = 0.98 (d) Ritonavir: y = -20.2x + 395, R^2 = 1.0 and (e) Ibuprofen: y = -50.5x + 351, R^2 = 0.99.

$\Delta H^f_{naproxen}$. Thermodynamic quantities such as T^f_d and ΔH^f_d are easily measured and the purpose of Fig. 4 was not to predict T^f_d and ΔH^f_d but to demonstrate that the melting point depression rate for drug-PEG systems could be described by equation (3).

From the knowledge of the melting point depression rate and the difference between the melting points of the two components, the eutectic composition may be predicted using equation (4). For ibuprofen, fenofibrate, naproxen, griseofulvin, ritonavir, flurbiprofen, temazepam, and indomethacin, the index was calculated to predict the approximate eutectic composition (Fig. 5). The predicted eutectic compositions and the true compositions were found to be in agreement (*cf.* Table III).

Comparing the phase diagrams of ritonavir with naproxen shows the importance of drug melting point depression rate. Although $(T^{0.5}_{mix}\text{-}T_p)_{ritonavir}$ is similar to $(T^{0.5}_{mix}\text{-}T_p)_{naproxen}$ ritonavir forms a monotectic system while naproxen forms a 15% eutectic mixture.

Thus the feasibility of developing eutectic solid dispersions can be evaluated from simple DSC measurements of T^f_d, ΔH^f_d and T^f_p. The index is only a screening tool because it does not consider difficulties such as racemization, phase transition, decomposition, incompatibility, slow dissolution in molten PEG etc. that may arise during the preparation of the eutectic dispersion. For example Lloyd *et al.* (13) facilitated the preparation of paracetamol in PEG 4000 dispersions by increasing the dissolution rate of acetaminophen in PEG by using smaller paracetamol particles, elevated temperatures, and longer holding time. Therefore, it is imperative to construct and characterize the phase diagram prior to developing a eutectic/monotectic formulation.

Other Crystalline Polymers

Equations (3) and (4) assume that the two components are immiscible in the solid state. It is also assumed that in solution the polymer is a minor component on a weight fraction scale, and the melting point depression caused by the minor component is small. As long as these assumptions are not grossly violated, and because the liquid phase interactions determine the nature of these phase diagrams, this PEG-drug analysis may be applied to other crystalline polymers. For example the poly-ε-caprolactone-flurbiprofen system was established to be a simple eutectic mixture with a composition of 25% (w/w) drug in the polymer at the eutectic point (23). The I_c of 1 for this system is consistent with the experimentally determined eutectic point. Griseofulvin and polyethylene stearate form a monotectic system (3) and the calculated I_c for this system is 3. Primarily crystalline polymers (which may be a homo-polymer, a di-block copolymer or a tri-block copolymer) do not accommodate appreciable amounts of guest molecules in the lattice to form solid solutions. Therefore, crystalline polymer-drug systems result in simple eutectic mixtures allowing equation (4) to be used to predict the eutectic composition.

CONCLUSIONS

This investigation demonstrated that for simple eutectic mixtures, the crystal energy of the drug plays a dominant role in determining the strength of PEG-drug interactions in the liquid phase and the eutectic composition. A modified van't Hoff equation was used to linearize the liquidus line. The slope of this line is a function of T^f_d and ΔH^f_d and describes the rate at which the eutectic point is approached. A dimensionless index I_c was defined to predict the eutectic composition and assist in evaluating the feasibility of developing eutectic mixtures without generating phase diagrams.

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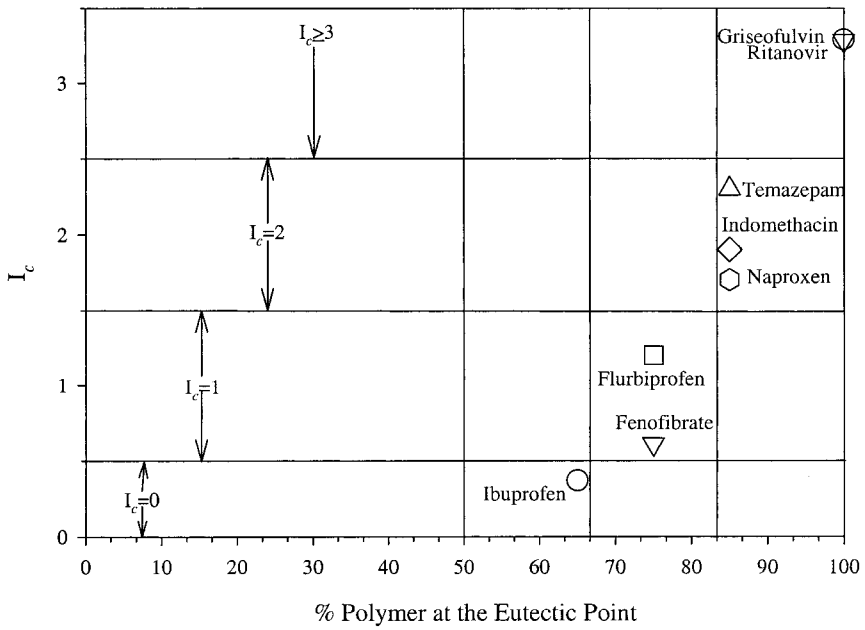

Fig. 5. $I_c$values calculated using equation (4) vs. observed eutectic composition.

