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Characterization of a diflunisal polyethylene glycol solid dispersion system

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Summary

This work involves the study of the nature of a possible interaction of diflunisal and polyethylene glylol (PEG) in solution and the solid state. Dynamic and equilibrium solubility studies, solvent power calculation and heat of solution determination were used to elucidate the mechanism of interaction in solution. Differential scanning calorimetric studies, infrared spectroscopy and hot stage microscopy were used to elucidate the mechanism of interaction in the solid state. From these studies it was concluded that no chemical interaction takes place between diflunisal and PEG neither in solution nor in the solid state. The increased solubility of diflunisal when dispersed in PEG could be attributed to one or more of several factors such as local solubilization action, reduction in particle size of the drug, alteration of the surface characteristics of the drug particles, increased thermodynamic activity and the high affinity of the drug to the polymer solution.

Introduction

Dissolution rate enhancement is one of the most commonly used approaches to improve the biological availability of drugs whose absorption is dissolution rate-limited. One of the techniques used to increase the dissolution rate of such drugs is by dispersing the drug in a water-soluble carrier such as polyethylene glycol (PEG). PEG has been used extensively to improve the dissolution and the bioavailability of drugs such as griseofulvin (Chiou and Riegelman, 1971a; Kaur et al., 1980a), hydroflumethiazide (Corrigan and Timoney, 1976), testosterone (Babar and Jarowski, 1983), tolbutamide (Miralles et al., 1982), indomethacin (Ford and Elliott, 1985), ibuprofen (Najib and Sheikh-Salem, 1987), phenytoin (Stavchansky and Gowan, 1984), dicumarol (Ravis and Chen, 1981), morphine (Chang and Jarowski, 1980) and chloramphenicol (Goldberg et al., 1965, 1966).

Diflunisal is a non-steroidal anti-inflammatory agent, it is poorly water soluble, and therefore its bioavailability is expected to be dissolution rate-limited. In the present work an attempt is made to improve the dynamic and equilibrium aqueous solubility of diflunisal by dispersing it in PEG. This involved the study of the possible interaction between diflunisal and PEG in solution and the solid state. Interaction in the solid state was

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studied by infrared spectroscopy (IR), differential scanning calorimetry (DSC) and hot-stage microscopy. Interaction in solution was studied by studying the equilibrium and dynamic solubilities of the free and dispersed drug and by calculating the solvent power of PEG to diflunisal and the heat of solution (ΔH) of the dispersed and free drug.

Materials and Methods

Materials

Anhydrous citric acid was purchased from Aldrich Chemical Co., Gillingham, Dorset, U.K. Diflunisal from Sigma Chemical Co., St. Louis, MO, U.S.A. Disodium phosphate and PEG-400 and -4000 were obtained from BDH Chemical Co., Poole, U.K.

Methods

Preparation of drug–PEG dispersions. Solid dispersions were prepared by the melt-solvent method (Chiou and Riegelman, 1971b). Diflunisal was dissolved in a minimum volume of methanol and added to the melted PEG. The resulting mass was allowed to cool at room temperature until completely solidified. Further drying was carried out under anhydrous calcium sulphate. All samples were examined within 24 h of preparation following sieving at 80/120 mesh for size uniformity. Each batch of the prepared dispersions was tested for content uniformity before use.

Differential scanning calorimetry. The thermograms of diflunisal, PEG and diflunisal–PEG dispersions of different ratios were determined as previously described (Najib et al., 1986).

Hot-stage microscopy. Approximately 1.0 mg of sample was placed on a microscope slide and heated at 1–5 ° C/min on a Koffler hot-stage fitted on Reichert Thermover microscope. The onset of melting was characterised by the first appearance of liquid and the completion of melting was considered as the final disappearance of solid.

Infrared studies. The spectra were recorded on Pye-Unicam SP3-100 Spectrophotometer using KBr 0.1 mm solution cell. All solution samples were prepared in acetone.

