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Release of Ibuprofen from Polyethylene glycol solid dispersions:- Equilibrium solubility approach

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Abstract

This work is an attempt to enhance the release of Ibuprofen by improving its aqueous solubility. This was done by dispersing the drug in a water soluble carrier such as polyethylene glycol (PEG). The solubility was found to depend on various factors such as method of preparation, carrier weight fraction and molecular weight and the pH of the medium. It was found that dispersions prepared by the fusion method gave higher solubilities than those prepared

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by the solvent technique. The solubility was found to vary with carrier molecular weight and its weight fraction. Decreasing the PEG molecular weight resulted in increased solubility. A polymer to drug ratio of 1:1 was found to give the highest solubility. The solubility decreased as the polymer weight fraciton was increased beyond this value. The solubility of the solid dispersion was found to be pH dependent. A greater solubility was obtained at higher pHs than at lower ones. This was attributed to the weakly acidic nature of Ibuprofen. Calculation of the heat of solution of the various systems studied showed that the non dispersed drug had a higher heat of solution than the dispersed systems. This was thought to be the cause of the higher solubility of the dispersions as compared to the original drug.

Introduction

The preparation of fast relrease solide dispersions by fusion and solvent techniques has been used to enhance the dissolution properties (1-5) and bioavailiability (6-9) of poorly water soluble drugs. Polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG) are the most commonly used polymers for the perparation of such dispersions. PVP has been used to enhance the release of a number of drugs such as sulphathiazole (4), reserpine (6) and indomethacin (11). The dissolution of prednisolone,

methyletestosterone,digitoxin (7) and Dicumarol (12) have been enhanced by the use of PEG fusion dispersions.

Ibuprofen is a poorly water soluble drug and therefore its bioavailability would be dissolution rate limited. Hence an increase in dissolution rate would result in an improved bioavailability. The Noye's-Whitney equation (13) states that the dissolution rate of a drug is directly related to its equilibrium solubility. In this work an attempt is made to increase the aqueous solubility of Ibuprofen by dispersing it in an inert water soluble carrier such as PEG. The effect of the polymer weight fraction and polymer molecular weight on the solubility of the drug is studied. The work also includes the determination of the effect of the pH on the solubility as well as calculation of the heat of solution of the different solid dispersion systems and physical mixtures of the drug and the polymer.

Materials and Methods

Materials: Ibuprofen, chloroform,sodium hydroxide and hydrochloric acid were obtained from Sigma Chemical Company U.K. Anhydrous calcium sulphate was obtained from Aldrich Chemical Company USA. PEG 1500, 4000 and 6000 were obtained from BDH, U.K.

Methods: In the preparation of the dispersions by the solvent method (1), the required amounts of drug

and polymer were weighed, dissolved in the minimum volume of chloroform. The choloroform was evaporated over a warm water bath. Further drying was carried out under anhydrous calcium sulphate. All samples were examined within 24 hrs after preparation.

Dispersion systems by the fusion method (14) were prepared by mixing the required amount of drug and polymer on a watch glass. The mixture was then heated till it was completely melted. Continuous stirring during the melting procedure prevented separation of the constituents. The melt was then rapidly solidified. The solidified mass was then size reduced and the required samples for solubility studies were taken from the mixture.

Equilibrium solubility studies were performed by adding an excess of the drug (0.05g) or an amount of the solid dispersion which contains this quantity to 10 mls of water at the required pH placed in a 25 ml stoppered conical flasks. The flasks were then placed in a shaking wtater bath adjusted to the required temperature. The flasks were then shaken for 24 hrs (a time which was found to be sufficient to reach equilibrium). The contents of the flasks were then transferred to a syringe and rapidly filtered through 0.3 μm membrane filter unit (millipore U.K. Ltd. London). The filtrates were then assayed for their drug contents spectrophotometrically at 263 nm.

Each experiment was repeated at least three times and the average values were taken. Physical mixtures of the drug and the polymer were prepared by mixing the ingredients in a glass morter in a geometric dilution technique till the two powders were homogeneously distributed within each other and the required samples were then taken from the mixtures for solubility studies. A drug: PEG 6000 (1:3) prepared by the fusion method was, unless otherwise stated, used in all studies.

