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Monitoring crystallisation of drugs from fast-dissolving oral films with isothermal calorimetry

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ABSTRACT

The aim of this study was to evaluate the potential of isothermal calorimetry to monitor and characterize crystallisation in drug-loaded fast-dissolving oral films.

Films of polyvinylpyrrolidone (PVP) containing indomethacin were cast into glass ampoules; stability was assessed by monitoring the power changes occurring with time. Three grades of PVP (K10, K25 and K40, where the number multiplied by 1000 gives the average molecular weight) were used. Indomethacin was seen to crystallise from all PVP grades over ca. 24–48 h at two study temperatures (25 and 37 °C), as denoted by a large exothermic event. At 25 °C the exothermic event was a single peak; at 37 °C two peaks were observed. Subsequent analysis of the crystals with differential scanning calorimetry (DSC) and polarized light microscopy determined that the stable γ-polymorph of indomethacin formed at 25 °C while both the γ- and metastable α-polymorphs formed at 37 °C. The calorimetric data were converted to relative crystallinity as a function of time and analysed with three crystallisation models (Avrami, Tobin and Urbanovici–Segal) to determine crystallisation kinetics. Of the three models applied the Urbanovici–Segal model best described the data, although this may be because this model contains a term that effectively accounts for deviation from the Avrami model. The rate constants determined were broadly consistent irrespective of the model used. Increasing polymer molecular weight did not generally affect the crystallisation rate, although an increase in temperature did result in a concomitant increase in crystallisation rate. The data suggest that isothermal calorimetry is able to monitor drug crystallisation in polymer films and therefore the technique could be a useful tool for conducting stability assays for fast-dissolving oral medicines.

1. Introduction

Fast-dissolving thin polymer films for rapid oral delivery are becoming an increasingly popular formulation option because of their wide and varied benefits. The films are designed to dissolve upon contact with a wet surface, such as the tongue, within a few seconds, meaning the consumer can take the product without the need for additional liquid. This convenience provides both a marketing advantage and increased patient compliance. Rapid dissolution is assured because the polymeric matrix is predominantly amorphous and the drug is dispersed throughout it, either as a molecular dispersion or as discrete particles. Most commercially available formulations, such as Ora-film™,[1] (benzocaine) or Theraflu®,[2] (dextromethorphan/phenylephrine HCl, diphenhydramine HCl/phenylephrine HCl or diphenhydramine HCl), are designed to deliver locally acting drugs or for mouth-freshening (such as Listerine PocketPaks™,[3]).

Formulation of these systems is usually straightforward; the polymer and drug are dissolved (or dispersed) in a solvent (often ethanol or water) and a film is cast by solvent evaporation. Because of the high molecular weight of the polymer, films are frequently amorphous and may have complicated physical forms. In the simplest cases the films may be monophasic (if the drug is molecularly dispersed) or multiphasic (if the drug is dispersed as discrete particles); depending on solubility and miscibility factors, drug-rich or

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[1] Ora-film is a registered trademark of Apothecus Pharmaceutical Corp.
[2] Theraflu is a registered trademark of Novartis AG.
[3] Listerine Pocketpaks is a registered trademark of Pfizer Inc.

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drug-poor regions may also exist. In any case they are described by the term solid dispersion.

From a pharmaceutical perspective, determining the stability of the film is of critical importance if the formulation is to be commercially viable. If the API is freely soluble in the polymer then the system should have excellent physical stability. If the API is not freely soluble in the polymer and is present at a supersaturated concentration then stability is an issue (Latsch et al., 2003); it is likely that the API will phase-separate from the polymer phase and subsequently crystallise. Since crystallisation of a dispersed component necessarily requires movement of molecules, molecular mobility and diffusion rates will be central to the stability profile of the system; this means that both the storage temperature and the level of residual solvent in the system will be important.

Monitoring the stability of these products is not straightforward. Visual inspection of the formation of crystals over time is possible, but requires a significant fraction of crystallisation to have occurred. Many classical analytical techniques cannot make measurements directly on heterogeneous samples where, as in this case, maintenance of physical form during the experiment is paramount. Differential scanning calorimetry (DSC) is widely used to study crystallisation of polymers, but its use is limited in cases such as the thin films discussed here where only the minor fraction of a sample is crystallising, simply because of the small sample mass of a typical experiment.