Equilibrium solubility studies. Equilibrium solubility studies were performed by placing a 50 mg sample of the drug–polymer solid dispersion or the required drug-to-polymer ratio containing this weight of the drug to each of a series of Erlenmeir flasks containing 10 ml of McIlvaine buffer solution adjusted to the required pH. The flasks were then placed in a water bath at 37 ± 0.1° C with continuous shaking for 24 h. 3 ml samples were then transferred to a syringe and rapidly filtered through an 0.3 μm millipore filter unit (Millipore, London, U.K.). The amount of drug dissolved was measured spectrophotometrically by reference to a suitable calibration curve. Each data point is the average of 3 individual determinations. In all cases the standard deviation (S.D.) was less than 3%.

Dissolution studies. The dissolution experiments were carried out in a USP dissolution apparatus (Erweka, DT-D6, F.R.G.) maintained at 37° C. 500 ml of distilled water were placed in the 1 litre flask. A stirring rate of 100 rpm was maintained throughout the experiment. 5 ml samples were withdrawn at the designated time intervals and immediately replaced with a similar volume of fresh dissolution medium. The samples were filtered and assayed for the amount of drug released as described above. This procedure was repeated for all dispersion studies. Each data point is the average of 3 individual determinations. In all cases the S.D. was less than 3%.

Calculation of the solvent power of PEG. The solvent power of PEG 400 was calculated by shaking an excess of the drug with solutions containing different volume fractions of PEG-400. The equilibrium solubility was then determined as described above.

Results and Discussion

The IR spectra of the drug, the polymer and the dispersion are shown in Fig. 1. The frequency of the O–H band in diflunisal is broad due to intermolecular and intramolecular hydrogen bonding. For diflunisal–PEG dispersion (1 : 1 w/w), the frequency of the O–H is also broad due to hydrogen bonding in diflunisal making it difficult

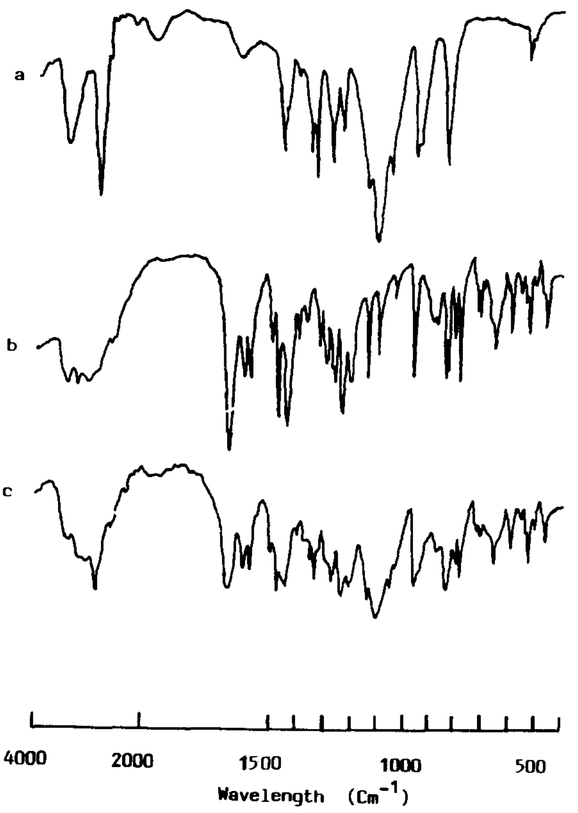

Fig. 1. The IR spectra of PEG (a), diflunisal (b) and dispersion (c).

