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Rapid communication

High speed DSC (hyper-DSC) as a tool to measure the solubility of a drug within a solid or semi-solid matrix.

Daniela Gramaglia [a], Barbara R. Conway [b], Vicky L. Kett [c], R. Karl Malcolm [c], Hannah K. Batchelor [b,*]

[a] *Department of Pharmaceutical Chemistry, University of Pavia, Via Taramelli 12, 27100 Pavia, Italy*
[b] *Medicines Research Unit, Aston University, Birmingham B4 7ET, UK*
[c] *School of Pharmacy, Queen's University of Belfast, 97 Lisburn Road, Belfast BT9 7BL, UK*

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Abstract

Conventional differential scanning calorimetry (DSC) techniques are commonly used to quantify the solubility of drugs within polymeric-controlled delivery systems. However, the nature of the DSC experiment, and in particular the relatively slow heating rates employed, limit its use to the measurement of drug solubility at the drug's melting temperature. Here, we describe the application of hyper-DSC (HDSC), a variant of DSC involving extremely rapid heating rates, to the calculation of the solubility of a model drug, metronidazole, in silicone elastomer, and demonstrate that the faster heating rates permit the solubility to be calculated under non-equilibrium conditions such that the solubility better approximates that at the temperature of use. At a heating rate of 400 °C/min (HDSC), metronidazole solubility was calculated to be 2.16 mg/g compared with 6.16 mg/g at 20 °C/min.

Keywords: High-speed DSC; Solubility; Metronidazole; Silicone

1. Introduction

The release characteristics of drugs from diffusion-controlled polymeric delivery systems are largely determined by the solubility and diffusivity of the drug within the cross-linked polymer network (Chien, 1992). However, quantifying the solubility of any substance within a polymer network is not straightforward. Simple saturation/filtration solubility studies, as performed for liquid solvents, are clearly not possible, and exhaustive release into a suitable medium will not discriminate between dispersed and dissolved drug (Ahmed et al., 2004). Historically, microscopy has been used to measure solubility within semi-solid or transparent solids with a lack of crystals indicating that all drug present is dissolved. The residual liquid separated from an ointment on storage has been used to

* Corresponding author. Tel.: +44 121 204 3903.
E-mail address: h.k.batchelor@aston.ac.uk (H.K. Batchelor).

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estimate the solubility of a drug within it (Koboyashi and Saitoh, 1998). X-ray powder diffractometry has been used to measure the solubility of salicylic acid in a hydrogel (Suryanarayanan et al., 1992), whereby the intensities of the salicylic acid peaks in the diffraction trace were linearly related to its weight percent in the formulations, permitting the solubility of the acid in the hydrogel to be estimated from the intercept. However, large degrees of variance were associated with this method (Suryanarayanan et al., 1992). The solubility of a drug in silicone oil has been used as a predictor for solubility within a silicone elastomer matrix (Malcolm et al., 2003a,b, 2004; Woolfson et al., 2003); this method assumes that the solubility characteristics within the relatively low molecular weight oil are similar to those within the cross-linked elastomer. The use of differential scanning calorimetry (DSC) for the quantitative measurement of the solubility of solid drugs dispersed in polymeric matrices was first described by Theeuwes et al. (1974). The method was based on the simple principle that the fraction of drug solubilised within the matrix does not contribute to the melting endotherm associated with the dispersed drug fraction. Thus, by plotting the measured ΔH_f values versus the drug concentrations for a range of loadings and extrapolating to zero ΔH_f, the solubility of the drug in the polymer could be estimated. However, the use of a relatively slow 10 °C/min scanning rate, as is typical for polymeric systems, provides sufficient time for the molecules within the crystal lattice of the drug substance to respond to the input of energy during the heating ramp by detaching from the lattice and further dissolving in the polymer matrix. As a consequence, the solubility value determined is that at the melting temperature of the drug. This DSC method has since been used to determine the solubility of propanolol (Bodmeier and Paeratakal, 1989), salicylic acid and chlorpheniramine (Jenquin and McGinity, 1994), penciclovir (Ahmed et al., 2004), and oxybutynin (Malcolm et al., 2002) in a range of polymer systems. A similar dynamic mechanical method has also been used to estimate drug solubility within silicone elastomer. Changes in storage modulus ($\Delta G'$) associated with melting of the drug within the silicone matrix were linearly related to drug loading, and extrapolation to zero $\Delta G'$ provided an estimate of solubility, once again at the drug's melting point (Malcolm et al., 2002).

