International Journal of Pharmaceutics, 74 (1991) 43–48
© 1991 Elsevier Science Publishers B.V. 0378-5173/91/$03.50
ADONIS 0378517391002733

IJP 02459

Characterisation of polyethylene glycols using solution calorimetry

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(Received 1 February 1991)
(Accepted 14 March 1991)

Key words: Polyethylene glycol; Solution calorimetry; Molecular weight; Thermodynamic analysis; Thermal treatment; Solid dispersion

Summary

The heats of solution of a range of polyethylene glycols (PEGs) have been measured using samples prepared under various heating and cooling protocols. The values obtained were shown to be highly sensitive to both PEG molecular weight and to the thermal history of the sample. A model has been proposed in order to interpret the results in terms of the energetics of the different stages of the dissolution process.

Introduction

The dissolution rates of poorly soluble drugs may be enhanced by incorporation into water-soluble carriers such as polyethylene glycol (Chiou and Riegelman, 1971). In order to understand the properties of such solid dispersions, it is necessary to have some knowledge of the characteristics of the carrier itself. In a previous study (Craig and Newton, 1991), the melting behaviour of a range of different molecular weight polyethylene glycols (PEGs) was examined. In the present investigation, solution calorimetry will be used to characterise the same samples of PEGs. This technique involves the measurement of heat changes resulting from the dissolution of a sample in a liquid (ΔH_s). This and other related methods have been used for the study of a number of pharmaceutical systems and phenomena, including complexation (Hardee et al., 1978), solid solutions (Grant and York, 1986), stability studies (Pikal and Dellerman, 1989), partition coefficient studies (Beezer et al., 1983) and as a bioassay technique (Beezer et al., 1986).

There are three principal advantages to the technique. The first lies in the direct nature of the measurement, as there is no invasive process involved other than the dissolution of the material. This is in contrast to DSC, whereby results are usually obtained at elevated temperatures and extrapolated back to give an indication of the solid structure at room temperature. Secondly, the technique offers a basis for comparison between samples. For example, the dissolution energetics of various tablet formulations have been

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measured and compared (Takagi and Kimura, 1984). Thirdly, the values of the heat of solution may lead to a mechanistic analysis of the process under study (e.g. Craig and Taylor, 1990). The principal disadvantage of the technique is that the dissolution process, and hence enthalpy of solution, involves several stages, including the breakage of bonds, wetting, liquid penetration, solvation, possibly rearrangement and conformational changes, etc. It is therefore difficult to separate and quantify these individual processes.

While the solution properties of PEGs have been extensively studied (Molyneaux, 1975), relatively little work has been performed on their heats of solution. Examples of published work include a study by Malcolm and Rowlinson (1957) in which measurements were taken of ΔH_s for a molecular weight range of 300–5000 at 353.3 K. Similarly, Maron and Filisko (1972) measured ΔH_s of PEG 6000 in a range of solvents, including distilled water. Ikeda et al. (1975) studied the crystalline-amorphous interfacial properties of PEGs 1500, 6000 and 20 000 using DSC and solution calorimetry. Kagemoto et al. (1971) reported heats of dilution of liquid PEGs in organic solvents, while Lakhanpal et al. (1968) measured the heats of solution of PEG-water systems up to a molecular weight of 4000.

In the present study, the effects of both molecular weight and thermal history on the values of ΔH_s have been investigated. The results obtained have been combined with the DSC data reported in a previous paper (Craig and Newton, 1991) and a model has been proposed in order to interpret the results in terms of the different stages involved in the dissolution process.

Materials and Methods

Polyethylene glycols 3400 (CSD, Cheshire), 6000 (CSD, Cheshire), 10 000 (BDH Chemicals, Poole) and 20 000 (BDH Chemicals, Poole) were characterised as previously described (Craig and Newton, 1991). The samples were flash cooled by immersion in liquid nitrogen, slow cooled at 5°C/h or left untreated, as described previously (Craig and Newton, 1991). The materials were ground and a sieve size of 120–250 μm used for all studies. A sample size of 45–50 mg was used, each study being repeated at least three times. In all calculations, the measured, as opposed to nominal number average molecular weights were used.