Results and Discussion

Fig. 1, shows the effect of the composition and technique of preparation of the solid dispersion on the equilibrium solubility of Ibuprofen. It is evident from the figure that both the solvent and the fusion techniques produced graphs of similar shapes. In both cases the solubility begins to increase as the polymer weight fraction is increased till it reaches a maximum value at polymer to drug ratio of 1:1. At polymer weight fraction greater than this ratio the solubility decreases. The figure also shows that greater solubilities were obtained for dispersion prepared by the fusion technique compared with those prepared by the solvent technique. This difference in solubilities could be due to the different

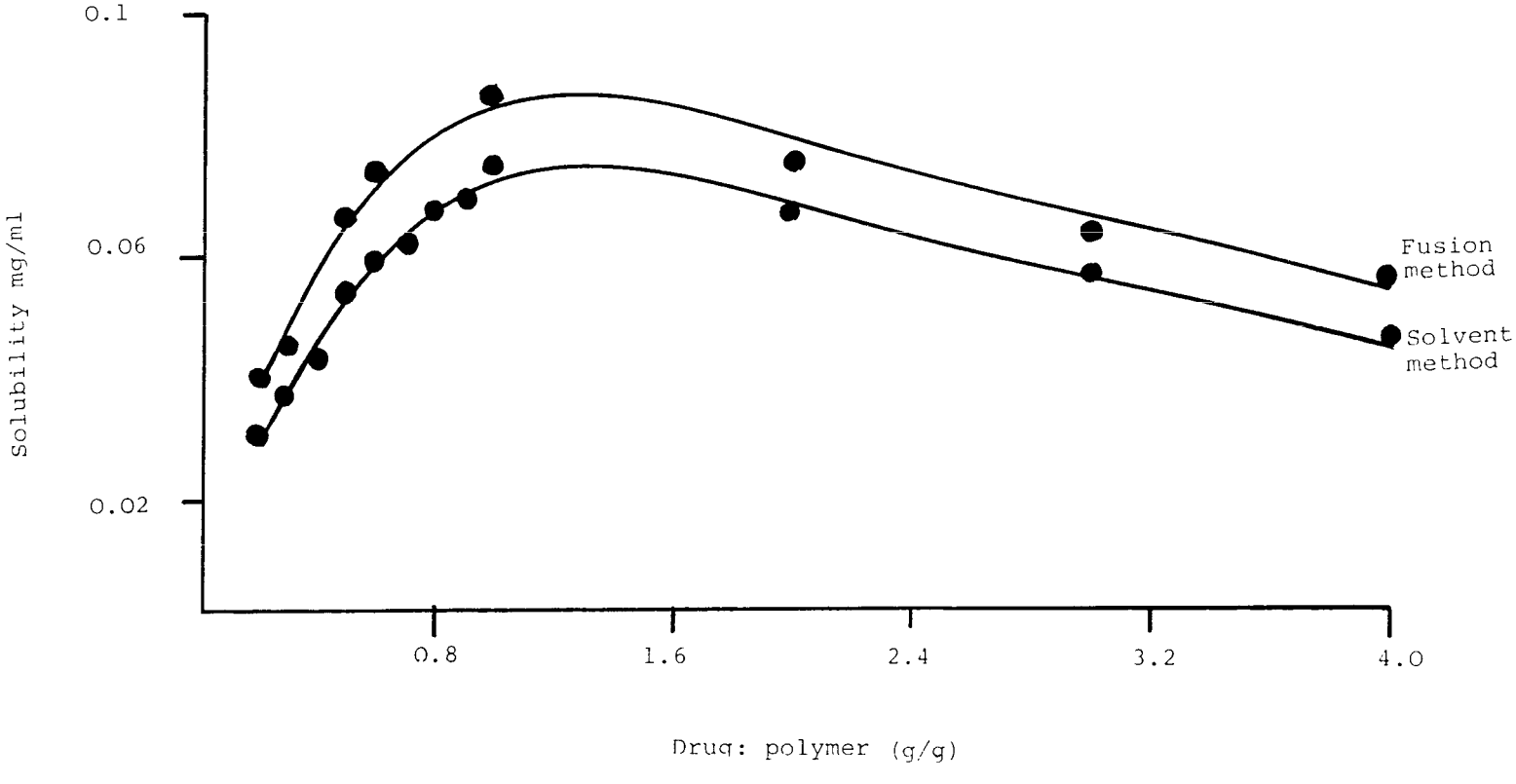

Figure 1.

The effect of PEG weight fractions on solubility of ibuprofen prepared by the fusion and solvent method.