Consideration of these issues led us to consider whether isothermal calorimetry (IC) might be a suitable alternative. Heat-flow (power) is an excellent parameter to record as it changes concomitantly with any physical or chemical processes occurring in a sample. The instrument does not impose any requirements on the sample, save that it can fit within an appropriate ampoule. The use of IC to study crystallisation in transdermal drug delivery systems (TDDS) has been reported for a number of actives (Latsch et al., 2003, 2004a,b). In these cases, 10 mm diameter disks were punched out of cast films and built up in layers in the calorimetric ampoule. One effect of this was that the shear forces imparted during punching caused increased crystallisation at the edges of the disks. In addition to changing the rate of crystallisation, loading discs in layers may limit thermal contact between the sample and the instrument. Here, we used a film forming apparatus (V-10 Evaporator, Biotage Ltd.) to cast drug-loaded thin polymer films directly onto the walls of the calorimetric ampoule; this approach overcomes both the drawbacks discussed above and results in a film of comparable thickness and physical form to one cast by conventional methods.

Thus the aim of the study was to evaluate the potential of IC to monitor and characterise crystallisation in fast-dissolving oral films. We chose indomethacin as our model drug because it is relatively unstable (with respect to crystallisation) in the amorphous form (Imaizumi et al., 1983) and rapidly crystallises to one of two polymorphs; γ- (or form I, m.p. 161 °C, Latsch et al., 2004a) and α- (or form II, m.p. 155 °C, Andronis and Zografi, 2000). In addition, a lot of work has been conducted on the mechanisms of crystal growth of indomethacin from the amorphous state (Andronis and Zografi, 1997, 1998, 2000; Andronis et al., 1997; Yoshioka et al., 1994). Indomethacin was formulated as a solid dispersion with polyvinylpyrrolidone (PVP) (used previously for preparing solid dispersions of indomethacin, Matsumoto and Zografi, 1999) and cast from ethanol (a fast-evaporating solvent in which both components are soluble). Crystallisation rate data were analysed using a number of crystallisation models (JMA, Avrami, 1939; Tobin, Tobin, 1973; Urbanovici–Segal, Urbanovici and Segal, 1990); the JMA model is a classical description of crystal growth which tends to fail at high fractions of crystallisation because it does not account for crystal growth impingement, while the Tobin model is modified to account for crystal growth impingement. The Urbanovici–Segal model contains an extra term that accounts for other deviations from the JMA model, such as the fact that this study involves crystallisation of one phase from a polymer matrix. Selection of the most appropriate model for analysis of crystallisation of actives from thin polymer films is discussed.

2. Materials and methods

γ-Indomethacin (USP grade) and various molecular weight PVP grades (K10, K25 and K40) were purchased from Sigma–Aldrich Ltd. (UK). Ethanol and methanol (both >99.5%) were purchased from Hayman Ltd. (UK). PVP (all grades), methanol and ethanol were used as received. γ-Indomethacin was purified by recrystallisation from ethanol. The α-form of indomethacin was prepared using the method of Yoshioka et al. (1994). Indomethacin (3 g) was dissolved in methanol (3 mL) at 80 °C. The solution was filtered through a 0.22 μm filter (Millipore) and then added to distilled water (20 mL) at room temperature. The α-polymorph precipitated and was collected with a Buchner funnel. Both polymorphs were subsequently stored in a desiccator under silica gel. The identities of the two polymorphs were confirmed with DSC, the α-form showing a melting endotherm at 155 °C and the γ-form showing a melting endotherm at 161 °C (data not shown), in agreement with literature values (Andronis and Zografi, 1997).

Solutions were prepared by dissolving drug (7.5 g) and the appropriate PVP grade (2.5 g) in ethanol (100 mL) with rapid stirring. An aliquot of the resulting solution (8 mL) was pipetted into a 20 mL glass ampoule (TA Instruments Ltd., UK) and loaded into the evaporator (V-10, Biotage Ltd., UK). The ampoule was spun at 6000 rpm and placed under vacuum (30 Pa). The instrument monitored the temperature of the solution with an infra-red thermometer; as solvent evaporated the temperature reduced, in this case to ca. 15 °C. Once all solvent had been removed the temperature rose and the instrument applied a drying programme by blowing hot air on the ampoule. Once the ampoule reached 30 °C, the drying stopped and the ampoule (now with a film cast on its inner surfaces) was removed. This process was repeated three times to build up the thickness of the film. Each ampoule was weighed before and after film formation; because the volume (24 mL in total) and concentration of solution were known, the mass data could be used to determine the ethanol content of the film. All cast films were translucent and yellow in colour, confirming that the drug was molecularly dispersed in the polymer matrix.

