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EVALUATION OF AN INDEX BASED ON VAN'T HOFF EQUATION TO PREDICT PEG–DRUG EUTECTIC COMPOSITION

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Abstract

Five poorly soluble drugs namely hydrochlorothiazide, menadione, propylthiouracil, quinine sulfate and sulfamerazine were used to evaluate the ability of an index (I_c) based on the van't Hoff equation to predict the eutectic composition at a higher heating rate than previously published. The term I_c is a dimensionless index which has been defined in the literature and is used to predict eutectic composition. This current work uses this study to determine if the correlation holds true at the higher heating rate of 10°C min^{-1}. The maximum deviation was observed for quinine sulfate, for which the predicted eutectic composition was 10% lower than what was observed with the DSC. It can be concluded that the Index developed here has a good correlation with the experimentally determined eutectic composition.

Keywords: eutectic, PEG, phase diagrams, van't Hoff equation

Introduction

Due to the fact that eutectics have definite advantages over solid dispersion systems, it is important to consider them as a primary means of enhancing the bioavailability of poorly soluble drugs [1]. Eutectic formulations are relatively simple to make, do not tend to segregate and do not suffer from any stability issues as in the case of solid dispersions where the amorphous drug tends to revert back to the more stable crystalline form [2].

Eutectics can be formulated in a variety of dosage forms such as tablets, capsules, creams and suppositories [3]. Reduction in particle size, polymorphism and formation of amorphous or metastable state are some of the mechanisms for the enhancement of the rate and extent of dissolution of eutectics [4–7]. Eutectics are also used to enhance transdermal permeation of drugs intended for local application. These formulations make use of the fact that lowering of the melting point of a drug results in enhanced transdermal permeation of topical drugs [8]. Eutectics have found limited application in pharmaceutics despite having such advantages. One of the

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reasons for this is that the eutectic composition might not be suitable for making the formulation. In other words, the carrier might be present to such an extent that the total mass of the formulation is too large to administer in the form of a tablet or a capsule. The other reason for the unpopularity of the eutectic systems is the fact that constructing a phase diagram is a laborious and time consuming process.

On the other hand, clompexation is a popular method which is employed due to the ease of preparation and multifold solubility enhancement which is usually observed. Although these agents are found to be effective but they are not devoid of toxicity. Cyclodextrins and their derivatives are most frequently used complexing agents and they have proven their utility time and again [9, 10].

The modified van't Hoff equation in which the mole fraction of the minor component, x_p has been replaced with w_p, which is the mass fraction, has been used to describe the initial melting point depression of the drug caused by the carrier. It's mathematical form is as follows:

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

where T_d^f is the melting point of the major component, w_p is the mass 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 w_p.

Based on the above equation, Law *et al.* [11] proposed a dimensionless index (I_c), which is the ratio of the difference in melting temperatures of the polymer and drug and the slope of the modified van't Hoff equation:

$$I_c = \frac{T_d^f - T_p^f}{R\left(T_d^f\right)^2 / \Delta H_d^f} \quad (2)$$

Table 1 shows the relationship between (I_c) and PEG–Drug eutectic composition as proposed by Law *et al*. These studies were performed at a heating rate of 2.5°C min^{-1} [11].

Table 1 The proposed relationship between I_c and PEG–Drug eutectic composition [11]

I_c value	w_p at the eutectic point	Percent (*w*/*w*) drug in PEG at the eutectic point
$0.0 \le I_c < 0.5$	$0.50 \le w_p < 0.67$	~35
$0.5 \le I_c < 1.5$	$0.67 \le w_p < 0.82$	~25
$1.5 \le I_c < 2.5$	$0.82 \le w_p < 1.00$	~15
2.5<Ic	Monotectic	Monotectic

Experimental

Materials

Hydrochlorothiazide, sulfamerazine, propylthiouracil and menadione were obtained from Sigma Chemical Co. and quinine sulfate was obtained from Merck & Co., Inc. The 200 proof ethyl alcohol was obtained from Pharmco Products Inc.

