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Research paper

Stability prediction of amorphous benzodiazepines by calculation of the mean relaxation time constant using the Williams–Watts decay function

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Abstract

The enthalpic relaxation of three amorphous benzodiazepines, diazepam, temazepam and triazolam was studied using differential scanning calorimetry for ageing temperatures which were below the glass transition temperature, and ageing times up to 16 h. Experimental determination of the relaxation enthalpy and the heat capacity change, both accompanying the glass transition, enabled us to calculate the extent of relaxation of the amorphous drugs at specific ageing conditions. Fitting of the relaxation function to the Williams–Watts two parameter decay function led to calculation of the mean relaxation time constant τ and the molecular relaxation time distribution parameter β. The mean relaxation time constants for the three drugs increased from approximately ten h at the glass transition temperature with more than eight orders of magnitude at 66 K below the glass transition temperature. It was found that the benzodiazepines exhibited significant molecular mobility until approximately 50 K below the glass transition temperature; below this temperature molecular mobility becomes unimportant with respect to the shelf life stability. Hence the presented procedure provides the formulation scientist with a tool to set storage conditions for amorphous drugs and glassy pharmaceutical products.

Keywords: Benzodiazepines; Amorphous drugs; Molecular mobility; Enthalpy relaxation; Glass transition temperature

1. Introduction

Although oral drug administration is by far the most convenient and most used route of drug administration, problems of low and variable bioavailability are not exceptional. Four factors are generally recognized to be responsible for compromising oral bioavailability: (i) low dissolution rate in aqueous environment, (ii) low permeation through biomembranes, (iii) systemical and/or presystemical metabolization, (iv) interaction with other components in the gastro-intestinal tract.

The formulation of poorly soluble drugs in solid dispersions has often been proposed in the pharmaceutical literature to improve the dissolution rate. To date, more than 500 papers have been published on solid dispersions; however, very few marketed products rely on the principle of solid dispersions. The reason for this discrepancy is that very often stability problems of physical and/or chemical origin are encountered. The physics of these systems is often poorly understood, and as a consequence, anticipation of stability problems related to solid dispersions is still inadequate. The preparation of solid dispersions either by fusion-cooling or solvent evaporation (spray-drying) methods, transforms the physical state of the drug often resulting in amorphous or partially amorphous drugs. Although amorphous systems generally show improved dissolution properties, from a thermodynamical point of view they are not stable, and the eventual devitrification is inevitable. In order to understand the behaviour of an amorphous drug dispersed in a polymer, it is necessary to first characterise

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and understand the physical behaviour of the pure amorphous drug. Therefore it is of crucial importance to identify and understand the factors that influence crystallisation from the glassy state and to have knowledge of the time scale of devitrification.

It has been shown by Yoshioka and co-workers [1] that indomethacin crystallises completely from the amorphous state at 30°C within several weeks while inhibition of crystallisation for periods longer than 6 months was only observed when the storage temperature was reduced to 4°C. An important physical parameter is the glass transition temperature, since it indicates a borderline between a region of low and high molecular mobility, hence the glass transition temperature dictates the conditions for optimal storage of an amorphous system (either the pure drug or a multicomponent amorphous system). In a paper by Hancock et al. [2], it was shown that indomethacin, sucrose and polyvinylpyrrolidon experience significant molecular mobility even at temperatures well below their glass transition temperatures, and they concluded that 50 K below the glass transition temperature seemed to be a general limit. Hence not only the glass transition temperature, but also the temperature at which the molecular mobility becomes irrelevant with respect to the life-time of a drug product dictates the storage conditions.

In the present paper, we report on the stability of three amorphous benzodiazepines: temazepam, diazepam and triazolam (Fig. 1). In order to find the temperature where molecular mobility is decreased to a level where it becomes negligible with respect to the expected life time of a drug, we investigated the mobility of these drugs below their glass transition temperatures using the Williams–Watts decay function [3]. We were particularly interested if the value of 50 K below the glass transition temperature was also a limit for the studied benzodiazepines, and hence could be regarded as a general borderline temperature of relevant molecular mobility with respect to the stability of glassy drugs/pharmaceutical products.

2. Materials and methods

2.1. Materials

Temazepam was kindly donated by Sanico (Turnhout, Belgium), diazepam by Roche (Basel, Switzerland), and triazolam by Pharmacia and Upjohn (Puurs, Belgium).