Ampoules were sealed (by means of a crimped aluminium cap with a rubber liner), transferred immediately to the calorimeter (TAM, TA Instruments Ltd.), allowed to reach thermal equilibrium (ca. 20 min) and then lowered to the measuring position of the instrument. The time taken from film casting to the commencement of data capture was always 30 min exactly, and this time period was added to the raw calorimetric data before analysis. Data (plotted with exothermic values as positive) were recorded with the dedicated software package Digitam 4.1 (one data point every 30 s, amplifier range 300 μW) for a minimum of 24 h. Experiments were conducted in triplicate and at two temperatures (25 and 37 °C, representing a typical storage condition and body temperature, respectively). All experiments used an empty glass ampoule as a reference. Data analysis, including model fitting by least squares minimization, was performed with Origin 7 (Microcal Software Inc., USA). The TAM was calibrated prior to use by the electrical substitution method. Experiments were performed in triplicate. Data are plotted as a mean ± rangebars.

DSC measurements were made with a Pyris 1 DSC (PerkinElmer Ltd.). Samples (ca. 2–5 mg) were sealed in non-hermetic aluminium pans and heated from 25 to 190 °C at 200 °C min^{-1} with a nitrogen purge gas. An empty pan was used as a reference and the instrument

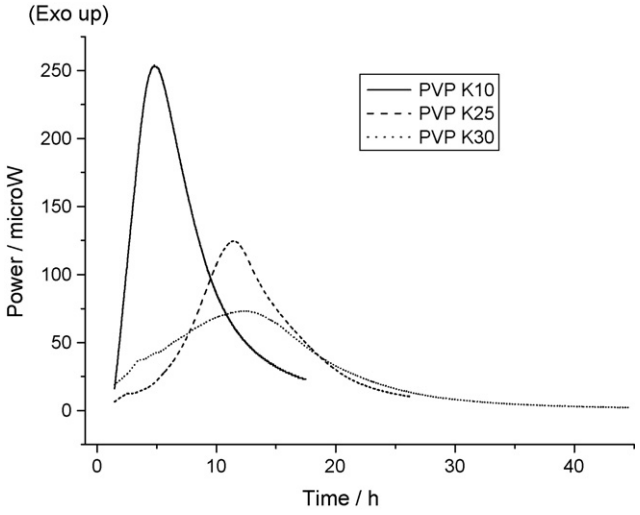

Fig. 1. Power–time data observed for indomethacin-PVP (all grades) films at 25 °C.

was calibrated for temperature and heat-flow with indium at the start of each day.

Polarized light microscopy images were taken with a Nikon Microphot-FXA microscope equipped with a 40× oil emulsion lens.

3. Results and discussion

Typical calorimetric data recorded for the three grades of PVP film, as a function of temperature, are shown in Figs. 1 and 2. Large exothermic peaks are seen in all cases, indicative of a crystallisation event. Upon removal from the calorimeter, visual inspection revealed that all the films that showed an exothermic peak contained crystallised drug. In some cases, crystallisation was not observed within the 48 h measurement period, although a pre-exponential phase was seen, indicating variability in crystallisation kinetics; this could be dependent upon film thickness. Because the films were cast while spinning, sometimes a thicker 'wave-like' region was observed in the film as it set and hence there was some variability in final film thickness. One consequence of this is that the mechanism of crystallisation will change depending upon whether the film is 'thick' or 'thin'. Trofimov et al. (2006) defined a thick film as one where the ratio of its height to area is greater than or equal to 5. Using a modified form of the Avrami equation (defined below) they showed that thin films follow a surface-induced crystallisation (SIC) model while thick films follow a volume-induced crystallisation (VIC) model. In practice, this means that for a thin film nucleation starts from a surface or interface while a thick film nucleates uniformly throughout the film's volume. It is likely that the films cast in this study are 'thin' in most areas according to this definition, but 'thick' in the wave regions.

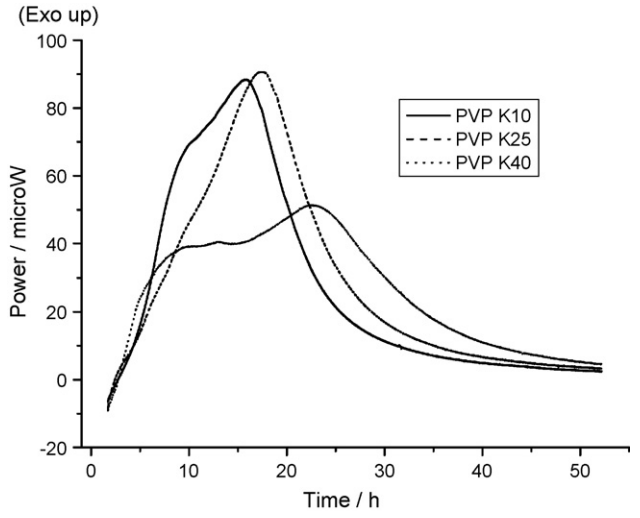

Fig. 2. Power–time data observed for indomethacin-PVP films (all grades) at 37 °C.