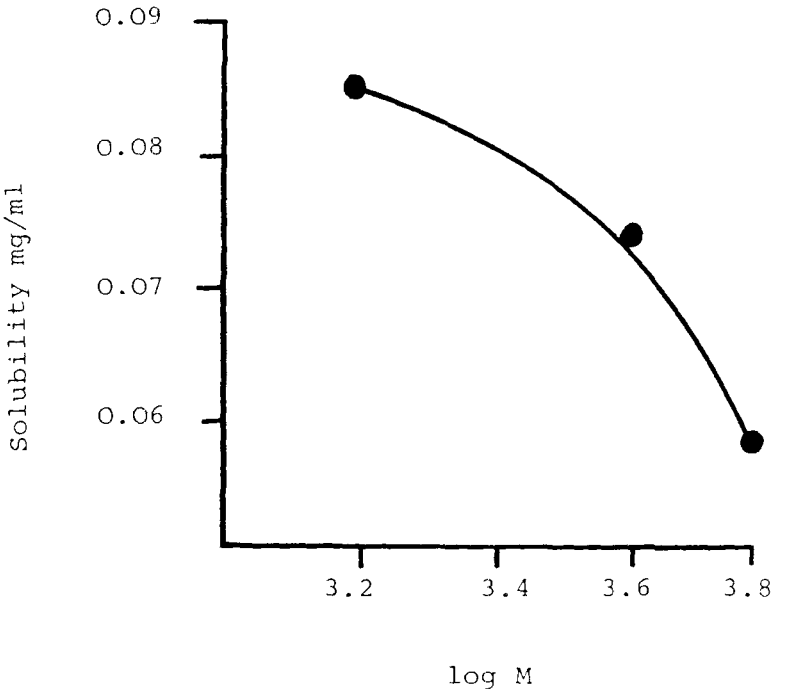

Figure 2.

The relationship between solubility and logarithm of PEG molecular weight (log M).

crystalline structures and hence energies of the dispersed systems obtained by these techniques (15,16).

The solubility of Ibuprofen from dispersions prepared with PEG of different molecular weight is shown in fig.2. It can be noted from the figure that the solubility of the drug increased with decreasing polymer molceular weight. Simlar findings have been reported for the release of hydroflumethiazide from PEG melt systems (17)

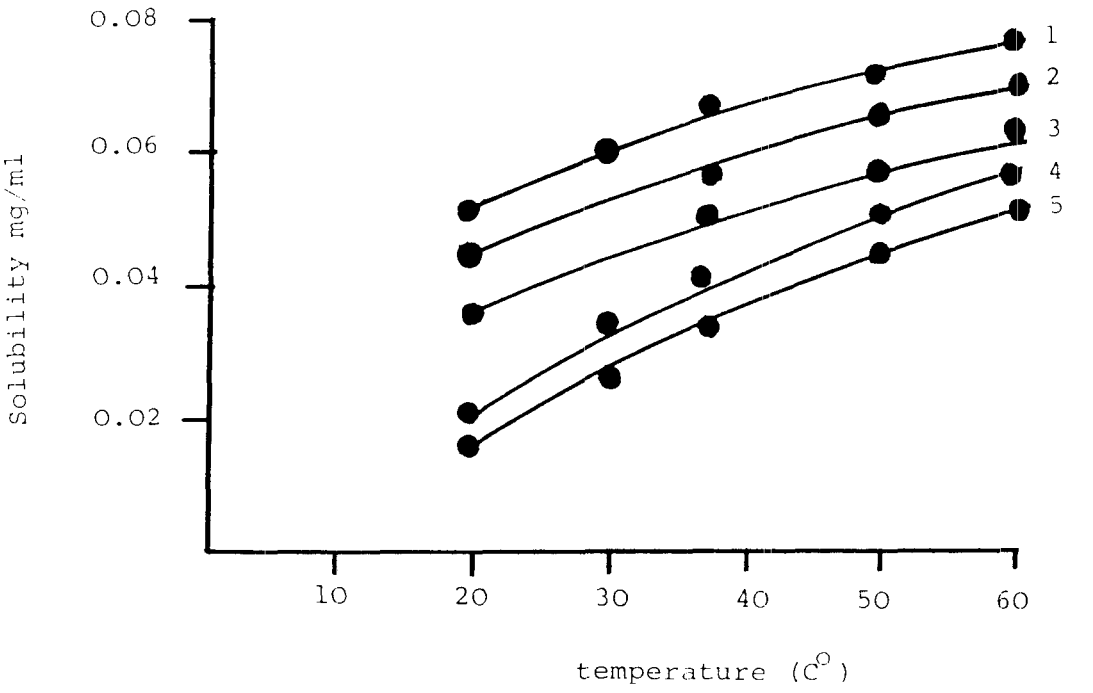

Figure 3.

