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Comparison of the Gordon-Taylor and Couchman-Karasch 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 (T_g) is often used to gain information about the stability of amorphous systems. Pure compounds or solid solutions stored below the T_g are more stable than compounds or mixtures stored at temperatures above the T_g . Polymers, such as polyvinylpyrrolidone (PVP), are useful excipients in the formulation of solid solutions. Due to their amorphous nature and high T_g (see Table) they lead to an increase in the T_g 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 T_g .

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

$$T_g(\text{mix}) = \frac{w_1 \cdot T_{g1} + K_1 \cdot w_2 \cdot T_{g2}}{w_2 + K_1 \cdot w_1} \quad K_1 = \frac{\rho_1 \cdot \Delta\alpha_1}{\rho_2 \cdot \Delta\alpha_2} \quad (1)$$

where T_g 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 expansivity at the T_g 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):

$$T_g(\text{mix}) = \frac{w_1 \cdot T_{g1} + K_1 \cdot w_2 \cdot T_{g2} + K_2 \cdot w_3 \cdot T_{g3}}{w_1 + K_1 \cdot w_2 + K_2 \cdot w_3} \quad (2)$$

$$K_1 = \frac{T_{g1} \cdot \rho_1}{T_{g2} \cdot \rho_2} \quad K_2 = \frac{T_{g2} \cdot \rho_2}{T_{g3} \cdot \rho_3}$$