A Tronac Model 450 adiabatic calorimeter (Tronac Inc., UT) was used for all studies. The apparatus consists of a dewar flask suspended in a constant temperature water bath, held at 298 K in the present study. The dewar flask was silvered in order to minimise the heat exchange between the dissolution fluid and the bath. 50 ml of water were pipetted into the flask. The solid sample was weighed into a 1 ml glass ampoule (Pharmacia LKB Biotechnology, Sweden) using a Model CL3 five figure balance (Stanton Instruments Ltd, Warley). The vial was sealed and suspended in the flask. The sample holder was then rotated at 600 rpm. The temperature of the solvent was measured using a thermocouple and indicated as voltage against time on a Servoscribe 1S chart recorder (Smith's Instruments, Cricklewood). A thermistor was used to heat the solvent to a temperature marginally below that of the bath. The slow equilibration between the solvent and the bath resulted in the curve on the chart recorder being effectively linear, the slope remaining constant before and after sample measurement, thus simplifying the analysis of the results. The system was left to equilibrate for at least 1 h, after which the ampoule was automatically broken by a plunger. Preliminary studies using empty vials showed the breaking process to have no discernible effect on the slope of the trace. This absence of response is in agreement with previous studies (Erb, 1984).

The PEG samples were sometimes found to form gels on initial contact with the solvent which dissolved extremely slowly, thus rendering measurement difficult. The equipment was therefore modified by placing a stainless-steel studded plate immediately below the ampoule in the holder. This led to improved breakage of the glass vial and hence distribution of the individual particles through the solvent.

Three calibration runs were performed. These involved engaging the thermistor for approx. 60 s, measured to ±0.1 s. The voltage and (indirectly) the current across the thermistor were measured using a Solartron 7040 Digital Voltmeter (Solartron Instruments, London), arranged in parallel to the calorimeter. Preliminary studies showed no discernible difference in the calibration response when the runs were performed before or after sample dissolution. The slopes of the initial and final curves were extrapolated and the vertical distance between the two measured manually. This distance was chosen in order to account for heating during sample dissolution due to the temperature gradient between the dewar flask and the bath. While a more accurate correction is available (Dickinson, 1914), this analysis cannot be applied manually to irregular profiles. As the curves found in the present case often showed a minimum before equilibration, the less accurate correction described above was used.

The power (P_0) dissipated to the solvent during the calibration run was calculated using the equation

$$P_0 = \frac{V(\mathrm{v}) \times V(\mathrm{i})}{R} \tag{1}$$

where V(v) is the voltage across the thermistor and V(i) is the voltage across a calibration resistor R. For the particular model used in the present study, this resistor had a value of 100.05 Ω. The current across the thermistor was therefore given by $V(\mathrm{i})/R$, which is multiplied by the thermistor voltage to give the power (P_0). As the power is given in J/s, multiplication by the time span of the calibration run gave the energy dissipated within the dewar flask in J. Therefore, the energy/distance (J/cm) value was calculated by dividing the energy by the vertical distance of the response. The distance corresponding to the sample was then measured and multiplied by the J/cm value to give the total energy of the dissolution process. This was then divided by the quantity of sample to give a specific value for the heat of solution.

The reliability of the equipment and the experimental technique were assessed by measuring the heat of solution of two standards, KCl (BDH, Poole) in water and Tris, or THAM (BDH, Poole) in 0.1 N HCl (BDH, Poole). The heat of solution of THAM was measured as −29.35 kJ/mol, compared to the literature value of −29.69 kJ/mol (Irving and Wadso, 1964). Similarly, the heat of solution of KCl was found to be 17.61 kJ/mol, compared to 17.51 kJ/mol (Irving and Wadso, 1964). The agreement between the experimental and literature results was considered satisfactory in both cases.

Results and Discussion

The untreated, slow cooled and flash cooled samples were analysed for each molecular weight, the results being given in Table 1. These values are of the same order of magnitude as those reported in previous studies (Ikeda et al., 1975). The flash cooled samples gave the least endothermic values for each molecular weight, while the slow cooled samples showed a rise in ΔH_s as the chain length increased. Otherwise, there was little discernible relationship between ΔH_s and either the molecular weight or the thermal history. However, it can be seen clearly that the technique is highly sensitive to changes in PEG structure, either in terms of chain length or crystal morphology.