Equipment

The MDSC 2910 (TA Instruments) was used with Thermal Advantage® and Universal Analysis 2000® software for the analysis of the scans. The DSC was calibrated using the melting points of indium (156.6±0.2°C) and zinc (419.5±0.3°C) standards. Samples were weighed using a Mettler MT 5 microbalance and open 100 μL aluminum pans were used for all the studies. A heating rate of 10°C min^{-1} was applied to all the binary mixtures. A stream of dry nitrogen was purged through the DSC cell at a rate of 50 mL min^{-1}. The onset temperatures were used to plot the phase diagrams in all cases. Ice was used to cool the DSC cell.

Procedure

The solvent evaporation technique was used in preparing all the mixtures as it ensured homogeneous mixing. The solvent used in this case was ethanol, which was removed by heating on the hot plate on low heat. The homogeneous mixtures in small beakers were then vacuum dried at room temperature for 2 h to ensure complete removal of the solvent. Samples were then powdered in a mortar and pestle and passed through a U.S. standard sieve # 60 (Fisher Scientific Company). They were then placed into 100 μL aluminum pans and were scanned from 25°C up to the melting temperature of the drug that depended on the type of the mixture used. A heating rate of 10°C min^{-1} was used for all the binary mixtures.

Results and discussion

Phase Diagrams

All the binary mixtures were prepared by the solvent evaporation method since it ensured homogeneous mixing. The mixtures were scanned at a heating rate of 10°C min^{-1}. Figure 1 shows the overlay of the DSC scans for Menadione and PEG 4000 mixtures as a representative of the DSC study.

Figure 2 through 6 shows the phase diagrams of the eutectic systems constructed on the basis of the DSC results. It can be seen that there is a sudden change in the melting point when the mixture approaches the eutectic point. The change is sharper as the melting point of the drug increases.

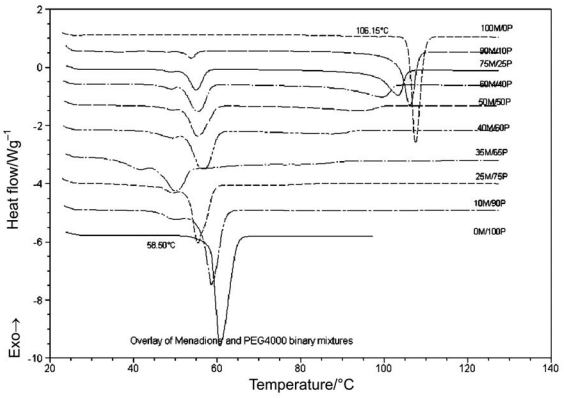

Fig. 1 Overlay of the DSC scans of menadione and PEG 4000 binary mixtures

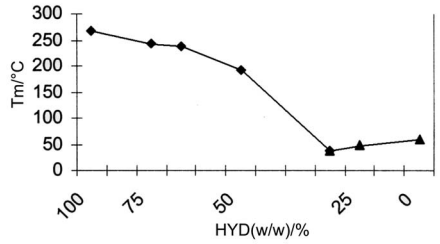

Fig. 2 The phase diagram for hydrochlorothiazide and PEG 4000

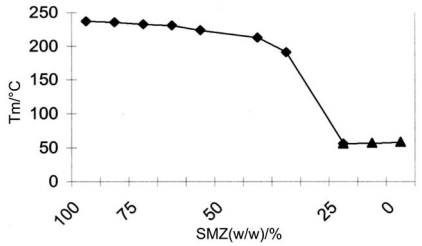

Fig. 3 The phase diagram for sulfamerazine and PEG 4000

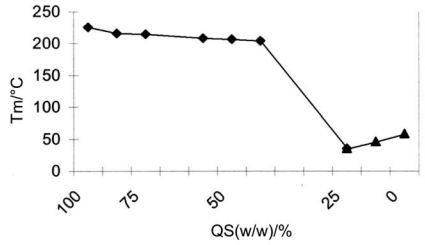

Fig. 4 The phase diagram for quinine sulfate and PEG 4000

Table 2 The equations and the *R*-square values of the five-line plots from the van't Hoff equation

