JPP Journal of Pharmacy and Pharmacology

JPP 2003, 55: 35–41

Received June 4, 2002
Accepted September 30, 2002
DOI 10.1211/002235702513
ISSN 0022-3573

Physical stability and enthalpy relaxation of drug–hydroxypropyl methylcellulose phthalate solvent change co-precipitates

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Abstract

The poorly water-soluble drug GWX was co-precipitated with hydroxypropyl methylcellulose phthalate (HPMCP) using a solvent change method. The two co-precipitate formulations made, with drug–HPMCP ratios of 2:8 and 5:5, were analysed using modulated temperature differential scanning calorimetry. They were found to consist of completely amorphous solid solution and a mixture of amorphous solid solution, crystalline drug and amorphous drug, respectively. Stability with respect to crystallization of the two co-precipitates and pure amorphous drug made by quench cooling was compared by storing preparations at 25°C and 40°C, under vacuum over P_2O_5, and at 75% relative humidity (r.h.). Humidity (75% r.h. compared with dry) had a larger influence on crystallization of the amorphous drug than temperature (25°C compared with 40°C). The solid solution phase in co-precipitates had a relatively higher stability than amorphous drug alone, with respect to crystallization, in presence of the plasticizer water, and crystalline drug. These findings were partly explained by evidence of decreased molecular mobility in the amorphous solid solution with respect to amorphous drug alone, using enthalpy relaxation measurements. At an ageing temperature of 65°C, the calculated half-life for enthalpy relaxation of the 2:8 drug–HPMCP ratio co-precipitate was about 6 orders of magnitude greater than that of amorphous drug alone, indicating a large difference in relative molecular mobility.

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Acknowledgement and funding: We wish to thank Hilary Cannon, Andy Theophillus, Francesca Bryant and Bob Lancaster for technical advice on characterization techniques. Laura Andrade-Benitez is thanked for assistance with graphics. GS would like to acknowledge funding support for this work by a Vernon Tews-University of Otago-GSK research fund.

Introduction

Drugs generally have a higher enthalpy in the amorphous compared with the crystalline state, and dissolution is therefore thermodynamically favoured in the former, according to the Gibbs free energy equation for dissolution (Martin et al 1983):

$$\Delta G_{diss} = \Delta H_{diss} - T\Delta S_{diss} \quad (1)$$

where G, H, T and S are Gibbs energy, enthalpy, temperature and entropy respectively, and Δ represents changes in these quantities during the dissolution process. This thermodynamic enhancement of solubility also increases the theoretical rate of dissolution according to the modified Noyes–Whitney relationship (Proudfoot 1988).

Another consequence of higher enthalpy, however, is that the thermodynamic driving force existing for amorphous drugs to change to a lower enthalpy (more stable) crystalline form is also increased (i.e., instability is inherent in amorphous drugs). Crystallization occurring either before or during contact with the dissolution medium may decrease rate or extent of dissolution.

One way of inhibiting drug crystallization and avoiding the aforementioned problems is by making an amorphous solid solution (i.e., an amorphous molecular dispersion of drug molecules among carrier molecules). If the carrier used has a lower molecular mobility than the drug, physical stability, as far as inhibition of crystallization is concerned, may be enhanced (Imaizumi et al 1983; Hilton & Summers 1986; Yoshioka et al 1995; Lipp 1998; Kachrimanis & Malamataris 1999; Matsumoto & Zografi 1999; Khouzag & Clas 2000). This is possible because even though thermodynamics still drives instability of the drug molecules in this state, kinetics may be altered to such an extent that crystallization occurs insignificantly slowly. Thus, mechanisms by which dis-

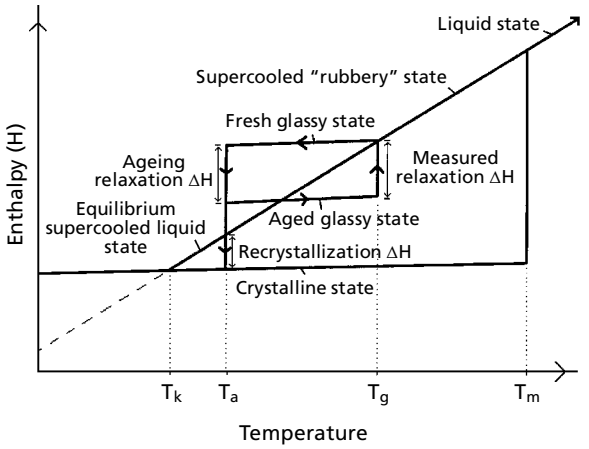

Figure 1 Schematic representation of enthalpy–temperature relationship for glasses in enthalpy relaxation processes (see text for explanation).