TABLE 1

Effect of heat treatment on the heats of solution of a range of molecular weight polyethylene glycol samples (standard deviations in parentheses)

Nominal molecular weight	Heat of solution (kJ/mol)		
	Untreated	Slow cooled	Flash cooled
3400	33.98 (0.76)	30.59 (1.40)	8.93 (0.37)
6000	90.73 (0.76)	57.53 (7.59)	31.22 (0.76)
10000	76.28 (5.07)	166.43 (7.60)	−28.61 (9.09)
20000	82.39 (3.11)	250.06 (15.53)	−120.68 (13.25)

The heat of solution represents the sum of the enthalpies of each stage of the dissolution process as a whole. By Hess's law, ΔH_s may be interpreted as the sum of any number of steps, providing that the starting point is the solid and the end product is the solution. The dissolution process can therefore be considered to consist of two theoretical stages. The first represents the breaking of the solid-state bonds, while the second involves all the processes whereby the individual molecules become incorporated into the solution. The bond breaking process is similar to a melting process and is thus represented by ΔH_F^{298}, corresponding to the formation of a supercooled liquid at 298 K (the temperature of dissolution). The second process is represented by ΔH_M, describing the mixing of the individual molecules with water.

The solution process can therefore be represented by

$$\begin{tikzcd}
\text{Solid} \arrow[dr, "\Delta H_F^{298}"] \arrow[dd, "\Delta H_s"'] & \\
& \text{Supercooled liquid} \arrow[dl, "\Delta H_M"] \\
\text{Solution} &
\end{tikzcd}$$

A related approach has been described by Paruta (1984), whereby the thermodynamic parameters associated with the formation of aqueous solutions of a series of alkyl *p*-aminobenzoates were calculated using a combination of solubility and DSC data. However, these calculations required the heat of solution to be obtained from the solubility data, thereby involving the use of van't Hoff plots of ln solubility against reciprocal temperature. These plots are expected to yield a straight line, the gradient of which gives the heat of solution. However, van't Hoff plots are frequently non-linear due to non-ideal behaviour of the solution systems (Grant et al., 1984), hence the reliability of the method is questionable. Calorimetric measurement of the heat of solution overcomes this problem, as the ΔH_s values are obtained directly. Maron and Filisko (1972) used a similar method to assess the dissolution of PEG 6000 in a range of solvents. The authors measured the heat of solution and of dilution, the latter being used to estimate ΔH_M.

In the present study, the value of ΔH_s is measured directly and ΔH_F^{298} is estimated from the DSC data presented in a previous report (Craig and Newton, 1991). The measured heats of fusion represent the energy required for dissociation at the melting point. These values must therefore be corrected in order to account for the temperature difference between the melting point and 298 K, the temperature at which the ΔH_s values were obtained.

The equation used was

$$\Delta H_F^{298} = \Delta H_F \cdot \frac{298}{T_M} \qquad (2)$$

where T_M and ΔH_F are the measured melting points and molar heats of fusion. This equation can be reached via two routes.

Firstly, Walden (1908) noted that the molar heats of fusion divided by the melting point of structurally related substances is approximately constant, which can be restated as the entropy of fusion being similar for such solids. This is shown by Gibbs equation

$$\Delta G = \Delta H - T\Delta S \qquad (3)$$

where ΔG is the free energy, ΔH is the enthalpy and ΔS is the entropy of the process. At the melting point, the solid and liquid are in equilibrium, hence $\Delta G = 0$. Therefore

$$\Delta S = \frac{\Delta H_F}{T_M} = \frac{\Delta H_F^{298}}{298} \qquad (4)$$

thus

$$\Delta H_F^{298} = \Delta H_F \cdot \frac{298}{T_M} \qquad (2)$$

The second route involves consideration of Kirchoff's equation

$$\Delta C_P = \frac{\mathrm{d}\Delta H_F}{\mathrm{d}T} \qquad (5)$$

which, on integration between T_M and 298 K, yields

$$\Delta H_F^{298} = \Delta H_F - \Delta C_P(T_M - 298) \qquad (6)$$

ΔC_P can be estimated as being equivalent to the entropy of fusion (James, 1986), hence

$$\Delta C_P = \frac{\Delta H_F}{T_M} \qquad (7)$$

Substitution into Eqn 6 gives

$$\Delta H_F^{298} = \Delta H_F - \Delta H_F \cdot \frac{(T_M - 298)}{T_M} \qquad (8)$$

hence

$$\Delta H_F^{298} = \Delta H_F \cdot \frac{298}{T_M} \qquad (2)$$

Therefore, ΔH_F^{298} can be readily estimated from the DSC data. According to the model previously outlined, the difference between ΔH_s and ΔH_F^{298} will equal ΔH_M, hence characterisation of the solution process is possible.