REFERENCES

1. W. L. Chiou and S. Riegelman. Pharmaceutical Applications of Solid Dispersion Systems. *J. Pharm. Sci.* **60**:1281–1302 (1971).
2. K. Sekiguchi and N. Obi. Studies on Absorption of Eutectic Mixture. I. A comparison of the Behavior of Eutectic Mixture of Sulfathiazole and that of Ordinary Sulfathiazole in Man. *Chem. Pharm. Bull.* **9**:866–872 (1961).
3. R. Kaur, D. J. W. Grant, and T. Eaves. Comparison of Polyethylene Glycol and Polyethylene Stearate as Excipients for Solid Dispersion Systems of Griseofulvin and Tolbutamide II: Dissolution and Solubility Studies. *J. Pharm. Sci.* **69**:1321–1326 (1980).
4. M. J. Alonso, P. Maincent, T. Gracia-Arias, and J. L. Vila-Jato. A comparative biopharmaceutical study of fresh and aging tolbutamide-polyethyleneglycols solid dispersions. *Int. J. Pharm.* **42**:27–33 (1988).
5. E. Saers and C. Nystrom. Physicochemical aspects of drug release. VI. Drug dissolution rate from solid particulate dispersions and the importance of carrier and drug particle properties. *Int. J. Pharm.* **47**:51–66 (1988).
6. D. Law, S. L. Krill, E. A. Schmitt, J. J. Fort, Y. Qiu, W. Wang, and W. R. Porter. Physicochemical Considerations in the Preparation of Amorphous Ritonavir/PEG 8000 Solid Dispersions. *J. Pharm. Sci.* **90**:1015–1025 (2001).
7. D. H. Doshi, W. R. Ravis, and G. V. Betageri. Carbamazepine and polyethylene glycol solid dispersions: preparation, in vitro dissolution, and characterization. *Drug Dev. Ind. Pharm.* **23**: 1167–1176 (1997).
8. D. Law, E. A. Schmitt, Y. Qiu, W. Wang, J. J. Fort, and S. L. Krill. Amorphous and Eutectic Solid Dispersion Systems of Model Lipophilic Compound, Fenofibrate. *AAPS PharmSci*. **1**:S–525 (1999).
9. D. Law, S. L. Krill, E. A. Schmitt, and J. J. Fort. *Novel Formulation Comprising Lipid Regulating Agents. PCT Int. Appl. WO* **0072829**:A1 (2000).
10. J. L. Ford and M. J. H. Rubeinstein. Phase Equlibria and Dissolution Rates of Indomethacin-Polyethylene Glycol 6000 Solid Dispersions. *Pharm. Acta Helv.* **53**:93–98 (1978).
11. E. S. Saers and D. Q. M. Craig. An investigation into the mechanism of dissolution of alkyl *p*-aminobenzoates from polyethylene glycol solid dispersions. *Int. J. Pharm.* **83**:211–219 (1992).
12. P. Mura, A. Manderioli, G. Bramanti, and L. Ceccarelli. Properties of Solid Dispersions of Naproxen in Various Polyethylene Glycols. *Drug Dev. Ind. Pharm.* **22**:909–916 (1996).
13. G. R. Lloyd, D. Q. M. Craig, and A. Smith. An Investigation into the paracetamol solid dispersions in PEG 4000 using hot stage differential interference contrast microscopy. *Int. J.Pharm.* **158**: 39–46 (1997).
14. M. E. Vasil'ev. Classification of the Phase Diagrams of Binary Metallic Systems According to Atomic Interaction Forces. *Russ. J. Phys. Chem.* **38**:473–476 (1964).
15. I. N. Levine. Multicomponent Phase Equilibria. *Physical Chemistry.* McGraw-Hill Book: New York, 1988 pp. 316–366.
16. D. Patterson, Y. B. Tewari, and H. P. Schreiber. Application of Gas-Liquid Chromatography to the Thermodynamics of Polymer Solutions. *Macromolecules* **4**:356–359 (1971).
17. F. Firouzi, H. Modarress, and G. A. Mansoori. Predicting Liquid-Liquid Transitions in Polymer Solutions Using the GCLF Equation of State. *Eur. Polym. J.* **34**:1489–1498 (1998).
18. I. Jasper and G. Bogdanic. The Influence of the Polymer Molar Mass on the Prediction of Solvent Activities in Polymer Solutions. *Polimeri* **16**:253–259 (1995).
19. M. R. Riazi and A. R. Khan. A Thermodynamic Model for Gas Adsorption Isotherms. *J. Colloid. Interface Sci.* **210**:309–319 (1999).
20. R. D. Newman and J. M. Prausnitz. Thermodynamics of Concentrated Polymer Solutions Containing Polyethylene, Polyisobutylene, and Copolymer of Ethylene with Vinyl Acetate and Propylene. *AICHE J.* **19**:704–710 (1973).
21. P. S. Savchenko. The Nature of Eutectics. *Russ. J. Inorg. Chem* **4**:186–189 (1959).
22. V. V. Podolinsky and Yu-N. Taran. Influence of Adsorption on Structure Formation in Eutectic Systems. *J. Cryst. Growth* **52**:82–87 (1981).
23. F. Lacoulonche, A. Chauvet, J. Masse, M. A. Egea, and M. L. Gracia. An investigation of FB Interactions with Poly(ethylene) glycol 6000, Poly(ethylene) glycol 4000 and Poly-ε-caprolactone by Thermoanalytical and Spectroscopic Methods and Modeling. *J. Pharm. Sci.* **87**:543–551 (1998).
24. D. J. W. Grant. Theory and Origin of Polymorphism. In Brittain, H.G (ed.) *Polymorphism in Pharmaceutical Solids.* Marcel Decker: New York, 1998 pp 1–34.
25. G. Van den Mooter, P. Augustijns, N. Blaton, and R. Kinget. Physicochemical characterization of solid dispersions of temazepam with polyethylene glycol 6000 and PVP K30. *Int. J. Pharm.* **164**:67–80 (1998).