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Comparison of the Gordon-Taylor and Couchman-Karasz equations for prediction of the glass transition temperature of glass solutions of drug and polyvinylpyrrolidone prepared by melt extrusion

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The glass transition temperature (Tg) is often used to gain information about the stability of amorphous systems. Pure compounds or solid solutions stored below the Tg are more stable than compounds or mixtures stored at temperatures above the Tg. Polymers, such as polyvinylpyrrolidone (PVP), are useful excipients in the formulation of solid solutions. Due to their amorphous nature and high Tg (see Table) they lead to an increase in the Tg of the entire amorphous system compared with the drug alone and should, therefore, increase the stability of the amorphous drug [1, 2]. However, PVP is hygroscopic, taking up large amounts of water under ambient conditions, a process that will decrease the overall Tg.

The Gordon-Taylor (GT) equation [3] is one means of predicting the Tg of amorphous solid solutions based on the weight fractions, Tg values and coefficients of thermal expansion of their components:

$$\mathrm{Tg(mix)} = \frac{w_1 \cdot Tg_1 + K_1 \cdot w_2 \cdot Tg_2}{w_2 + K_1 \cdot w_2} \qquad K_1 = \frac{\rho_1 \cdot \Delta\alpha_1}{\rho_2 \cdot \Delta\alpha_2} \quad (1)$$

where Tg is the experimentally determined glass transition temperature, w the weight fraction, ρ is the density of the amorphous components, $\Delta\alpha$ is the change in thermal expansitivity at the Tg and the subscripts 1 and 2 represent the two components of the mixture (that is, drug and polymer). As $\Delta\alpha$ values are not readily determinable the Simha-Boyer rule [4], which assumes volume additivity, is routinely applied, leading to the commonly used version of the GT equation, which is described below for a ternary system (that is, drug, polymer and water):

$$\mathrm{Tg(mix)} = \frac{w_1 \cdot Tg_1 + K_1 \cdot w_2 \cdot Tg_2 + K_2 \cdot w_2 \cdot Tg_3}{w_1 + K_1 \cdot w_2 + K_2 \cdot w_3} \quad (2)$$

$$K_1 = \frac{Tg_1 \cdot \rho_1}{Tg_2 \cdot \rho_2} \qquad K_2 = \frac{Tg_2 \cdot \rho_2}{Tg_3 \cdot \rho_3}$$

The Couchman-Karasz (CK) equation [5] is similar to the GT equation, but derives K from the heat capacity change at the Tg (ΔCp):

$$K_1 = \frac{\Delta Cp_2}{\Delta Cp_1} \quad (3)$$

The CK equation has received little attention in the pharmaceutical literature, primarily because of limitations in