The above model was tested as follows. When the various heat-treated polyethylene glycols dissolve, the values of ΔH_M should be constant for any molecular weight, irrespective of thermal history. This is because ΔH_M is a function of the structure and behaviour of the individual molecules, hence the arrangement of the chains within the crystal lattice should have no bearing on this parameter. ΔH_F^{298}, however, is highly dependent on the crystal structure and may therefore vary with thermal history (Craig and Newton, 1991). As ΔH_s is the sum of ΔH_F^{298} and ΔH_M, this enthalpy will likewise vary with thermal history. All three parameters may be dependent on molecular weight as both ΔH_F^{298} and ΔH_M are expected to alter as the chain length increases.

The values of ΔH_s, ΔH_F^{298} and ΔH_M for the polyethylene glycol samples are shown in Table 2. The flash cooled samples have not been included as the multiple peaks found for the melting endotherms (Craig and Newton, 1991) prevent the calculation of ΔH_F^{298} by the given equations.

TABLE 2

ΔH_s, ΔH_F^{298} and ΔH_M for polyethylene glycols at 298 K

Nominal molecular weight	Heat treatment	ΔH_s (kJ/mol)	ΔH_F^{298} (kJ/mol)	ΔH_M (kJ/mol)
3400	Untreated	34.0	682.3	−648.3
	Slow cooled	30.6	649.8	−619.2
6000	Untreated	90.7	1374.6	−1283.9
	Slow cooled	57.5	1307.7	−1250.2
10000	Untreated	76.3	2588.9	−2512.6
	Slow cooled	166.4	2683.4	−2517.0
20000	Untreated	82.4	3510.7	−3428.3
	Slow cooled	250.1	3755.1	−3505.0

Analysis by paired Student's *t*-test between the slow cooled and untreated samples shows the means of the two sets of ΔH_M values to remain constant to a 5% confidence level. This indicates that for a given molecular weight, ΔH_M does not show significant dependence on the previous heat treatment, which is in agreement with the model previously outlined. The theory also accounts for the apparent absence of a discernible relationship between ΔH_s and either the PEG molecular weight or the heat treatment, as these enthalpy values appear to be a combination of a large endothermic melting process and a similarly large exothermic mixing reaction. While both these processes show rank orders with molecular weight, the sum of the two (ΔH_s) may not necessarily exhibit the same trends.

However, the assumption that differences in crystal structure will only affect ΔH_F^{298} rather than ΔH_M will not always be valid. The enthalpy of wetting may vary with crystal structure, as may the enthalpy of any rearrangement reactions taking place in solution. However, these limitations aside, the theory provides a simple and useful means of quantifying the solution process, effectively involving only two sets of measurements.

Conclusions

The sensitivity of solution calorimetry to the molecular weight and thermal history of PEG samples has been demonstrated. This is of relevance to the study of solid dispersions, as the results indicate that the solution properties of PEG samples may vary according to the heating and cooling protocol used. A model has been proposed in order to interpret the data, using a combination of differential scanning and solution calorimetry. While it is obviously desirable to refine this model in order to account for the assumptions mentioned previously, this will almost inevitably necessitate the use of more complex measurements. The above system has the advantage that the experimental techniques involved are comparatively simple, hence facilitating a more complete understanding of the processes involved in the dissolution of polyethylene glycols.

Acknowledgements

We would like to thank the Science and Engineering Research Council for financial assistance during the course of the project. Thanks are also due to Ms Susan Barker for translation services.

References

Beezer, A.E., Hunter, W.H. and Storey, D.E., Enthalpies of solution of a series of m-alkoxy phenols in water, *n*-octanol and water-*n*-octanol mutually saturated: derivation of the thermodynamic parameters for solute transfer between the solvents. *J. Pharm. Pharmacol.*, 35 (1983) 350–357.