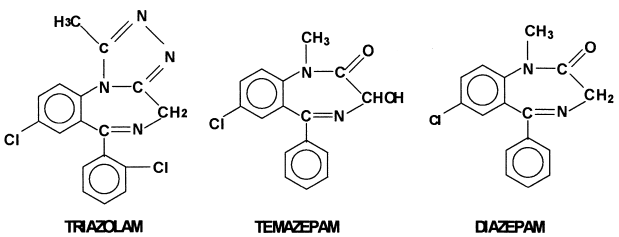

Fig. 1. Chemical structure of triazolam, temazepam and diazepam.

The crystalline drugs were transformed into the amorphous state by heating them at 10 K/min to 10 K above the melting point, followed by quench cooling to 40 K below their glass transition temperature. After this procedure, the drugs were tested for chromatographic purity using a previously described HPLC method [4]. The samples were stored at least 40 K below their glass transition temperature in the presence of P_2O_5 until use.

2.2. Thermal analysis

Differential scanning calorimetry (DSC) measurements were carried out using a Perkin-Elmer DSC-7 differential scanning calorimeter (Perkin-Elmer, Norwalk, CT) equipped with a liquid nitrogen subambient accessory (Perkin-Elmer, Norwalk, CT). Samples (2–6 mg) were weighed and analysed in closed aluminium pans under a nitrogen purge. Pure water and indium were used to calibrate the DSC temperature scale and enthalpic response. Heat capacity determination was carried out using an accurately weighed amount of pure, crystalline sapphire as calibrant. Data were treated mathematically using the Pyris Software 3.03 (Perkin-Elmer, Norwalk, CT).

Since the storage temperature of each amorphous drug was different with respect to its glass transition temperature, each sample was heated to 20 K above its glass transition temperature at 10 K/min, before starting the ageing procedure. Samples were then cooled at 10 K/min to 100 K below their glass transition temperature, and immediately heated at 10 K/min to either 16, 25, 46, or 66 K below their glass transition temperatures. The samples were stored at these temperatures for either 3 min, 1.6, 4, 8, 12, or 16 h, and subsequently heated at 5 K/min to 30 K above their glass transition temperatures. In order to calculate the molecular mobility, the recovery of enthalpy and the change in heat capacity at the glass transition temperature were measured.

2.3. Data analysis

The optimal set of the mean relaxation time constant (τ) and the relaxation time distribution parameter (β) values for fitting of the experimental data, was calculated using the Levenberg–Marquardt minimization procedure provided in the Micromath Scientist 2.0 software (Micromath scientific software, Salt Lake City, UT).

3. Results and discussion

Pure temazepam, diazepam and triazolam were transformed from the crystalline to the amorphous state by quench cooling of the melted drugs. As reported previously, cooling at a high or a low rate always resulted in the formation of a glass. The glass transition temperature was 315.2 (±0.4) K, 339.2 (±1.6) K, and 356.5 (±0.3) K for diazepam, temazepam and triazolam, respectively, at a heat-

ing rate of 3 K/min. Heating or cooling at different rates resulted in a slightly different glass transition temperature and magnitude of the accompanying enthalpy relaxation endotherm. In the present study, the quench cooled glasses were reheated through their glass transition temperatures at 5 K/min, which was found to be a good compromise between high resolution and low sensitivity of the thermal response.

Many drugs do not immediately crystallize when they are cooled through their melting point, but they form a supercooled liquid instead [5–8]. Further cooling leads to such high viscosities that molecular mobility is impaired, thereby inhibiting further recrystallization, and the possibility exists that this supercooled liquid becomes an immobile glass with a frozen-in molecular conformation, typical of some higher temperature supercooled liquid.

The basis for calculation of the molecular mobility is the fact that a DSC scan of an aged sample shows the presence of an endothermic relaxation peak the intensity of which depends upon the ageing conditions of time and temperature. This is a general feature of structural relaxation of glassy materials, and is illustrated in Fig. 2 for diazepam. The endothermic peak accompanying the glass transition temperature, also called ‘overshoot peak’, is generated as a consequence of enthalpy recovery. In some cases, e.g. thermosetting resins, the endothermic peak can be located well below the glass transition temperature resulting from relaxation mechanisms reaching equilibrium far below the glass transition temperature [9]. Fig. 3 shows the enthalpy relaxation of triazolam as a function of the ageing time for different ageing temperatures. For the three drugs, the relaxation enthalpy increased with increasing ageing time, but decreased with increasing ageing temperature in a non-linear way. It can thus be assumed that there is a maximal value of the relaxation enthalpy for every ageing temperature: $\Delta H_\infty = \lim_{(t\to\infty)}\Delta H$. At low (with respect to the glass