Hyper DSC (HDSC) may overcome the disadvantage associated with conventional thermal methods such as DSC and DMTA for determining solubility in polymer systems whereby solubility can only be measured at the drug melting temperature. The fast heating rates do not inhibit the sample from responding to the energy imputed (as seen by no changes in heats of fusion for melt transitions between heating rates) but can affect and inhibit kinetically controlled transitions such as recrystallisation, polymorph interconversion (McGregor et al., 2004); therefore, in this case the high heating rates may inhibit further solubilisation due to the increase in solubility profile caused by increasing the temp that may otherwise occur during slower scans. In order to demonstrate the utility of this approach, this study describes the use of HDSC to measure the solubility of the model drug metronidazole within silicone elastomer.

2. Materials and methods

Crystalline metronidazole (M3761) was purchased from Sigma, UK. A two-part, platinum-catalysed silicone elastomer system, Silastic 9280/60E was purchased from Dow Corning, USA.

2.1. Preparation of the silicone films

Parts A and B of the silicone elastomer kit were blended in a 1:1 ratio to produce the silicone elastomer mix. Metronidazole was added and mixed (1, 2.5, 5, 7.5 and 10%, w/w) to produce active elastomer mixes. Each mix was then placed between two glass microscope slides separated by 1-mm spacers before curing in a preheated oven at 80 °C for 24 h and then at 120 °C for 1 h. The resulting matrices were refrigerated in airtight containers until required.

2.2. HDSC experimental protocol

HDSC experiments were carried out using a diamond DSC (Perkin-Elmer, Pyris series 5.0), calibrated for temperature and enthalpy at each heating rate using an indium standard (Perkin-Elmer). Samples (4.55 ± 0.45 mg) were cut from the metronidazole-loaded silicone matrices and placed in hermetically

sealed aluminium pans (Perkin-Elmer); an empty pan was used as a reference in all cases.

Measurements were performed over a temperature range to include the melting temperature of the drug (20–250 °C). Heating rates of 20, 100 and 400 °C/min were used within the study. Helium was used as the purge gas (20 mL/min). The calculation of the area under the transition peak permitted the evaluation of the energy associated with the phase transition, ΔH_f and so the calculation of solubility. The area under the melting endotherm was calculated from the onset to the end of the peak using the Pyris series 5 data analysis package, (Perkin-Elmer). A blank (non-drug-containing) silicone film was also measured to ensure that there were no background thermal events. It has already been demonstrated that linear control of heating rate can be achieved at scan rates up to 500 °C/min using this equipment (Saunders et al., 2004).

3. Results and discussion

The DSC scan of the blank silicone matrix demonstrated a flat baseline with no thermal events over the temperature range investigated. Pure metronidazole demonstrated a melting endotherm at 160 °C at all scanning rates. The enthalpy of fusion was 163 ± 3, 158 ± 3 and 162 ± 5 J/g at heating rates of 20, 100 and 400 °C/min, respectively, with no significant difference in this value at all heating rates investigated. However, the size of the endotherm increased dramatically as the scan rate increased, this is because DSC output is measured in mW (mJ/s); therefore, faster heating rates increase the size of the power signal due to an alteration in heat capacity (J/(g °C)). Fig. 1 clearly shows that increasing the heating rate increases the peak magnitude, this trend is similar to that observed by Saunders et al. (2004).

Metronidazole-loaded silicone matrices (1, 2.5, 5, 7.5 and 10%, w/w) were prepared and investigated at scan rates of 20, 100 and 400 °C/min. Fig. 2 shows the effect of increasing drug concentration on the melting endotherm, with higher concentrations causing the size of the melting endotherm to increase, as it relates to the concentration of undissolved drug present in the formulation at the melting temperature. By plotting ΔH_f against the drug loading concentration and extrapolating to zero ΔH_f, as in Fig. 3, the solubility of metronidazole in the silicone matrix may be determined. Linear trend lines were fitted using Microsoft Excel with regression values in each case being greater than 0.99. The solubility values, calculated as the *x*-intercept using these trend lines, were: 0.616% (w/w) (20 °C/min), 0.493% (w/w) (100 °C/min) and 0.216% (w/w) (400 °C/min). Microscopically, the solution process of a drug crystal in a polymer composition can be visualised as consisting of two consecutive steps: (i) the dissociation of drug molecules from the crys-

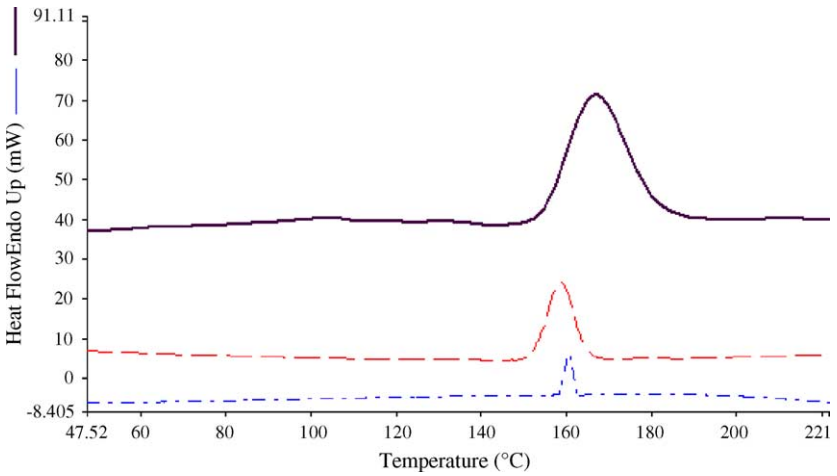

Fig. 1. Typical melting endotherms obseved for metronidazole (10%, w/w) in silicone at heating rates of 20 (– – –), 100 (– – –) and 400 °C/min (—).