Drug	M. V./ g mol^{-1}	T_d^r/ K	ΔH_d^r/ kJ mol^{-1}	Index/ I_c	%Drug *w*/*w*/ OEP	PEP	Line equation	R^2
HYD	297.73	541.8	31.14	0.9759	~30	~25	*Y*= –215.03X+541.95	0.9996
MEN	172.17	379.2	19.02	0.2688	~35	~35	*Y*= –177.32X+383.13	0.9822
PTU	170.20	492.0	22.00	0.6390	~25	~25	*Y*= –231.00X+499.03	0.9697
QS	782.97	498.6	16.15	0.6214	~35	~25	*Y*= –268.25X+497.34	0.9974
SMZ	264.30	509.9	37.56	1.2440	~25	~25	*Y*= –143.10X+514.10	0.9294

HYD = Hydrochlorothiazide; MEN = Menadione; PTU = Propylthiouracil; QS = Quinine sulfate; SMZ = Sulfamerazine; M.W. = Molecular Mass; OEP = Observed Eutectic Point (% drug *w*/*w*); PEP = Predicted Eutectic Point (% drug *w*/*w*); Line Equation see Fig. 6.

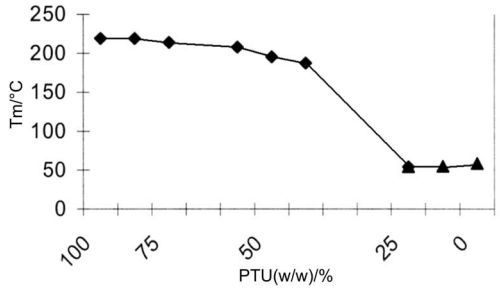

Fig. 5 The phase diagram for propylthiouracil and PEG 4000

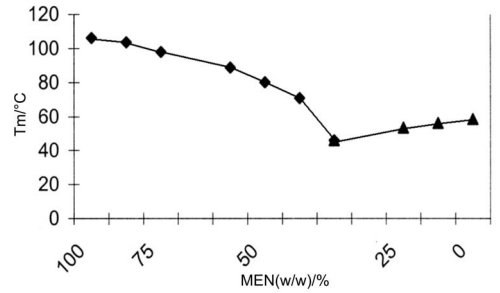

Fig. 6 The phase diagram for menadione and PEG 4000

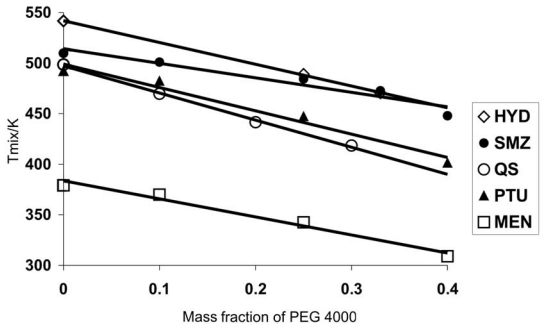

Fig. 7 The melting point depression of drugs caused by PEG 4000

Modified van't Hoff plots and Ic

All of the studied drugs were found to form eutectics with PEG 4000, which is characterized by the lowest melting single endotherm. Figure 7 shows the line plots of the modified van't Hoff equation for the five drugs. This linear relationship is valid only when the polymer is the minor component of the binary mixture although polymer is the major component at eutectic composition. Since most drugs do not effect the polymer melting point depression to a great extent, an analogous equation where drug is the minor component might not be useful in predicting eutectic point [9]. It can also be seen that the linearity of these line plots is also quite good. Table 2 illus-

trates the observed and predicted eutectic point and important parameters related to the line plots.

Conclusion

It was observed that the 'Higher heating rate index' (I_c) has a good correlation with the results obtained from the DSC. It has the ability to predict the eutectic composition even at 10°C min^{-1}. Except for quinine sulfate, all the predictions were quite accurate. For quinine sulfate, the calculated point was 10% lower than that found by the phase diagram although the linearity of the line plot was quite good. This discrepancy can be explained by the fact that the value of I_c for quinine sulfate was found to be 0.6214, which is quite close to 0.5, the upper limit for the range of value of I_c that predicts the eutectic point at 35% of the drug concentration. This further demands more investigation in this field in order to narrow down these ranges to make more accurate predictions. This study shows that the DSC throughput is now enhanced by four with continuing good prediction. In summary, the index can be used successfully to forecast the eutectic point and can be used as a preformulation screening tool for the feasibility of developing a formulation without actually constructing the phase diagrams.

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