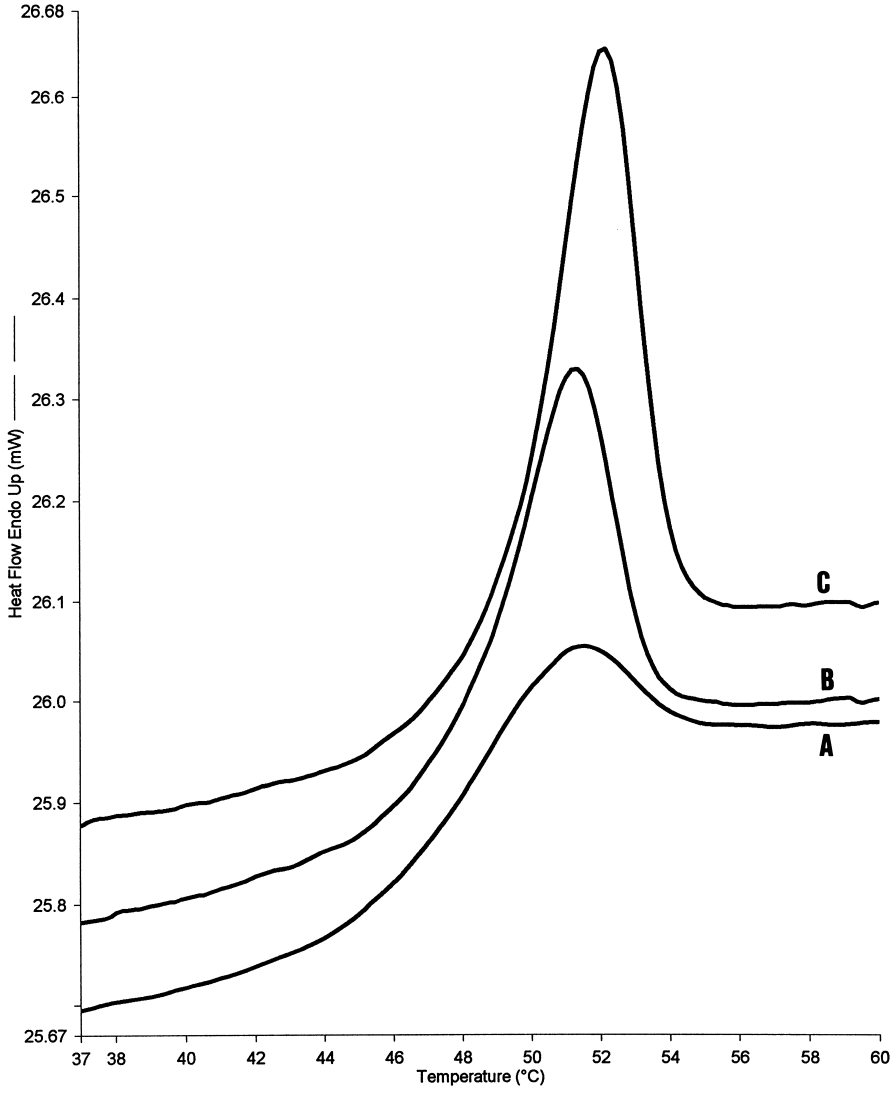

Fig. 2. Thermograms of diazepam showing the relaxation enthalpy after different ageing conditions: A, Tg-46 K, t = 4 h; B, Tg-25 K, t = 4 h; C, Tg-25 K, t = 16 h.

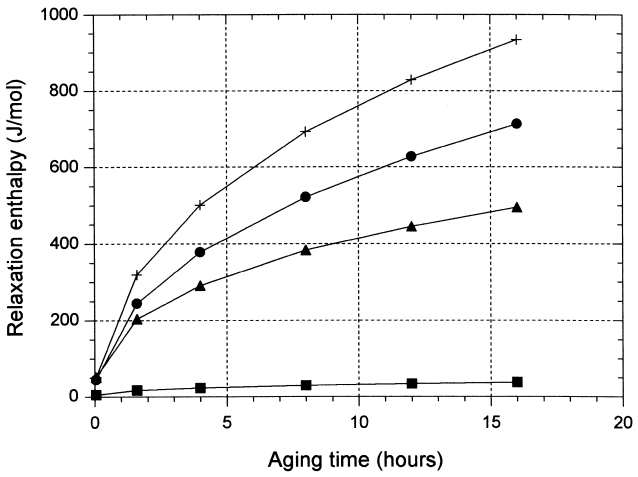

Fig. 3. Variation of the relaxation enthalpy with ageing conditions for triazolam (B = Tg-66 K, O = Tg-46 K, X = Tg-25 K, + = Tg-16 K).