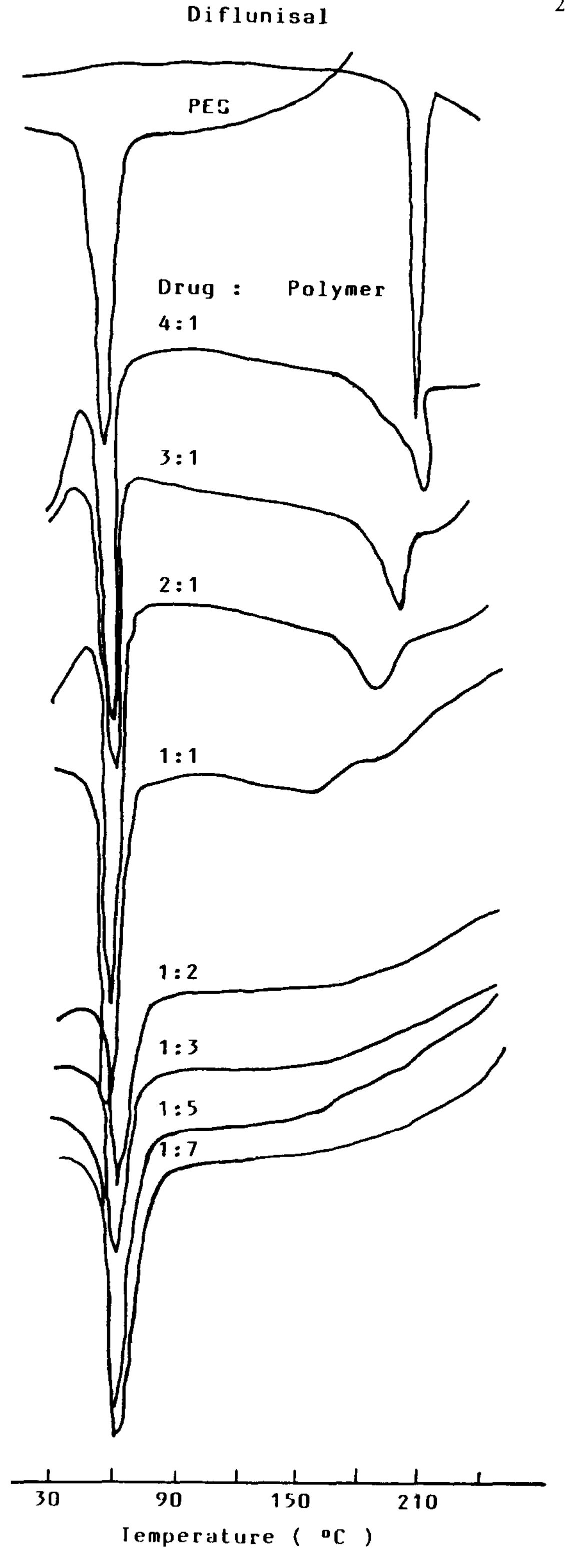

Fig. 2. The DSC curves of diflunisal–PEG dispersions of different ratios.

to detect any hydrogen bonding interaction between the drug and the polymer. Further, the frequency of the C = O of the COOH group in diflunisal and in the solid dispersion appeared at 1670 cm^{-1} indicating that the carboxylic group of the drug is not involved in any type of a chemical interaction in the solid dispersion. Similar results were obtained for other drug–polymer ratios.

The DSC curves of diflunisal, PEG-4000, and diflunisal–PEG-4000 solid dispersions of different ratios are shown in Fig. 2. The DSC curves of diflunisal and PEG-4000 exhibit only one endothermic peak corresponding to the melting point of diflunisal (214.2°C) or PEG-4000 (63.0°C). The DSC curves of the solid dispersions show one or two endothermic peaks depending on the ratio of drug-to-polymer. At high ratios of the drug (4:1, 3:1 and 2:1) the DSC curves indicate two endothermic peaks: one occurs at low temperature and corresponds to the melting of PEG-4000 whereas the other occurs at high temperature and corresponds to the melting of diflunisal. At the 1 : 1 drug-to-polymer ratio, the endothermic peak corresponding to the melting of diflunisal shifted to a lower temperature (153.5 ° C) and lost its sharp and distinct appearance. As the ratio of drug-to-polymer decreases (1 : 2, 1 : 3, 1 : 5 and 1 : 7), the DSC curves show one endothermic peak corresponding to the melting of PEG-4000. The disappearance of the endothermic peak corresponding to the melting of diflunisal is due to its solubility at lower concentration in the melted PEG-4000. Physical mixtures of diflunisal and PEG-4000- (Fig. 3) showed exactly the same thermal behavior as the solid dispersions of the same composition. The similarities between the DSC data of the solid dispersion and the physical mix indicates the absence of a chemical interaction between diflunisal and PEG-4000.