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

$$K_1 = \frac{\Delta C_{p2}}{\Delta C_{p1}} \quad (3)$$

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

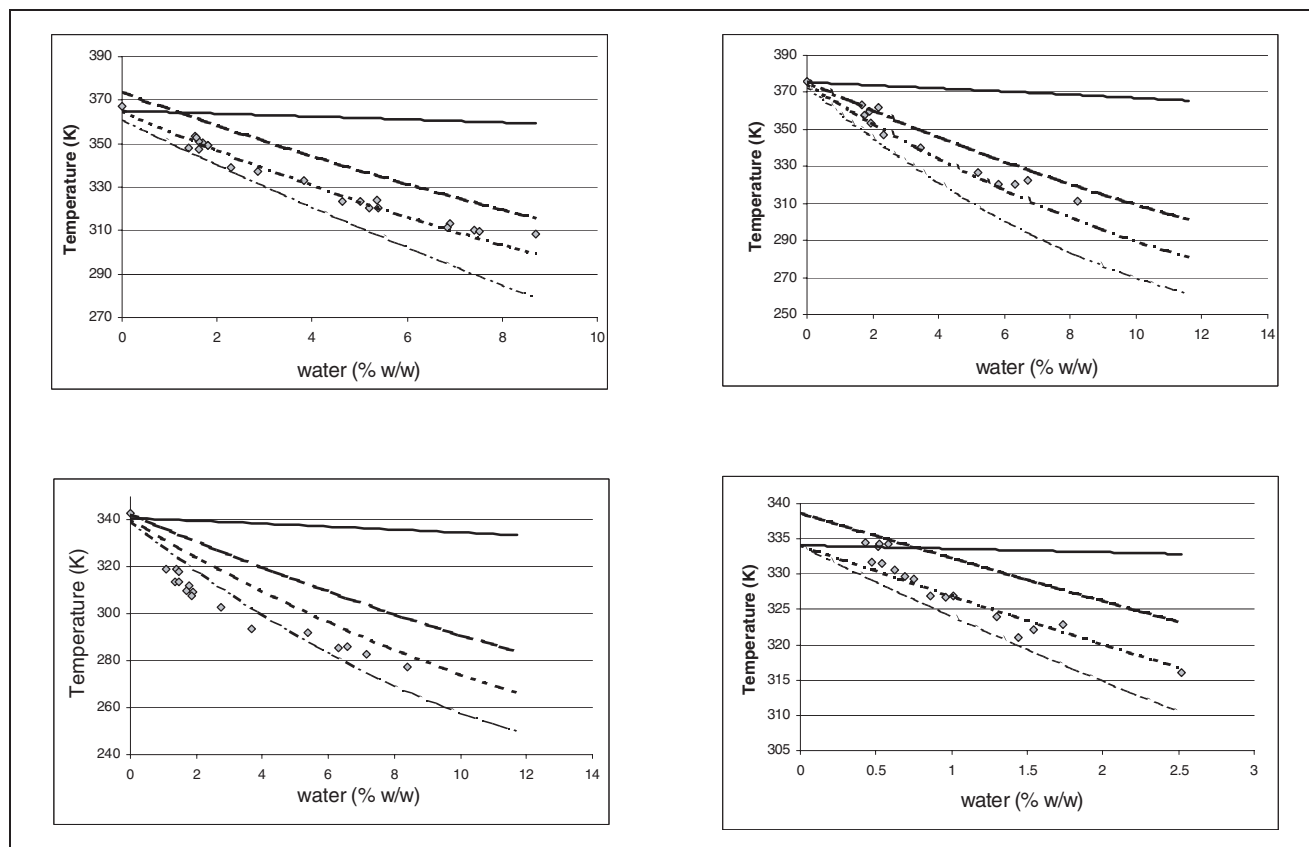


Fig: Glass transition temperatures of solid solutions measured by MTDSC compared to values predicted by the GT and CK equation. Top-left: Indomethacin/PVP (1 : 1), top-right: Nifedipine/PVP (1 : 1), bottom-left: Tolbutamide/PVP (1 : 1) bottom-right: Indomethacin/PVP (4 : 1). Solid line: CK equation based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

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

Compd.	T _{g onset} (°C)	T _{g mid} (°C)	T _{g end} (°C)	ΔC _p (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 ΔC_p values for drugs and polymers. However, with the application of modulated temperature DSC (MTDSC), which allows accurate heat capacity and T_g analysis, the CK equation may be more easily applied. In this study a comparison of the GT and CK equations for prediction of the T_g 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 T_g of drug/polymer mixtures in the presence of water, using the GT or CK equation, one needs to know the T_g and ΔC_p value for water respectively. Forster et al. have tabulated several values for the T_g and ΔC_p of water commonly used in the literature [6]. The T_g 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 ΔC_p values for water given in the literature differ dramatically, including values of 0.10, 0.11, 1.38, and 1.94 J · g⁻¹ · K⁻¹ [6].

The change in heat capacity values through the T_g event (ΔC_p) for amorphous indomethacin, nifedipine, tolbutamide and PVP are shown in the Table along with the corresponding T_g values. Using these values one can model the T_g 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 T_g values for melt extrudates are shown in the Figure. The CK equation using 1.38 J · g⁻¹ · K⁻¹ as the ΔC_p value for water, generally gave the closest fit to the experimental values. The CK equation using 0.1 J · g⁻¹ · K⁻¹ as the ΔC_p value for water, did not model the experimental values correctly. In the case of tolbutamide/PVP, the CK equation based on 1.94 J · g⁻¹ · K⁻¹ for the ΔC_p 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 T_g (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 · g⁻¹ · K⁻¹ as the ΔC_p 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 T_g for solid solutions and therefore, allows the use of the CK equation for T_g prediction of solid solutions. Assuming

that the value of 1.38 J · g⁻¹ · K⁻¹ for the ΔC_p of water at the T_g is correct, the CK equation provided a more accurate prediction of the experimental T_g 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 ΔC_p 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 ΔC_p 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 T_g 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-α radiation, 30 kV, 40 mA, sample size: approx. 300 mg).

2.4. Density determination

Density measurements were performed using a nitrogen pycnometer (AccuPyc 1330, Micrometrics, USA) with a cell size of 1.0 cm³.

2.5. Moisture analysis

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

2.6. T_g 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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