One major drawback of the calorimetric approach is that the calorimeter records powers from all events occurring in the sample and hence in this case the observed 'overall' power–time data may not result solely from a crystallisation process. All power–time data shown in Figs. 1 and 2 were preceded by a decaying exothermic signal (not plotted for clarity). Events that may contribute to this initial region are friction from loading, relaxation of the amorphous regions of the film and solvent evaporation into the head space. It is likely that the friction effects occur relatively rapidly (within the first 30 min) although evaporation and relaxation of the film are likely to occur throughout the measurement period. However, the power value fell in all cases very near to zero prior to the crystallisation peak, so while it was not possible to subtract this effect, it is reasonable to assume that it is a minor component of the data used to determine crystallisation kinetics.

The aim of this study was to focus on the use of calorimetry to monitor the stability of drug-loaded polymer films, and to demonstrate methods for quantitative analysis, rather than to develop a robust formulation, and so we opted not to optimise the film-forming process, which does mean there is some inherent variability in the data. However, it is immediately apparent from the data in Fig. 1 that at 25 °C one crystallisation event is seen, whereas in Fig. 2 at 37 °C two events are discernable.

Dealing with the 25 °C case first, the films were removed from the calorimeter and examined with polarized light microscopy. The images showed only needle-like crystals, indicative of the γ-polymorph, Fig. 3. DSC analysis of the crystals showed a melting point of 161 °C, Fig. 4, consistent with the γ-form.

The polarized light microscopy images at 37 °C showed the presence of both the needle-like crystals of the γ-form and the spherule-like crystals of the α-form, Fig. 3, suggesting that the two exotherms seen in the calorimetric data corresponded with crystallisation to each polymorph. DSC analysis of the crystals gave melting points of 155 and 164 °C, Fig. 4 respectively, confirming the presence of both the α- and γ-polymorphs.

Observation of the formation of both polymorphs of indomethacin below its glass transition temperature (T_g, 42 °C Latsch et al., 2004a) is unusual in light of much work suggesting that at temperatures below T_g the drug crystallises only to the γ-form but above T_g both polymorphs crystallise (Andronis and Zografi, 1997, 2000), although in the present work the drug is present as a molecular dispersion in a polymeric matrix, rather than as a single phase, which will inevitably alter the position of T_g and the relaxation. Andronis et al. (1997) note that since Ostwald's step-rule (Ostwald, 1897) proposes that formation of phases will progress through a series of available crystalline states in order of decreasing entropy, it might thus be expected that the α-form would appear before the γ-form; they also comment that phase selection will depend on both the kinetics and thermodynamics of crystallisation and that phase selection will be dependent upon the activation energy barrier to nucleation (ΔG^*):

$$\Delta G^* = \frac{16\pi\sigma^3}{3\Delta G_v^2} \quad (1)$$

where σ is the crystal–amorphous interfacial energy and ΔG_v is the Gibbs free energy change per unit volume for transformation of the amorphous phase to the crystalline phase. Since ΔG_v is the dominant term and is greater for the stable crystalline phase,

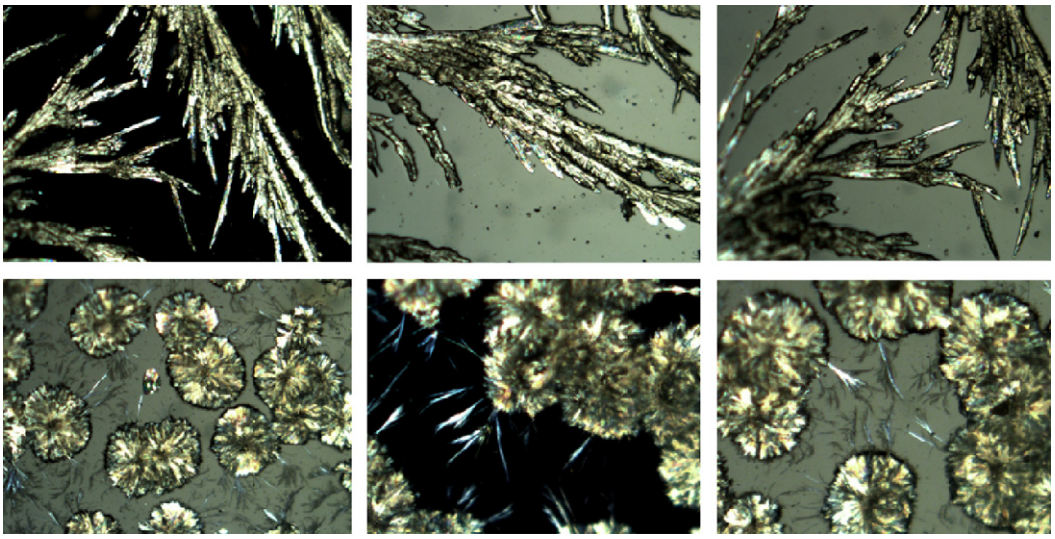

Fig. 3. Polarized light microscopy images of indomethacin-PVP films after removal from the calorimeter. Top row (l-r): PVP K10, PVP K25, PVP K40 all at 25 °C. Bottom row (l-r): PVP K10, PVP K25, PVP K40 all at 37 °C.