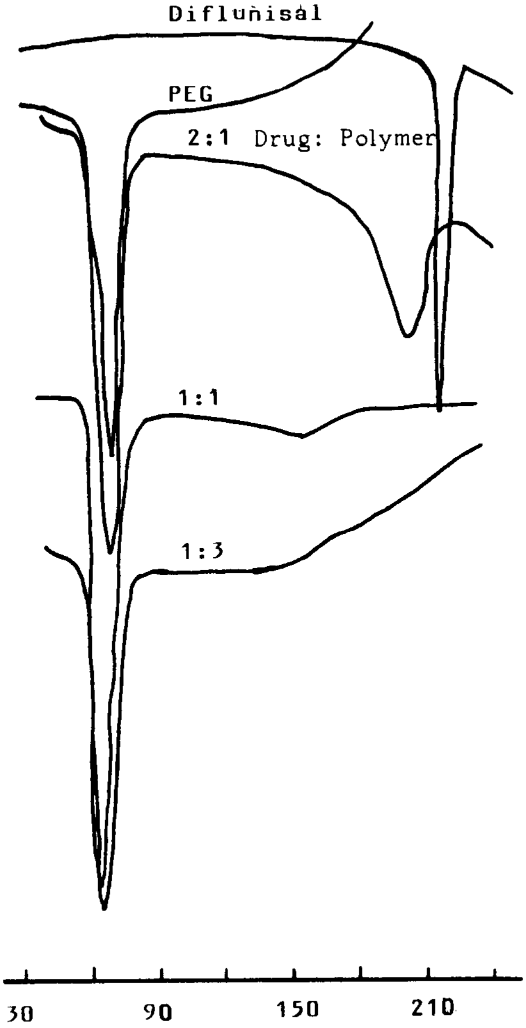

Fig. 3. The DSC curves of diflunisal–PEG physical mixtures of different compositions.

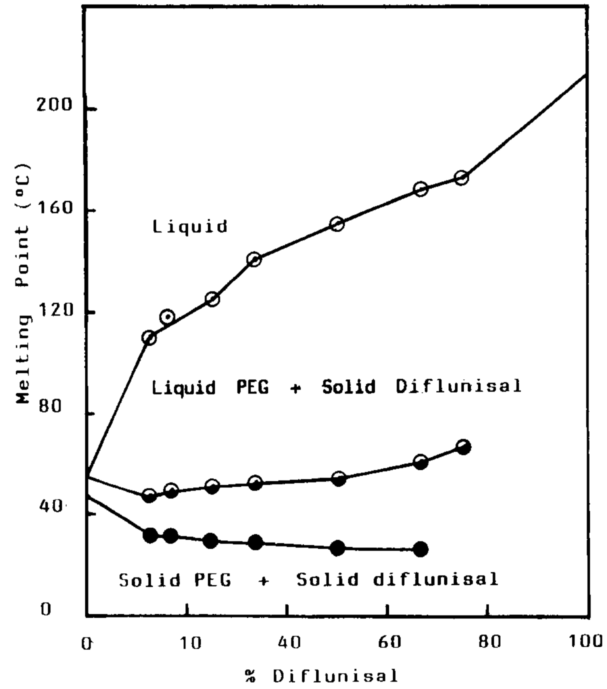

Fig. 4. Binary phase diagram of diflunisal–PEG dispersions.

Hot-stage microscopy of the solid dispersions or the physical mixtures of the drug and the polymer of all compositions showed two melting points: at 48–65 ° C for PEG-4000 and at 110–174 ° C for diflunisal. The phase diagram constructed using hot-stage microscopic data is shown in Fig. 4 and represents a monotectic system. It has the form of a eutectic diagram in which one arm is missing and in which the lower melting component (PEG-400) replaces the eutectic composition. The rising liquidus curve on the left of the monotectic diagram corresponds to the solubility of diflunisal in liquid PEG. This type of system was reported for griseofulvin and for