solution is altered are not simply due to higher enthalpy in the amorphous state, but may also involve carrier-controlled diffusion, and have recently been reviewed elsewhere (Craig 2002).

The higher enthalpy of a glass compared with its corresponding equilibrium supercooled liquid and crystalline state at the same temperature is shown in Figure 1.

Structurally, glasses are liquids whose molecules are, so-to-speak, frozen in non-equilibrium conformations, due to greatly reduced conformational mobility upon vitrification (Cowie et al 1997). Depending on temperature and presence of plasticizers, however, molecular mobility may be sufficient such that by conformational rearrangement, molecules may relax and lose their excess enthalpy (Hancock & Zografi 1997). Relaxation will theoretically occur until the enthalpy of the equilibrium supercooled liquid state, or crystalline state below the Kauzmann temperature T_K (Kauzmann 1948), has been attained.

When heating an aged or relaxed glass from ageing temperature (T_a) through the glass transition temperature (T_g) (Figure 1), the enthalpy which has been lost upon relaxation must be regained from the surroundings before the glass re-attains enthalpy of the equilibrium supercooled liquid state (also known as the rubbery state below the melting point temperature T_m (Smith 1993)). This can be detected as an endothermic peak over the glass transition region, and quantified using differential scanning calorimetry (DSC). Greater resolution of the endotherm can be achieved using modulated temperature DSC (MTDSC).

Multiple, and possibly independent, thermodynamic and molecular processes are thought to contribute to measurable enthalpy relaxation of glasses (Ediger et al 1996), and therefore the corresponding physical interpretation of relaxation rates is highly complex (Ediger et al 1996; Shamblin et al 2000). However, the enthalpy relaxation measurable by techniques such as MTDSC is generally thought to be the result of an overall process that is self-retarding – its rate being dependent on how much above equilibrium the enthalpy is at any time (Cowie et al 1997). Kohlrausch–William–Watts-type equations (Ediger et al 1996) have been widely used as models which are fitted to enthalpy relaxation data (Hancock et al 1995; Cowie et al 1997; Shamblin & Zografi 1998; Aso et al 2000; Craig et al 2000; Six et al 2001; Van den Mooter et al 2001):

$$\phi(t_a) = \exp -(t_a/\tau)^{\beta} \quad (2)$$

where ϕ is the proportion of unrelaxed glass at aging time t_a, and the relaxation time constant τ and stretching factor β are characteristic of the particular system under investigation.

The corresponding enthalpy relaxation of the particular system can then be modelled by:

$$\Delta H(t_a) = \Delta H_{\infty}(1-\phi(t_a)) \quad (3)$$

where $\Delta H(t_a)$ and ΔH_{∞} are the relaxation enthalpy after t_a and the theoretical maximum relaxation enthalpy, respectively.

Theoretically,

$$\Delta H_{\infty} = \int_{Ta}^{Tg} \Delta C_p(T)\,dT \quad (4)$$

where ΔC_p is the heat capacity change of the glass between the ageing temperature T_a and T_g. If C_p is approximately constant between T_a and T_g, the only appreciable ΔC_p is due to the glass transition, and ΔH_{∞} can be closely approximated by

$$\Delta H_{\infty} \approx \Delta C_p(T_g - T_a) \quad (5)$$

Since molecular mobility may be used as an indicator of the likelihood of crystallization (Hancock et al 1995; Shamblin et al 1999; Aso et al 2000), enthalpy relaxation during isothermal ageing exists as an alternative to direct stability testing for amorphous formulations. Although only inferential with respect to stability, such measurements can yield numeric values to compare formulations. This method may yield comparative information faster than direct stability testing methods, and may be used to show differences between two formulations, which do not crystallize during direct stability testing.