The effect of temperature on solubility of ibuprofen from different systems 1) Drug:PEG 1500 Dispersion 2) Drug:PEG 4000 Dispersion 3) Drug:PEG 6000 Dispersion 4) Drug:PEG Physical mix 5) Drug.

and sulphathiazol from PVP dispersions (18). In order to explain these findings, the effect of temperature on solubility was studied.

The effect of temperature on solubility was determined for dispersions prepared with various molecular weight fractions of PEG as well as for the pure drug and physical mixture of the drug and the polymer. Fig. 3,

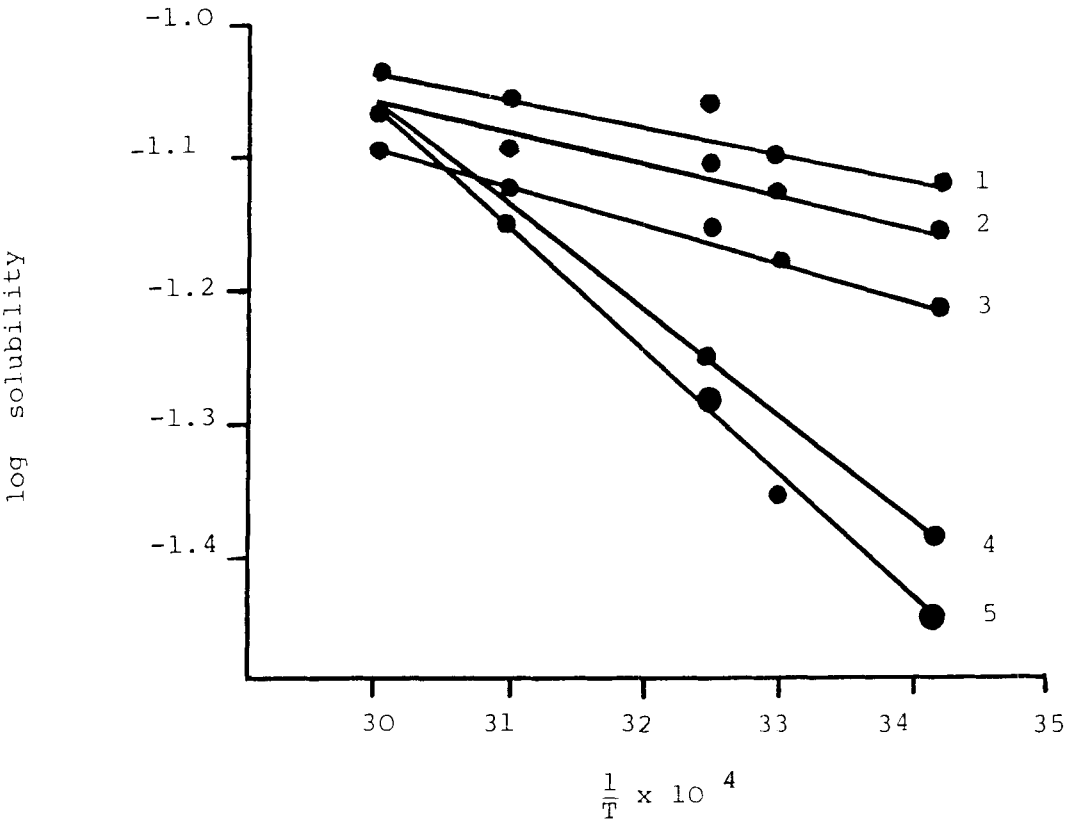

Figure 4.

The van't Hoff plot of the various systems 1) Drug:PEG 1500 Dispersion 2) Drug:PEG 4000 Dispersion 3) Drug:PEG 6000 Dispersion 4) Drug:Physical mix 5) Drug.

shows the results obtained. It is evident from the figure that in all cases the soulbility increases with increase in temperature indicating that the solution process is endothermic, thus heat is absorbed when the drug dissolves. Fig. 4, is the van't Hoff plot for these

TABLE 1.

Heat of solutions of the various systems used.