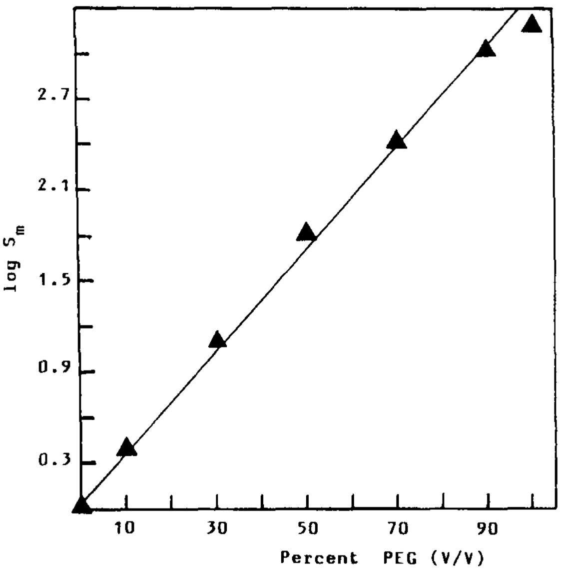

Fig. 5. The logarithm of solubility of diflunisal in PEG 400 solution as a function of PEG volume fraction.

tolbutamide solid dispersions with polyoxyethylene 40 stearate and PEG-2000 (Kaur et al., 1980b). This gives a further indication of the absence of chemical interaction between diflunisal and PEG-4000.

In order to gain an insight into the nature of a possible interaction between diflunisal and PEG in solution, solvent power calculation, and dynamic and equilibrium solubility studies for free and dispersed diflunisal were performed. The solvent power of PEG-400 for diflunisal (σ) was calculated using the equation (Yalkowsky and Roseman, 1981):

$$\log S_m = \log S_w + \sigma f_c$$

where S_w and S_m are the molar solubilities of the solute in water and PEG solution, respectively, and f_c is the volume fraction of PEG. Fig. 5 shows that a linear relationship was obtained when log S_m was plotted against f_c. The slope of this line is σ and the intercept is log S_w; σ was found to be 3.360. The value of σ is indicative of the high affinity of the drug for the polymer and is directly related to the activity coefficient of the drug in the polymer. It also reflects reduction of the interfacial tension of the water and hence intermolecular forces and polarity caused by the presence of PEG. σ is also related to the molecular hydrophobic surface area of the solute (Yalkowsky et al., 1975). Therefore, the greater the value of σ of a cosolvent system to a drug, the greater is the solubilizing action to that particular drug.

The equilibrium solubility of diflunisal dispersed or physically mixed with PEG at various compositions is shown in Fig. 6. The figure demonstrates the significant effect of PEG on the solubility of diflunisal. This effect, however, was dependent on the concentration of PEG. The solubility of the dispersed drug was found to be identical to that of the physical mixture of the same composition. This finding is indicative of the absence of a chemical reaction between the drug and the polymer which could occur during the preparation process. Therefore the samples may differ only with respect to some of their physical properties such as particle size, surface area, wettability and the nature of the hydrodynamic layer (Goldberg et al., 1966; Chiou and Riegelman, 1971b).

The dissolution of the drug dispersed in PEG (Fig. 7) was faster than from the physical mixture of the same composition (Fig. 8) and both were faster than the dissolution of the pure drug. The increased dissolution in the case of the dispersed drug could be attributed to one or more of several factors such as the local solubilization effect, particle size reduction and alteration of the surface properties of the particles. The effect of these factors is increased as the polymer content of the drug is increased. Hence, the dissolution rate of the drug is increased with increase in PEG content of the dispersion. The increase in the dissolution of the drug when physically mixed with PEG is possibly due to a local solubilization action operating in the microenvironment or the diffusion layer immediately adjacent to the drug particle in the early stages of the dissolution process as the polymer dissolves in a short time. Thus improving the wettability and hence the dissolution of the drug particles (Goldberg et al., 1966).