In preliminary experiments, GWX, an orally active analgesic belonging to biopharmaceutical classification system (BCS) type II (low aqueous solubility, high permeability), was co-precipitated with the enteric polymer hydroxypropyl methylcellulose phthalate (HPMCP) (Sertsou et al 2002). It was found that co-precipitates with a high percentage of drug incorporated into solid solution were associated with a high rate and extent of drug dissolution. In this study, the effect of humidity and temperature on the amorphous form of GWX, and GWX-hydroxypropyl methylcellulose phthalate co-precipitates, with respect to crystallization, was investigated. Co-precipitate that consisted of a single amorphous solid solution phase was then compared with amorphous drug with respect to enthalpy relaxation behaviour.

Materials and Methods

Materials

GWX powdered drug substance was synthesised by the Chemical Development Department of GlaxoSmithKline, Stevenage, UK. Hydroxypropyl methylcellulose phthalate (HPMCP, HP-55F) was obtained from Shin-Etsu Chemical Industry Co. Ltd, Tokyo, Japan. All reagents used were analytical grade and used without further purification. All water used was purified by reverse osmosis.

Preparation of co-precipitates

Drug–HPMCP mixtures, 2:8 and 5:5 weight ratio, were completely dissolved in acetone and the resulting solution was pumped drop-wise into stirred $HCl_{(aq)}$ anti-solvent (pH 4.5), maintained at 5°C in a jacketed glass vessel.

Immediately after addition of all the drug–HPMCP–solvent solution to the anti-solvent, resulting co-precipitates were filtered under vacuum using Whatman no. 54 filter paper, and then dried in an oven under vacuum at 45°C, −800 mbar for 24 h.

Dried co-precipitates were then milled in a Pulverisette 7 ball-mill (Fritsch, Idar-Oberstein, Germany), for three 3-min intervals at 400 rev min^{-1}, with a pause of 5 min between each interval. Four 15-mm zirconium oxide balls were used as grinding media in a 40-mm diameter, 45 mL zirconium oxide cylindrical milling chamber. The resulting powder from five 4-g samples from each drug–HPMCP ratio co-precipitate were mixed with a spatula to make 2 samples for sieving.

Milled co-precipitates were sieved for 15 min using a Gilsonic GA1 vibrating auto-siever (Gilson Co. Inc., Worthington, USA), and the size fraction between 45 and 125 μm was retained for stability and enthalpy relaxation studies.

Preparation of amorphous GWX

Five grams of drug contained in an 80-mm diameter stainless-steel beaker was heated in an oven to 190°C. The beaker containing molten drug was then immediately placed on an aluminium block bathed in liquid nitrogen, and allowed to cool under a stream of nitrogen gas. The average rate of quench cooling of the molten drug to 20°C was 6°C s^{-1}, as measured by a Digitron 2022T Type K thermocouple thermometer (Digitron Instrumentation Ltd., Hertford, UK). Quench-cooled drug was removed from the beaker, ground gently with a mortar and pestle, sieved as described above and stored with desiccant in amber glass jars until immediately before use in experiments.

Stability study

Duplicate 300-mg samples of 45–125-μm size fractions of crystalline, co-precipitate and amorphous drug powder were placed in 2-mL amber glass vials without lids. Vials were then placed in: incubators generating a temperature of 25°C, and a relative humidity (r.h.) of 75% (25/75); incubators generating 40/75; desiccators under sealed vacuum containing P_2O_5 placed in the 25°C incubator above (25/dry); or desiccators at 40/dry.

Analyses were performed on samples at t = 0, 1 week, 2 weeks, 4 weeks and 12 weeks.

Modulated temperature DSC

Modulated temperature differential scanning calorimetry (MTDSC) was carried out on samples in aluminium pans with pin-holed lids, using a TA Instruments DSC 2920 Modulated DSC scanning calorimeter (TA Instruments Inc., Delaware, USA) with a refrigerated cooling system, and employing a nitrogen gas purge (20 mL min^{-1}). The calorimeter was calibrated using indium and sapphire for temperature and heat capacity, respectively. Lissajous analysis (Hill et al 1999) of pre-event sections of sample thermograms were made to check that the calorimeter measured heat flow and modulated the temperature of samples in a controlled manner with each method used below.