Beezer, A.E, Volpe, P.L., Gooch, C.A., Hunter, W.H. and Miles, R.J., Quantitative structure-activity relationships: microcalorimetric determination of a group additivity scheme for biological response. *Int. J. Pharm.*, 29 (1986) 237–242.

Chiou, W.L. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, 60 (1971) 1281–1302.

Craig, D.Q.M. and Newton, J.M., Characterisation of polyethylene glycols using differential scanning calorimetry. *Int. J. Pharm.*, 74 (1991) 33–41.

Craig, D.Q.M. and Taylor, K.M.G., Calorimetric investigation of liposome formation. *J. Pharm. Pharmacol.*, 42 (1990) 29P.

Dickinson, H.C., Combustion calorimetry and the heats of combustion of cane sugars, benzoic acid and naphthalene. *Bull. Bureau Stds.*, 11 (1914) 189–255.

Erb, D.M., Solution calorimetry-an alternative method for the quantification of the solid state properties of drugs. PhD Thesis, University of Iowa, U.S.A., 1984.

Grant, D.J.W. and York, P., A disruption index for quantifying the solid state disruption induced by additives or impurities. 2: Evaluation from heat of solution. *Int. J. Pharm.*, 28 (1986) 103–112.

Grant, D.J.W., Mehdizadeh, M., Chow, A.H.-L. and Fairbrother, J.E., Non-linear van't Hoff solubility-temperature plots and their pharmaceutical interpretation. *Int. J. Pharm.*, 18 (1984) 25–38.

Hardee, G.E., Otagiri, M. and Perrin, J.H., Microcalorimetric investigation of pharmaceutical complexes. *Acta Pharm. Suec.*, 15 (1978) 188–199.

Ikeda, M., Suga, H. and Seki, S., Thermodynamic studies of solid polyethers: 5. Crystalline-amorphous interfacial thermal properties. *Polymer*, 16 (1975) 634–640.

Irving, R.J. and Wadso, I., Use of tris(hydroxymethyl)aminomethane as a test substance in reaction calorimetry. *Acta Chem. Scand.*, 18 (1964) 195–201.

James, K.C., *Solubility and Related Properties, Drugs and the Pharmaceutical Sciences*, No. 28, Dekker, New York, 1968, p. 140.

Kagemoto, A., Itoi, Y., Baba, Y. and Fujishiro, R., The heats of dilution of the oligomeric ethylene oxide/alcohol solutions. *Makromol. Chem.*, 150 (1971) 255–261.

Lakhanpal, M.L., Singh, H.G., Singh, H. and Sharma, S.C., A comparative study of heats of mixing of polyoxyethylene glycol-water and polypropylene glycol-water systems. *Ind. J. Chem.*, 6 (1968) 95–98.

Malcolm, G.N. and Rowlinson, J.S., The thermodynamic properties of aqueous solutions of polyethylene glycol and dioxane. *Trans. Faraday Soc.*, 53 (1957) 921–930.

Maron, S.H. and Filisko, F.E., Heats of solution and dilution for polyethylene oxide in several solvents. *J. Macromol. Sci.-Phys.*, B6 (1972) 79–90.

Molyneaux, P., Synthetic polymers. In Franks, F. (Ed.), *Water: A Comprehensive Treatise*, Vol. 4, Plenum, New York, 1975, chap. 7, pp. 618–634.

Paruta, A.N., Thermodynamics of aqueous solutions of alkyl *p*-aminobenzoates. *Drug Dev. Ind. Pharm.*, 10 (1984) 453–465.

Pikal, M.J. and Dellerman, K.M., Stability testing of pharmaceuticals by high-sensitivity isothermal calorimetry at 25°C: cephalosporins in the solid and aqueous solution states. *Int. J. Pharm.*, 50 (1989) 233–252.

Takagi, S. and Kimura, T., Thermal analysis on distribution and dissolution of medicinal preparations by solution calorimetry. *Kinki Dai. Riko. Kenk. Hokoku*, 20 (1984) 97–106.

Walden, P., Uber die Schmelzwarne, Spezifische Kohasion und Molekulargrosse bei der Schmelztemperatur. *Z. Elektrochem.*, 14 (1908) 713–724.