the activation energy barrier will be lower for this form and its formation will be favoured if the mechanism of crystallisation is nucleation controlled. Andronis et al. (1997) note, however, that under some circumstances the interfacial free energy can be lower for the metastable crystal–amorphous interface and this will favour nucleation of the metastable form. It is the fine balance in these terms that governs which phase crystallises and it appears that in our system the balance point has been shifted to slightly lower

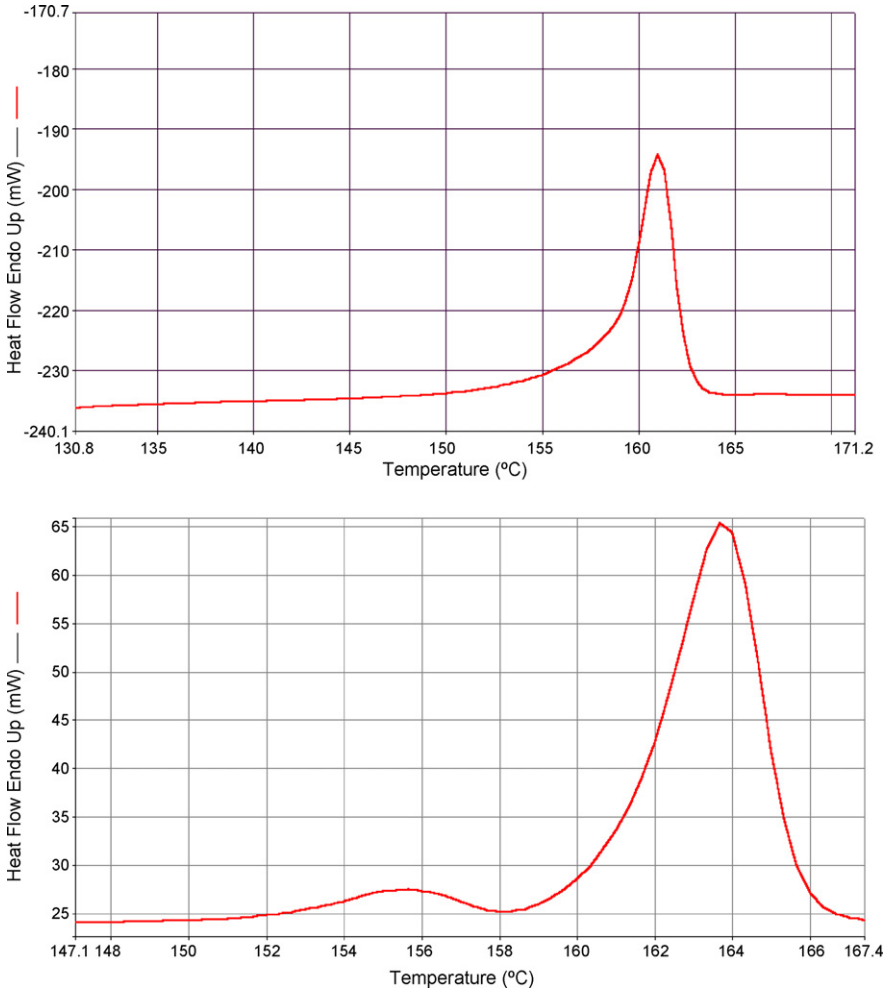

Fig. 4. DSC data for indomethacin-K10 films after removal from the isothermal calorimeter. Top: after storage at 25 °C. Bottom: after storage at 37 °C.

Table 1
Summary of the kinetic parameters obtained by fitting the crystallisation data for the PVP-indomethacin films at 25 °C to the Avrami, Tobin and Urbanovici–Segal models with least squares minimization. See text for a discussion of these values.

Model	K10			K25			K40		
	K (h^{-1})	n	r	K (h^{-1})	n	r	K (h^{-1})	n	r
Avrami	0.004 ± 0.0039	2.8 ± 0.6	n/a	0.0008 ± 0.0007	2.8 ± 1.0	n/a	0.016 ± 0.014	1.8 ± 0.4	n/a
Tobin	0.089 ± 0.049	3.9 ± 0.8	n/a	0.059 ± 0.019	3.6 ± 1.2	n/a	0.09 ± 0.005	2.4 ± 0.5	n/a
U–S	0.099 ± 0.061	4.3 ± 0.1	2.5 ± 0.8	0.052 ± 0.025	3.3 ± 1.6	1.4 ± 0.5	0.07 ± 0.005	2.0 ± 0.4	1.3 ± 0.2

than 42 °C, although the data are consistent with previous studies in that the stable polymorph crystallises at low storage temperatures while both polymorphs crystallise near the T_g. The data also show the importance of studying the stability of formulated products directly, rather than relying on stability data of individual components.