Quantification of phases present in samples (5–6 mg) was carried out using the following heating program: heating to 60°C at 20°C min^{-1} from ambient temperature; isothermal for 5 min at 60°C with modulation amplitude ±0.25°C, and period 50 s; heating to 200°C at 2°C min^{-1} with the same modulation parameters as above.

Enthalpy relaxation study

Sample annealing

Aluminium sample pan-lid combinations were weight matched to within ±0.1 mg of the reference pan. The calorimeter described above was used to heat amorphous samples (3–4 mg) at 20°C min^{-1} to 15°C above their T_g (measured at point of inflection). After holding isothermally for 5 min, pans were immediately removed from the DSC and placed in the bottom of a stainless-steel beaker, which was floating in liquid nitrogen in another container. After 30 s of cooling, samples were immediately transferred to desiccators containing P_2O_5, which were placed under vacuum, sealed, and put into ovens at the appropriate ageing temperatures.

Measurement of relaxation enthalpy

Aged samples were removed from desiccators at the appropriate time and immediately heated in the above calorimeter using the following method: heat to 15°C below T_g at 20°C min^{-1}; isothermal for 5 min with modulation amplitude ±0.25°C, and period 50 s; heating to (T_g+15)°C at 2°C min^{-1} with the same modulation parameters as above; isothermal for 30 s at (T_g+15)°C with the same modulation parameters as above; cooling to (T_g−15)°C at 2°C min^{-1} with the same modulation parameters as above.

Thermo-gravimetric analysis

Analysis of residual solvent in co-precipitates was determined by thermo-gravimetric analysis (TGA) using a TA Instruments Hi-Res TGA 2950 Thermogravimetric

Analyzer (TA Instruments Inc., Delaware, USA). Samples (10–15 mg) were heated at a rate of 10°C min^{-1} in aluminium pans. The percent by weight of residual solvent was taken to be the percentage weight change of the sample occurring between ambient temperature and 100°C.

X-ray analysis

X-ray powder diffractometry (XRPD) was carried out with a Philips X'Pert MPD powder diffractometer (Philips Electronics, Einhoven, Netherlands), employing a CuK_α source operating at 40 kV, 55 mA. Scanning rate used was 0.02° 2θ s^{-1}, with step size 0.02° 2θ.

Drug concentration

Drug content of co-precipitates were determined by HPLC. A Hewlett Packard HP1090A liquid chromatograph attached to a HP series 1100 UV detector (Hewlett Packard, Waldbronn, Germany), detecting absorbance at 270 nm was used. The system was run in reversed phase, with a Hypersil BDS 5 μm C-18 column, 4.6 mm i.d. × 200 mm (Hypersil, Cheshire, UK) at 30°C. The mobile phase 48 : 52 acetonitrile–water was pumped through the column at a flow rate of 1.5 mL min^{-1}. Injection volume was 20 μL.

Statistical analysis

One-way analysis of variance was used to detect presence of statistically significant differences in the following measurements between groups of data from different time points during the stability study : percentage of drug present which was incorporated into solid solution (solid dispersion formulations); percentage amorphous drug content (amorphous drug formulation); percentage crystalline drug content (crystalline drug). The level of significance used was $\alpha = 5\%$.

An iterative non-linear regression algorithm based on the Levenberg–Marquardt method (Press et al 1987) was used to obtain best fit β and τ parameters in equation 2, for enthalpy relaxation data.

Results and Discussion

Characterization of solid dispersions

MTDSC was used to calculate the amounts of amorphous and crystalline drug in samples, using physical mixtures of drug and HPMCP as quantitative standards. Standard curves obtained from physical mixtures using this technique have been described previously (Sertsou et al 2002). The estimated limit of detection (LOD) and limit of quantitation (LOQ) of this technique for amorphous and crystalline drug were found to be 1% and 4%, and 1% and 3% w/w, respectively.

Determination of the amount of drug incorporated into solid solution

Since the total drug content of co-precipitates can be determined using HPLC and TGA (to correct for any moisture in standards), a mass balance of drug present in 3 phases (crystalline drug, amorphous drug and drug incorporated into solid solution) is possible. Crystalline drug and amorphous drug can be quantified using melting endotherm and re-crystallization exotherm calibration curves, respectively. The difference between the two gives the original amount of crystalline drug before heating. The total amount of drug, less original amounts of crystalline and amorphous drug, gives, by difference, the amount of drug incorporated into solid solution, which was calculated for samples.