System	ΔH KJ $K^{-1}mol^{-1}$
Drug	19.128
Drug-PEG Physical mix	16.081
Drug:PEG 6000 dispersion	5.614
Drug:PEG 4000 dispersion	4.679
Drug:PEG 1500 dispersion	4.056

systems. It can be seen from the figure that linear plots were obtained in all cases. The heat of solution was calculated from the slopes of these plots. The values obtained are shown in table 1.

The heat of solution as indicated from the table was highest for the pure drug followed by the physical mixture and then the solid dispersions. Dispersions prepared with the higher molecular weight fractions have higher heat of solutions than those prepared with the lower ones. Higher heat of solution are associated with high lattice energy and therefore a large amount of heat has to be absorbed before dissolution takes place. Therefore as the solid disperesed systems exhibited lower

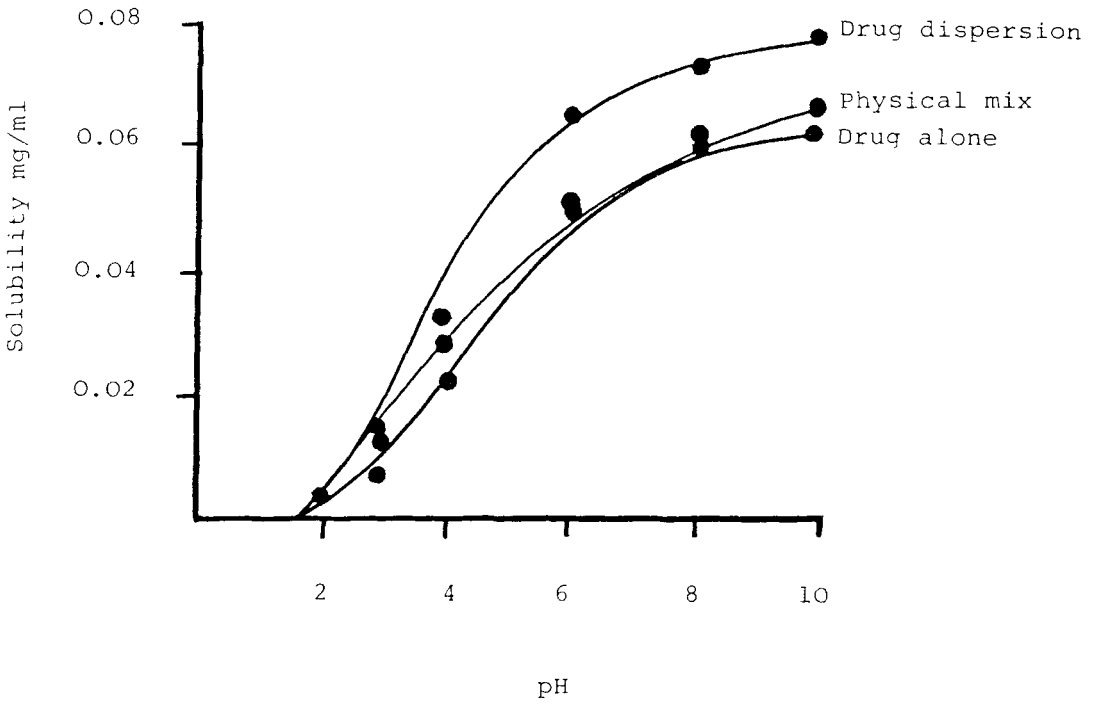

Figure 5.

Effect of pH on the solubility of drug and drug:PEG physical mix and dispersion.

heat of solutions, they showed a greater aqueous solubilities. Fig. 5, shows the effect of pH on the solubility of Ibuprofen, Ibuprofen-PEG physical mix and Ibuprofen-PEG solid dispersion. The figure shows that at any one pH the solubility of the dispersed systems was higher than that of the physical mixture or the drug alone. However the solubility-pH profile was identical in all cases. The solubility was low at low pHs and then incre-

ased as the pH increased to pH 8. At pH values greater than 8 the solubility remained constatnt. This behaviour is to be expected since Ibuprofen is a weak acid. Hence it will be weakly ionised at low pHs and fully ionised in alkaline media.

In conclusion the equilbrium solubility of Ipuprofen was found to increase by dispersing the drug in an inert water soluble carrier such as PEG. An optimum ratio of drug to polymer which produced the highest solubility was found to be 1:1. The solubility was found to be higher with lower molecular weight fractions of PEG than the higher ones. The increase in solubility of the solid dispersions could be partly due to the dispersed systems having lower heat of solutions than either the physical mixture or the drug.

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