With any stability assay it is important to be able to be able to determine a rate constant, since this allows quantitative comparison of formulations. Here the active is crystallising and hence it is possible to construct a plot of relative crystallinity (θ_t) as a function of time because:

$$\theta_t = \frac{\int_0^t (dq/dt)\,dt}{\int_0^\infty (dq/dt)\,dt} = \frac{q}{Q} \quad (2)$$

where q is the heat change to time t and Q is the total heat change upon complete crystallisation. The resulting isotherms can subsequently be analysed with an appropriate model. Frequently the Avrami model (Avrami, 1939) is employed:

$$\theta_t = 1 - \exp[-(K_a t)^{n_a}] \quad (3)$$

where K_a is the Avrami rate constant and n_a the Avrami exponent. The rate constant gives a quantitative parameter for expressing the stability of a system (it is first-order and has units of time^{-1}) while the exponent (which should be an integer) gives information of the mechanism of nucleation and crystal growth. While it is widely used, the Avrami model does have limitations, especially during the later stages of crystallisation where it assumes no crystal impingement. It also assumes that the nucleation rate is either zero (i.e. there are pre-existing nuclei) or that it is constant (Sun et al., 1996). Many modifications to the Avrami model have been proposed. Recently Supaphol (2001) compared the use of the Avrami model with several other models for the crystallisation of syndiotactic polypropylene. One of these models, developed by Tobin (1973), attempts to account for crystal growth impingement and is given by:

$$\theta_t = \frac{(K_t t)^{n_t}}{1 + (K_t t)^{n_t}} \quad (4)$$

where K_t is the Tobin rate constant and n_t is the Tobin exponent. A further model, which is in effect a generalization of the Avrami model, was proposed by Urbanovici and Segal (1990):

$$\theta_t = 1 - [1 + (r+1)(K_{us} t)^{n_{us}}]^{1/(1-r)} \quad (5)$$

where K_{us} is the Urbanovici–Segal rate constant, n_{us} is the Urbanovici–Segal exponent and r is a parameter that satisfies the condition $r > 0$. When $r = 1$, Eq. (5) reduces to the Avrami equation. Supaphol (2001) notes that the physical meaning of the term r is unclear, and it may be the case that it is simply a parameter that determines the degree of deviation of the Urbanovici–Segal model from the Avrami model. For both the Tobin and Urbanovici–Segal models, the terms K and n (with respective subscripts) retain the same physical meaning and units as those of the Avrami model, although in the case of the Tobin model the value of the exponent need not be integral.

Again, dealing with the 25 °C data first as these exhibited only a single crystallisation event, plots of relative crystallinity as a function of time were constructed for each PVP grade, Fig. 5. The data were then fitted to the three models discussed above by least squares minimization. The fits obtained are also plotted in Fig. 5, while the fitting parameters are given in Table 1. Visually it is apparent that the Urbanovici–Segal model gives a better fit than either the Avrami or Tobin models, although this is perhaps not unexpected given the comments on the r-parameter noted earlier and the fact that the study system contained a number of components.

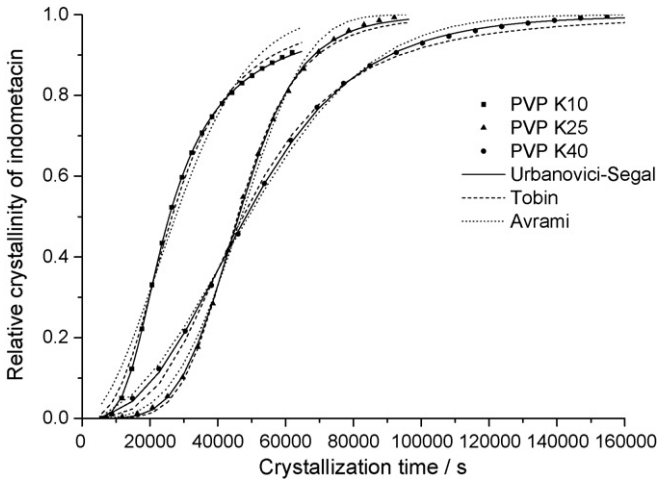

Fig. 5. Relative crystallinity of indomethacin as a function of time for PVP-indomethacin films at 25 °C and the fit lines obtained by fitting to the Urbanovici–Segal, Tobin and Avrami models. Note that the experimental data are plotted with only 20 points for clarity.