Analysis as such indicated that 2 : 8 and 5 : 5 drug–HPMCP ratio co-precipitates contained 20% and 50% w/w drug respectively, and that 100% and 37% of this drug was incorporated into solid solution, respectively.

Stability study

HPLC results showed no significant sign of chemical degradation. There was no appearance of extra peaks, or reduction in peak height compared with that of freshly prepared standards, for any samples at any time point. XRPD diffractograms did not show any evidence of polymorphism in any formulations.

No significant change of crystallinity in the crystalline drug (control) material was detectable. Amorphous drug content of the originally amorphous drug formulation changed significantly with time at 75% r.h. conditions. There was no significant change, however, in the amorphous drug content between any time points in dry conditions (Figure 2).

Drug–HPMCP 2 : 8 and 5 : 5 co-precipitates were found to contain not more than 4% w/w of amorphous drug (as a solitary phase), throughout the stability study. Since this is very close to, or below, the LOQ (see above), any trend analysis with respect to quantitation of this phase in the co-

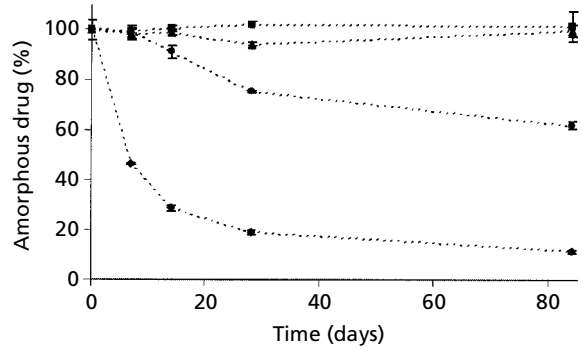

Figure 2 Change in amorphous drug content of pure amorphous drug after time at storage conditions: 25/dry (▲); 40/dry (■); 25/75 (●); 40/75 (◆). Error bars represent mean ± s.d. (n = 2).

precipitates during the stability study would be too uncertain, and has not been attempted.

The percentage of total drug present, which was incorporated into solid solution, for 2:8 and 5:5 drug–HPMCP co-precipitates was 100 (7) and 37 (3)% (mean (±s.d.)), respectively, and this did not change significantly with time in the co-precipitate formulations at any storage condition, indicating the high physical stability of the amorphous solid solution phase.

From the stability testing conditions used, the larger destabilizing effect on the amorphous drug formulation appears to be presence of water rather than elevated temperature, as there was no significant re-crystallization of amorphous drug at either 25/dry or 40/dry conditions.

In contrast, the co-precipitate formulations also remained unchanged at 25/75 and 40/75 conditions. Furthermore, resistance of the solid solution phase to crystallization in the 5:5 drug–HPMCP co-precipitate occurs in the presence of considerable amounts of crystalline drug ($\geqslant 55\%$ w/w of total drug present), which might be expected to act as a seeding material. This stability is possibly explained by the inhibition of molecular mobility that is imparted to drug molecules in the solid solution by HPMCP ($T_g \approx 141^\circ C$), even in environments with considerable amounts of water at 75% r.h.

Enthalpy relaxation study

Enthalpy relaxation of amorphous drug and the amorphous 2:8 drug–HPMCP co-precipitate formulations were investigated. MTDSC thermograms showing examples of different degrees of enthalpy relaxation in these amorphous formulations are shown in Figure 3.

Relaxation enthalpy was calculated by subtracting the non-reversing relaxation enthalpy measured upon cooling (thought to be due to frequency effects (Royall et al 1998)) from that measured upon heating. Moisture content of aged samples was determined by TGA to be $< 0.2\%$ w/w.