The alteration of the thermodynamic activity of the drug as a result of dispersing it in PEG was studied by determining the values of the heat of

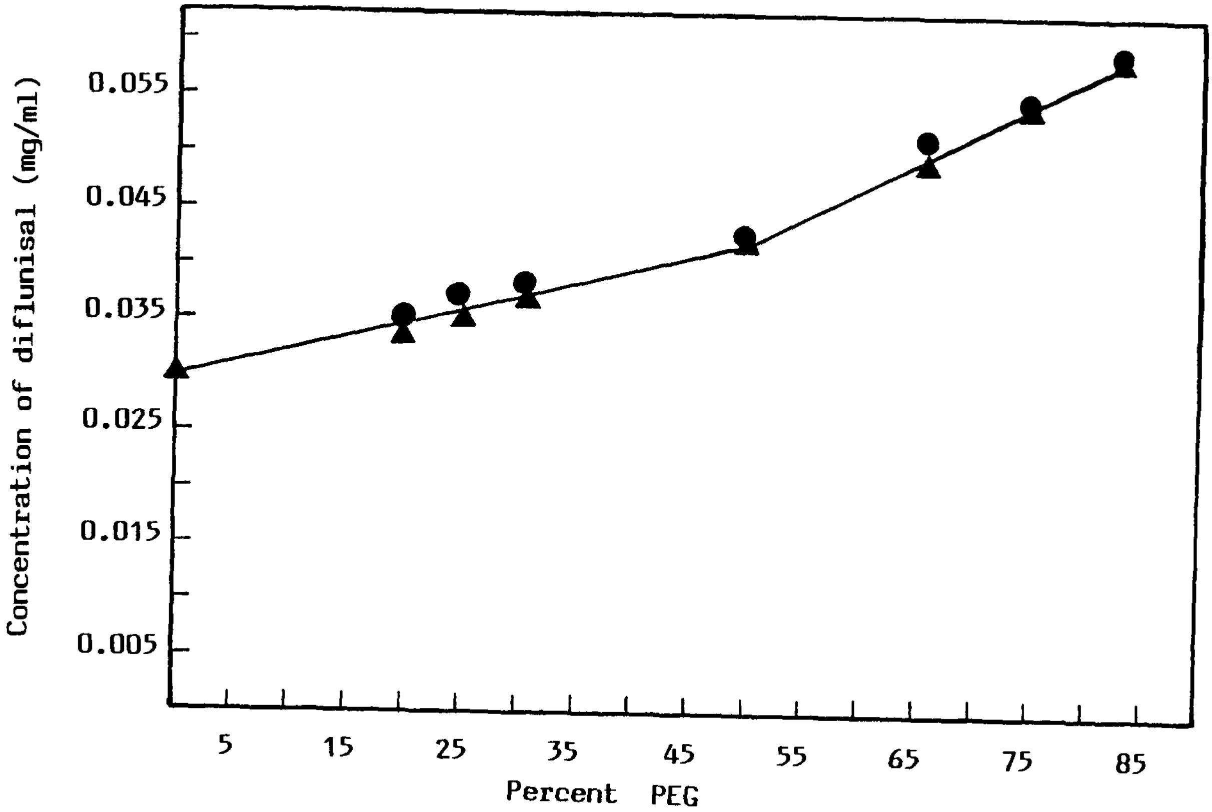

Fig. 6. The equilibrium solubility of diflunisal physically mixed (▲) or dispersed in PEG (●) as a function of percentage of PEG.