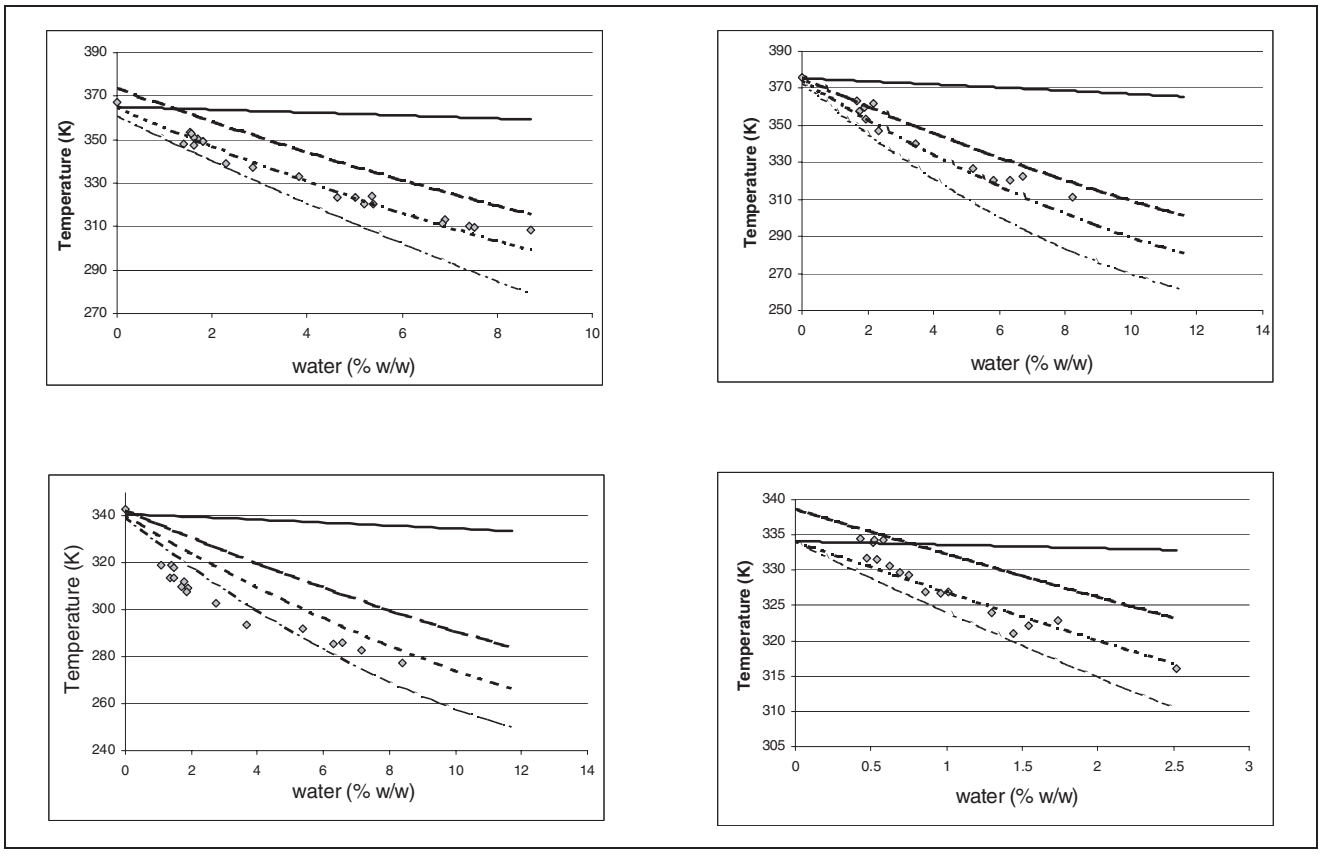

Fig: Glass transition temperatures of solid solutions measured by MTDSC compared to values predicted by the GT and CK equation. Top-left: Indomethacin/PVP (1 : 1), top-right: Nifedipine/PVP (1 : 1), bottom-left: Tolbutamide/PVP (1 : 1) bottom-right: Indomethacin/PVP (4 : 1). Solid line: CK equation based on 0.11 $J \cdot g^{-1} \cdot K^{-1}$ for the ΔCp of water; dashed line: GT-equation based on 136 °C for the Tg of water; dotted line: CK equation based on 1.38 $J \cdot g^{-1} \cdot K^{-1}$ for the ΔCp of water; dashed-dotted line: CK equation based on 1.94 $J \cdot g^{-1} \cdot K^{-1}$ for the ΔCp of water.

Table: Glass transition temperatures (Tg) and change in heat capacity at the Tg (ΔCp) for indomethacin, nifedipine, tolbutamide and PVP

Compd.	Tg_{onset} (°C)	Tg_{mid} (°C)	Tg_{end} (°C)	ΔCp (J/g/°C)
Indomethacin	42.3 ± 0.04	45.6 ± 0.2	48.4 ± 0.2	0.40 ± 0.02
Nifedipine	42.4 ± 0.7	45.0 ± 0.6	47.6 ± 0.5	0.30 ± 0.02
Tolbutamide	−2.7 ± 0.9	1.3 ± 0.1	5.3 ± 0.4	0.39 ± 0.01
PVP	158.4 ± 0.9	164.4 ± 0.3	170.6 ± 1.7	0.25 ± 0.01

accurately determining ΔCp values for drugs and polymers. However, with the application of modulated temperature DSC (MTDSC), which allows accurate heat capacity and Tg analysis, the CK equation may be more easily applied. In this study a comparison of the GT and CK equations for prediction of the Tg of drug/PVP melt extrudates (1 : 1 w/w) as a function of moisture content of the extrudates with experimentally determined values was investigated. Incorporation of water as a third component is critical because of the difficulty in preventing moisture uptake of PVP under realistic storage conditions of pharmaceutical glass solutions.

To be able to model the Tg of drug/polymer mixtures in the presence of water, using the GT or CK equation, one needs to know the Tg and ΔCp value for water respectively. Forster et al. have tabulated several values for the Tg and ΔCp of water commonly used in the literature [6]. The Tg values range between 134 °C and 143 °C, with a value of 136 °C being most commonly used. For the application of the CK equation however, the situation is much less clear, as ΔCp values for water given in the literature differ dramatically, including values of 0.10, 0.11, 1.38, and 1.94 $J \cdot g^{-1} \cdot K^{-1}$ [6].