T_g and ΔC_p measurements for samples are shown in Table 1. These values were used to estimate the theoretical maximum relaxation enthalpy ΔH_∞, using equation 5. The fraction of theoretical maximum relaxation still to occur was plotted vs ageing time for both amorphous formulations (Figure 4). β and τ parameters, obtained after equations 2 and 3 were fitted to experimentally measured enthalpy relaxation data, are shown in Table 1. Higher β or τ parameters obtained from the 2:8 drug–HPMCP co-precipitate compared with amorphous drug at similar ($T_g - T_a$) values lead to curves which appear to have a less sudden initial decrease in the fraction of theoretical maximum relaxation remaining. In the 2:8 drug–HPMCP co-precipitate, which consists of a single solid solution phase, superimposition of relaxation processes of the two components may also be leading to flatter relaxation–time curves.

The half-life ($t_{1/2}$), defined as the time for which the relaxation enthalpy reaches half its theoretical maximum, calculated by

$$t_{1/2} = (\ln(2))^{1/\beta}\tau \qquad (6)$$

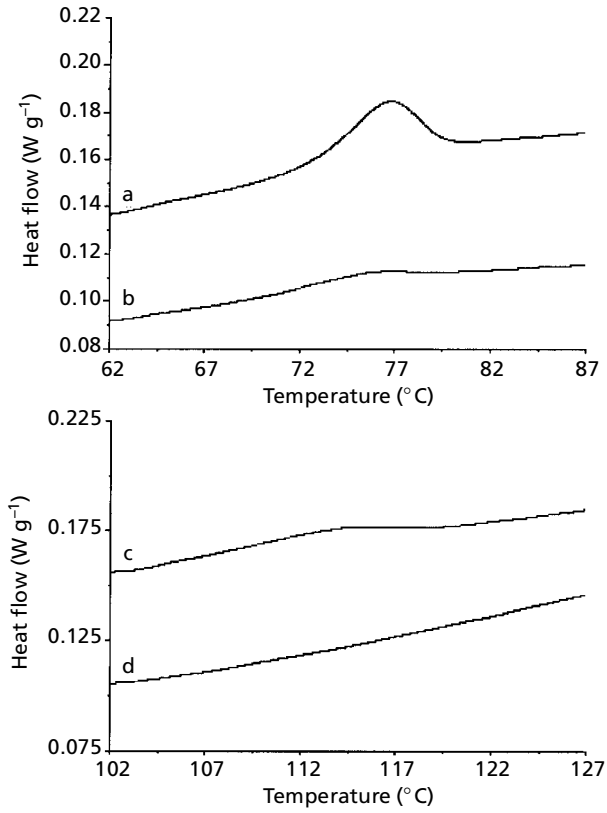

Figure 3 Total heat flow MTDSC heating thermograms over the glass transition temperature region of amorphous drug after ageing for 16 h at 65°C (a) or 35°C (b) and of 2:8 drug–HPMCP co-precipitate after ageing for 16 h at 105°C (c) or 65°C (d). Thermograms have been shifted along abscissa for presentation purposes.

is shown for all experiments in Figure 5.

Estimated relaxation half-lives of amorphous drug alone and the drug–HPMCP solid solution are directly comparable in Figure 5 at the 65°C ageing temperature. The difference of several orders of magnitude points to the decreased overall molecular mobility, which HPMCP causes in the solid solution. The solid solution at this temperature ($T_g - 50.6$) is probably nearing its T_K (Hancock et al 1998).

It has been postulated that enthalpy relaxation data may be used to indicate absolute physical stability for amorphous pharmaceuticals (e.g. by assigning a shelf-life as the time required for 10% of material to have fully relaxed) (Hancock 2002; Shamblin et al 2000). According to Figure 1, however, crystallization occurs after enthalpy has dropped below the equilibrium supercooled liquid-state level, and therefore such shelf-life assignments seem rather arbitrary, particularly if the amorphous pharmaceutical's performance has not been correlated to degree of relaxation. Furthermore, if crystallization causes the greatest deleterious effect on product performance, an assumption made when using enthalpy relaxation data on their own to indicate absolute shelf-lives must be that the stability of equilibrium supercooled liquid states of all amorphous pharmaceuticals being compared are the same. Unless data

Table 1 Glass transition temperature (T_g), associated heat capacity change (ΔC_p) at T_g, and ($T_g - T_a$) of enthalpy relaxation experiments with corresponding fitted relaxation constants τ and β, for amorphous drug and 2:8 drug–HPMCP co-precipitate.