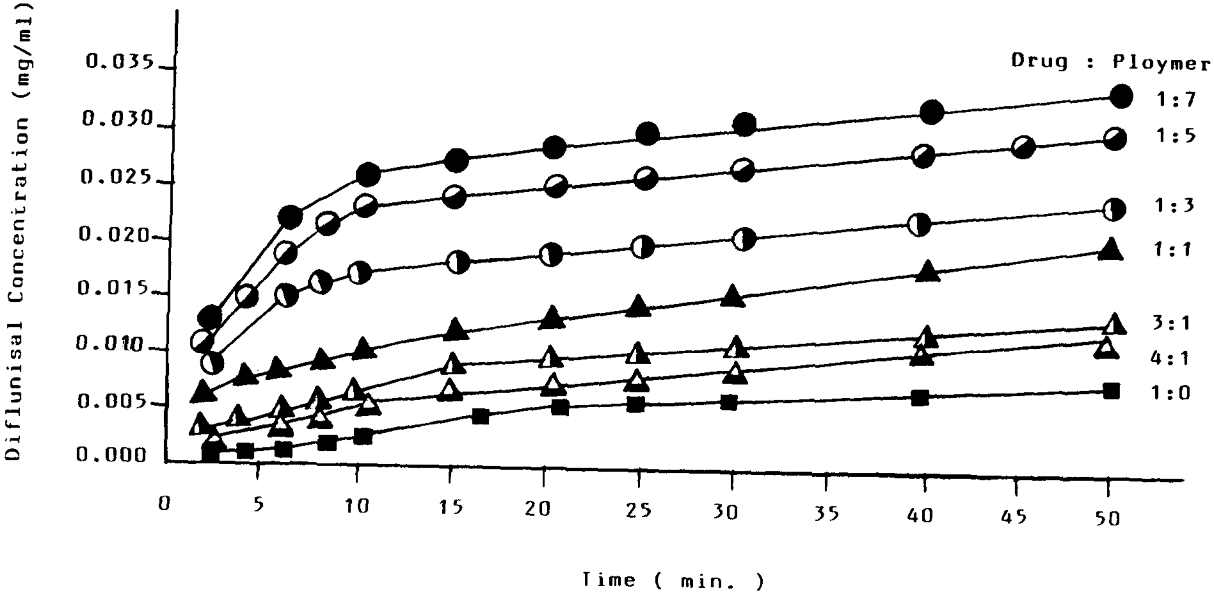

Fig. 7. The release of diflunisal from PEG dispersions of different compositions.

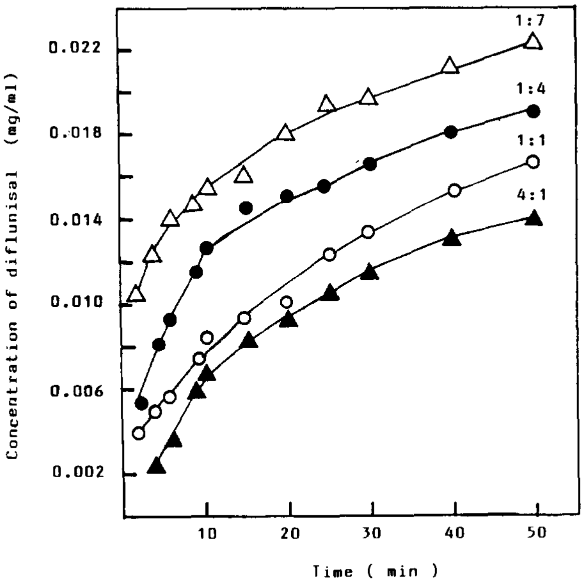

Fig. 8. The release of diflunisal from PEG physical mixtures.

solution (ΔH) of the drug when dispersed in PEG. The values of ΔH obtained are shown in Table 1. It is evident from these values that increasing the proportion of PEG decreases the value of the corresponding ΔH of the drug. The decrease in ΔH is indicative of a high thermodynamic activity. Therefore, as the concentration of PEG in the dispersion is increased, the thermodynamic activity of the drug is decreased. This would result in a reduced thermodynamic stability and therefore the aqueous solubility of the drug is increased.

In conclusion, the IR, DSC, hot-stage microscopy, dynamic and equilibrium solubility data suggest that no chemical interaction takes place between diflunisal and PEG neither in the solution nor in the solid state. The increased solubility of diflunisal, when dispersed in PEG, could be attributed to one or more of several factors such as local solubilization action, reduction in particle size of the drug and alteration of the surface characteristics of the drug particles. Thermodynamic studies showed that the dispersed drug has a higher thermodynamic activity and therefore greater aqueous solubility than the free drug. The high solvent power of PEG for diflunisal is indicative of the high activity of the drug in the polymer solution and hence greater solubility.

TABLE 1

Heat of solution values (ΔH) for diflunisal dispersed in PEG

Dispersion composition Drug : PEG	ΔH (kJ·mol^{-1})
1:0	23.125
4:1	21.470
2:1	16.871
1:1	10.19
1:3	09.81
1:5	09.712
1:7	09.560

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