Several trends are apparent in the data. Firstly, all three models gave broadly consistent rate constants, although the exponent values varied greatly. From the perspective of a stability assay this is encouraging, as knowledge of the overall rate of crystallisation is arguably more important that knowing the mechanism. The rates of crystallisation are relatively fast (PVP itself has been shown to stabilise indomethacin in the amorphous state, Imaizumi et al., 1983, at least when present in small amounts). This may be ascribed to the relatively high ethanol contents of the cast films (around 20% v/w, Table 2), which will plasticise the film and increase the molecular mobility of the drug. Secondly, the rate of crystallisation does not decrease (within error) with increasing PVP molecular weight. This is a little surprising, given that molecular mobility and diffusion of the drug through the polymer matrix are likely to be rate limiting factors in crystallisation, but it may be the case that the degree

Table 2
Ethanol contents for each PVP-indomethacin film as a function of temperature.

PVP grade	Temperature (°C)	Ethanol content (% v/w)
K10	25	17.7 ± 0.5
K10	37	20.9 ± 3.5
K25	25	21.5 ± 3.0
K25	37	19.5 ± 0.7
K40	25	22.8 ± 2.7
K40	37	19.5 ± 3.7

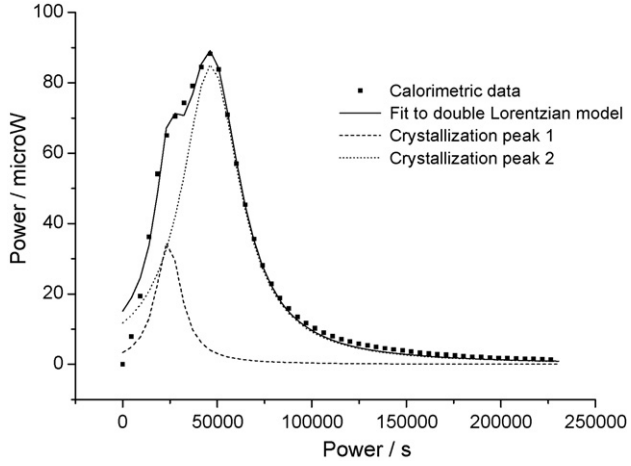

Fig. 6. Power–time data for an indomethacin-PVP K10 film at 37 °C and the fit lines obtained by fitting to a double-Lorentzian model. Note that the experimental data are plotted with only 50 points for clarity.

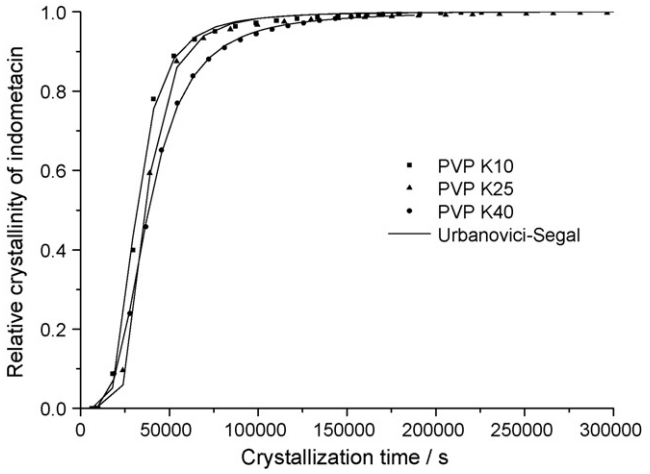

Fig. 7. Relative crystallinity of indomethacin (first crystallisation) as a function of time for PVP-indomethacin films at 37 °C and the fit lines obtained by fitting to the Urbanovici–Segal model. Note that the experimental data are plotted with only 20 points for clarity.

of cross-linking between PVP grades is constant that the micro-environment experienced by the drug is the same for all polymers. Thirdly, the exponent values did not correlate with increasing polymer molecular mass, nor did they suggest a consistent mechanism. This may be because the models used are optimised for homogeneous systems (i.e. pure drug), rather than the solid dispersions studied here, or may reflect the general variability in crystallisation behaviour in the films, presumably because of the effects of film thickness noted earlier. Finally, the value of the *r*-parameter reduces with increasing molecular mass. This may suggest that as the polymer mass increases crystallisation becomes more 'Avrami-like'. This is tentatively supported by the fact that for PVP K40 the exponent values of ca. 2–3 are much more consistent with what would be expected from this type of system, suggesting crystal growth in three dimensions.