Amorphous drug					**2:8 drug–HPMCP co-precipitate**				
T_g (°C)	ΔC_p (J g^{-1} K^{-1})	$T_g - T_a$ (°C)	τ (h)	β	T_g (°C)	ΔC_p (J g^{-1} K^{-1})	$T_g - T_a$ (°C)	τ (h)	β
76.8 (0.2)	0.31 (0.01)	11.8	2	0.43	115.6 (0.5)	0.22 (0.03)	10.6	16	1.33
		21.8	31	0.50			20.6	146	0.79
		31.8	22805	0.26			30.6	169	1.21
		41.8	100784	0.30			50.6	7000000	0.39

The T_g value reported is the inflection point of the glass transition event in the reversing MTDSC thermogram. The average (s.d.) of five determinations is reported for T_g and ΔC_p.

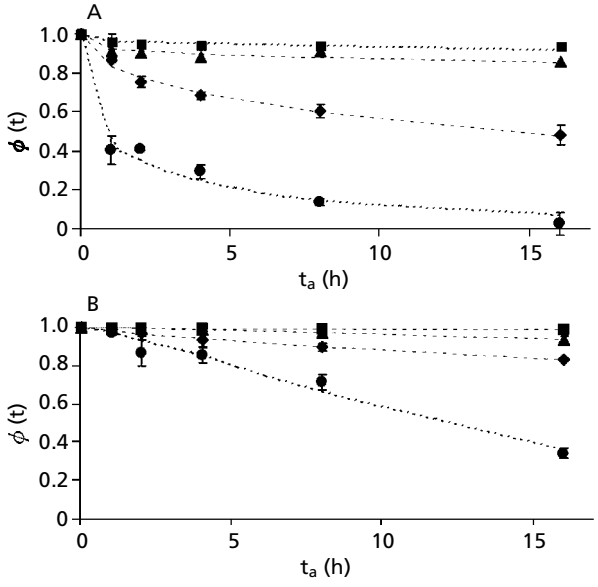

Figure 4 Fraction of theoretical maximum enthalpic relaxation still to occur (ϕ(t)), at ageing time t_a for amorphous drug at ($T_g - T_a$) = 41.8 (■), 31.8 (▲), 21.8 (◆), 11.8 (●) (A) or 2:8 drug–HPMCP co-precipitate at ($T_g - T_a$) = 50.6 (■), 30.6 (▲), 20.6 (◆), 10.6 (●) (B). Curves with dashed lines are those calculated using equation 2, with τ and β parameters listed in Table 1. Error bars represent mean±s.d. (n = 2).

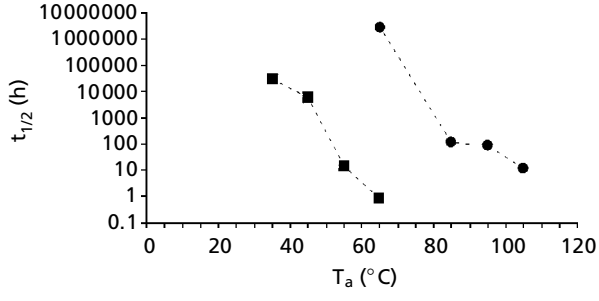

Figure 5 Relaxation enthalpy half-life ($t_{1/2}$) of amorphous drug (■) and 2:8 drug–HPMCP ratio co-precipitate (●), aged at temperature T_a.

showing this to be the case are demonstrated, enthalpy relaxation experiments are limited to providing only an indication of relative molecular mobility in pharmaceuticals while in the glassy state. They may not necessarily be adequate substitutes for conventional or accelerated physical stability testing which measure crystallization.

Conclusions

Stability study results indicated that humidity (75% r.h. compared with dry) had a larger influence on stability of the amorphous drug formulation than did temperature (25°C compared with 40°C). The solid solution phase in co-precipitates was also shown to have a relatively higher stability than amorphous drug alone, with respect to crystallization, in presence of the plasticizer water, and crystalline drug. These findings were partly explained by evidence of decreased molecular mobility in the amorphous solid solution with respect to amorphous drug alone, shown using enthalpy relaxation measurements.

Comparison of half-lives for enthalpy relaxation was a successful and rapid indicator of relative molecular mobility, and relative likelihood of crystallization for the two formulations tested.

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