The change in heat capacity values through the Tg event (ΔCp) for amorphous indomethacin, nifedipine, tolbutamide and PVP are shown in the Table along with the corresponding Tg values. Using these values one can model the Tg of glass solutions (melt extrudates) containing drug and PVP at a 1 : 1 mass ratio and increasing amounts of moisture, using the GT and CK equations. Plots of the predicted versus the experimentally determined Tg values for melt extrudates are shown in the Figure. The CK equation using 1.38 $J \cdot g^{-1} \cdot K^{-1}$ as the ΔCp value for water, generally gave the closest fit to the experimental values. The CK equation using 0.1 $J \cdot g^{-1} \cdot K^{-1}$ as the ΔCp value for water, did not model the experimental values correctly. In the case of tolbutamide/PVP, the CK equation based on 1.94 $J \cdot g^{-1} \cdot K^{-1}$ for the ΔCp of water gave the closest fit to the experimental values. In no cases did the GT equation provide the best fit to the experimental data. These findings are important, as deviations of the measured from the theoretically predicted values of the Tg (in the pharmaceutical literature usually based on the GT equation) are often interpreted as an indication of an interaction (mostly hydrogen bonding) between the components in the glass solution [7]. However, using the CK equation with 1.38 $J \cdot g^{-1} \cdot K^{-1}$ as the ΔCp value for water, these deviations appear to be smaller, than when using the GT equation. Suspected interaction between drug and polymer on the basis of a predictive equation should therefore always be investigated/confirmed using other techniques, such as spectroscopic methods.

This study has shown that MTDSC is a useful way of accurately measuring the heat capacity change at the Tg for solid solutions and therefore, allows the use of the CK equation for Tg prediction of solid solutions. Assuming that the value of 1.38 $J \cdot g^{-1} \cdot K^{-1}$ for the ΔCp of water at the Tg is correct, the CK equation provided a more accurate prediction of the experimental Tg of drug/PVP mixtures as a function of moisture uptake.

Experimental

1. Materials

Indomethacin, nifedipine and tolbutamide were purchased from Sigma Aldrich. PVP (k30, average MW 50000) was provided by GSK (Ware, UK). Nifedipine samples were protected from light at all times.

2. Methods

2.1. Determination of glass transition temperature and heat capacity change of water-free systems

For ΔCp measurements a TA Instruments 2920 DSC (Surrey, UK) was used in the modulated temperature mode. Pure drugs were prepared as glasses by melting 20 mg in sealed Al-pans with a pierced lid, followed by holding the samples isothermally for 5 min before cooling at a rate of 100 °C min^{-1}. PVP samples were dried at 150 °C in Al-pans with a pierced lid and then equilibrated at 120 °C for 15 min. A similar process was used for determination of the ΔCp for water-free drug/PVP blends.

2.2. Preparation of solid solutions prepared by melt extrusion

Physical mixtures of drug and polymer (1 : 1 mass ratio) were melt extruded using a Brabender Plasti-corder PL2000 (Duisburg, Germany). The milled extrudates were stored at 25 °C/75% RH, 25 °C/60% RH and 25 °C/< 10% RH, to prepare systems with varying moisture contents. Only samples that remained entirely amorphous (as determined by XRPD) were used for Tg determination.

2.3. X-ray powder diffraction (XRPD)

Samples were analysed with a Philips X'Pert MPD (count time 1 s, step size 0.04 °2θ, Ni-filtered Cu-kα radiation, 30 kV, 40 mA, sample size: approx. 300 mg).

2.4. Density determination

Density measurements were performed using a nitrogen pycnometer (AccuPye 1330, Micrometrics, USA) with a cell size of 1.0 cm^3.

2.5. Moisture analysis

Moisture analysis was perfomed by thermogravimetry (TGA, TA Instruments) and Karl Fischer titration (Turbo 2 blending Karl Fischer, Orion, UK).

2.6. Tg determination by thermal analysis

Samples (5–10 mg) were sealed in Al-pans to prevent water loss and heated at a linear rate of 2 K min^{-1} with an oscillation of ± 0.25 K every 40 s using a TA Instruments 2920 DSC (Surrey, UK).

Note: All measurements were performed in triplicate.

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