The data recorded at 37 °C are more difficult to analyse, because the two crystallisation events overlap and hence a method of separating them must be used. It was found that a double-Lorentzian model satisfactorily described the data (Fig. 6) and allowed separation of events. One consideration with this approach is that the curves so obtained are completely symmetrical, which is not the case with the real data, given the effects of crystal growth impingement noted earlier. The individual curves were then analysed as above (Figs. 7 and 8). Since the Urbanovici–Segal model was found to describe the 25 °C data best, this model only was used to analyse the 37 °C data; the parameters obtained are given in Table 3 (first crystallisation event) and 4 (second crystallisation event) and

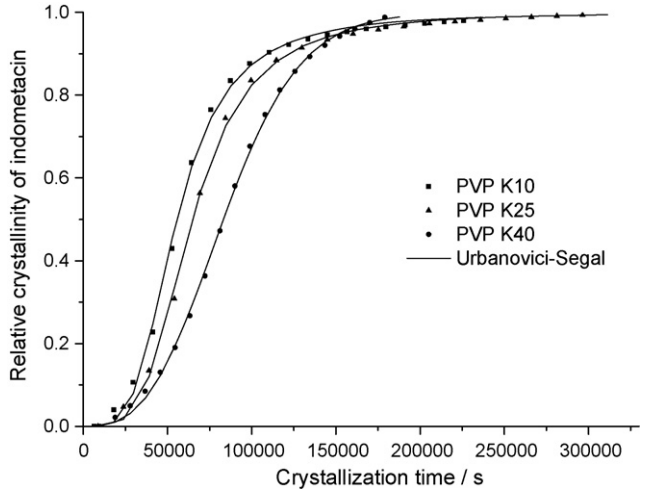

Fig. 8. Relative crystallinity of indomethacin (second crystallisation) as a function of time for PVP-indomethacin films at 37 °C and the fit lines obtained by fitting to the Urbanovici–Segal model. Note that the experimental data are plotted with only 20 points for clarity.

Table 3
Summary of the kinetic parameters obtained by fitting the crystallisation data for the PVP-indomethacin films (first phase) at 37 °C to the Urbanovici–Segal model with least squares minimization. See text for a discussion of these values.

Model	K10[a]			K25			K40		
	K (h^{-1})	n	r	K (h^{-1})	n	r	K (h^{-1})	n	r
U–S	0.106	4.0	1.4	0.121 ± 0.03	5.1 ± 0.2	2.3 ± 1.0	0.098 ± 0.006	3.2 ± 0.3	2.0 ± 0.05

[a] Only one sample of the K10 film crystallised within 48 h.

Table 4
Summary of the kinetic parameters obtained by fitting the crystallisation data for the PVP-indomethacin films (second phase) at 37 °C to the Urbanovici–Segal model with least squares minimization. See text for a discussion of these values.

Model	K10[a]			K25			K40		
	K (h^{-1})	n	r	K (h^{-1})	n	r	K (h^{-1})	n	r
U–S	0.059	3.1	1.3	0.06 ± 0.01	3.0 ± 0.2	1.7 ± 0.4	0.037 ± 0.001	2.5 ± 0.2	1.2 ± 0.4

[a] Only one sample of the K10 film crystallised within 48 h.

the fit lines are drawn in Figs. 7 and 8. Again, the exponent values are highly variable and in some cases have non-physical meanings, although the rate constants are of a consistent order of magnitude with the 25 °C data. Assuming that the first crystallisation at 37 °C is to the γ-form, then the rate constants are generally faster at the higher temperature, as would be expected. There is no trend in the *r*-parameter, although it should be remembered that it is not real experimental data that are being fitted (Tables 3 and 4).

4. Summary

Assessing the stability of thin films containing a drug is not straightforward; the present study has demonstrated that IC has the potential to monitor stability non-invasively by recording the heat of crystallisation of the drug. Further, quantitative analysis of the data is possible by converting the data to relative crystallinity as a function of time and fitting to a crystallisation model. Casting the films directly in the ampoule avoids the formation of crystal nucleates caused when cutting discs of films cast conventionally. Of the three models applied the Urbanovici–Segal model best describes the data, although this may be because this model contains a term that effectively accounts for deviation from the Avrami model. The rate constants determined were broadly consistent irrespective of the model used. Indomethacin was seen to crystallise out of the matrix in all formulations, although the crystallisation time was highly variable, presumably because of inconsistent film thickness and ethanol content. However, some trends were apparent; at 25 °C the drug crystallised solely to the stable γ-polymorph but at 37 °C both the γ-polymorph and the metastable α-polymorph were formed. This trend is concordant with literature data, but the temperature at which the metastable polymorph forms is lower. Increasing polymer molecular mass did not change the crystallisation rate, although an increase in temperature resulted in a concomitant increase in crystallisation rate. The data suggest that isothermal calorimetry could be a useful tool for conducting stability assays for fast-dissolving oral films.

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