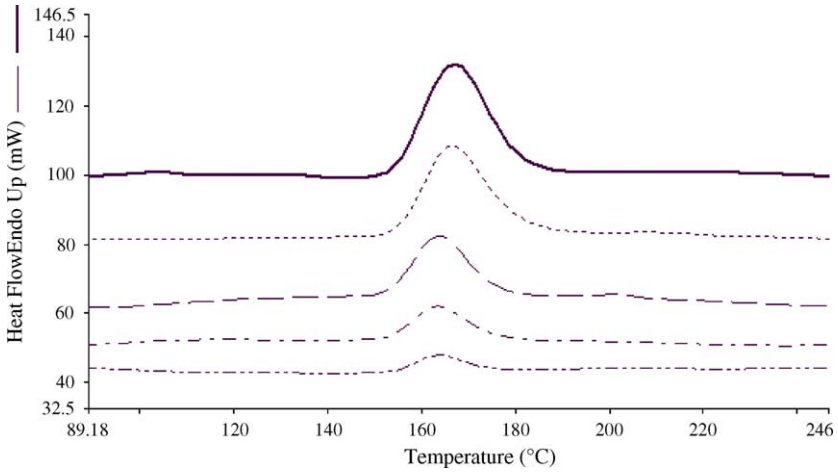

Fig. 2. DSC Data at 400 °C/min heating rate of the 1 (– - - –), 2.5 (– – –), 5(– – –), 7.5 (- - -) and 10% (—) (w/w) metronidazole:silicone samples.

tal lattice and (ii) the solvation of these dissociated molecules into the surrounding polymer. Given that the first step is also involved in the melting process, it is apparent that the observed decrease in solubility with increasing heating rate must be largely attributed to the time-dependent solvation process. The faster heating rates provide insufficient time for the drug molecules to dissolve in the polymer. This study shows that the solubility calculated was dependant on the scan rate used, however, the faster the scan rate the better the prediction of solubility as the kinetic events are minimised.

The 0.616% (w/w) solubility value for metronidazole in silicone elastomer obtained at 20 °C/min using conventional DSC is comparable to that calculated previously for the solubility of metronidazole in low viscosity silicone oil (0.006 mg cm^{-3} or 0.06%, w/w) (Malcolm et al., 2003a,b). However, the former value is likely to overestimate the solubility for the reasons outlined earlier, while the latter value does not take account of the very real physicochemical differences between liquid silicone and silicone elastomer, as discussed in previous studies (Malcolm et al., 2002). The value of 0.216% (w/w) obtained by the HDSC method at 400 °C/min is a more realistic estimate in that it is measured in silicone elastomer under conditions that serve to minimize the effects of temperature on solubility.

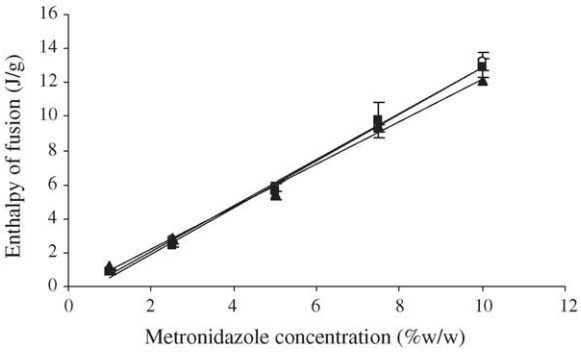

Fig. 3. An example of a plot of metronidazole concentration against the enthalpy of fusion ((◯) 20, (■)100 and (▲) 400 °C/min heating rate), $n = 4$.

4. Conclusions

This study has shown that hyper DSC offers a simple, fast and effective way to measure the solubility of a drug within a solid polymer matrix. Faster heating rates reduce further dissolution of drug into the matrix with heating and thus a more realistic estimation of silicone solubility at working temperature is provided. In this case a solubility of 0.216% (w/w) metronidazole in silicone was predicted using HDSC. Solubility prediction is dependant upon the scan rate used, the high speed DSC enables data to be collected at higher heating rates with no loss in quality of data, thus fast scan rates should be used where possible.

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