transition temperature) ageing temperatures, relaxation times will become very large, therefore, ΔH_∞ can only be determined accurately at ageing temperatures near to the glass transition temperature [9]. However, in order to determine approximate values of ΔH_∞, one can either extrapolate the liquid enthalpy curve down to temperatures below the glass transition region, or when it is assumed that the heat capacity change (ΔCp) is independent of the temperature, ΔH_∞ for a particular ageing temperature T can be calculated using the following equation:

$$\Delta H_\infty = (Tg - T)\Delta C_p \quad (1)$$

The heat capacity change that accompanied the glass transition was 130.4 (±9.4)J/mol p K, 125.1 (±10.7) J/mol p K, and 134.1 (±11.3) J/mol*K, for diazepam, temazepam, and triazolam, respectively. The next step in the evaluation of the relaxation enthalpy is a kinetic analysis in order to determine the time scale of relaxation. This can be performed by the introduction of the relaxation function Φt, which describes the extent of relaxation for a pair of temperature and time conditions. Φt can be written as

$$\Phi_t = [H(T_x, t_x) - H_\infty(T_x)] / [H(T_x, t_0) - H_\infty(T_x)] \quad (2)$$

or

$$\Phi_t = 1 - (\Delta H / \Delta H_\infty) \quad (3)$$

where the numerator of Eq. (2) is the excess enthalpy.

The experimental determination of the excess enthalpy at a given ageing time is obtained by calculating the area under the endothermic relaxation peak. The error (RSD) on the reported values (mean of three determinations) ranged between 6%, for low ageing temperatures, and less than 1%, for high ageing temperatures. A large contribution to the error resulted from the extrapolation of the baseline to that of the supercooled liquid, which is somewhat arbitrary in conventional DSC.

The calculation of the mean molecular relaxation time constant τ was done by fitting the relaxation function to a two parameter function, which has been referred to as the Williams–Watts function [3]:

$$\Phi_t = \exp -(t/\tau)^\beta \quad (4)$$

This empirical decay function was developed to describe non-symmetrical dielectric relaxation behaviour, and has since then frequently been applied to quantify the structural relaxation process in glassy polymers [10–12]. In this equation, β is a parameter which describes the distribution of molecular relaxation times, and consequently ranges between 0 and 1, where the latter indicates a single relaxation time. Fig. 4 (panels A–D) shows the relaxation function for temazepam calculated with Eq. (3), as a function of the ageing time *t*. The symbols indicate the calculated values, whereas the line represents the fitting using Eq. (4). For the three drugs, the fitting of the data to the two parameter decay function was satisfactory and much better than fitting to a single parameter model [9] (data not shown). As a variation to this two parameter model, we also evaluated the model proposed by Cowie and Fergusson [13], which is also based on the Williams–Watts relaxation function, but with ΔH_∞ also as an adjustable parameter. This approach was only successful for ageing temperatures near to the glass transition temperature, since at lower temperature e.g. starting from 25 K below Tg, ΔH_∞ decreased. This phenomenon, which has no physical meaning can probably be explained by the wide range of ageing temperatures applied. The calculated parameters are summarized in Table 1. The values of the β parameter decrease when the ageing temperature decreases and this might indicate that the approach towards the equilibrium is slowed at lower temperatures. Statistically, the difference between temazepam and diazepam was not significant, which is not surprising regarding the similarities in their structures. On the other hand, the β value was significantly different for triazolam. In any case, the β values were significantly different from 1, which indicates a distribution of time scales rather than one single relaxation time. Similar β values were reported by Hancock et al. (2) for indomethacin, whereas slightly higher values were noted for sucrose.

The mean relaxation time constant increased at lower ageing temperatures for the three drugs, reaching very high values at 66 K below Tg. From Fig. 5, which shows a plot of log τ as a function of the scaled temperature Tg-T, it is obvious that the order of magnitude of the mean relaxation time constant is similar for the three benzodiazepines studied. Least square fitting through the data indicate that the mean relaxation time constant is around 10 h at the glass transition temperature, whereas it increases dramatically at lower ageing temperatures.

Although the Williams–Watts decay function is only a mathematical tool describing the shape of the relaxation function, the similarity in the results obtained with these structurally related benzodiazepines demonstrates the validity of the approach and indicates the usefulness in providing a tool to predict the life time of glassy pharmaceuticals, and

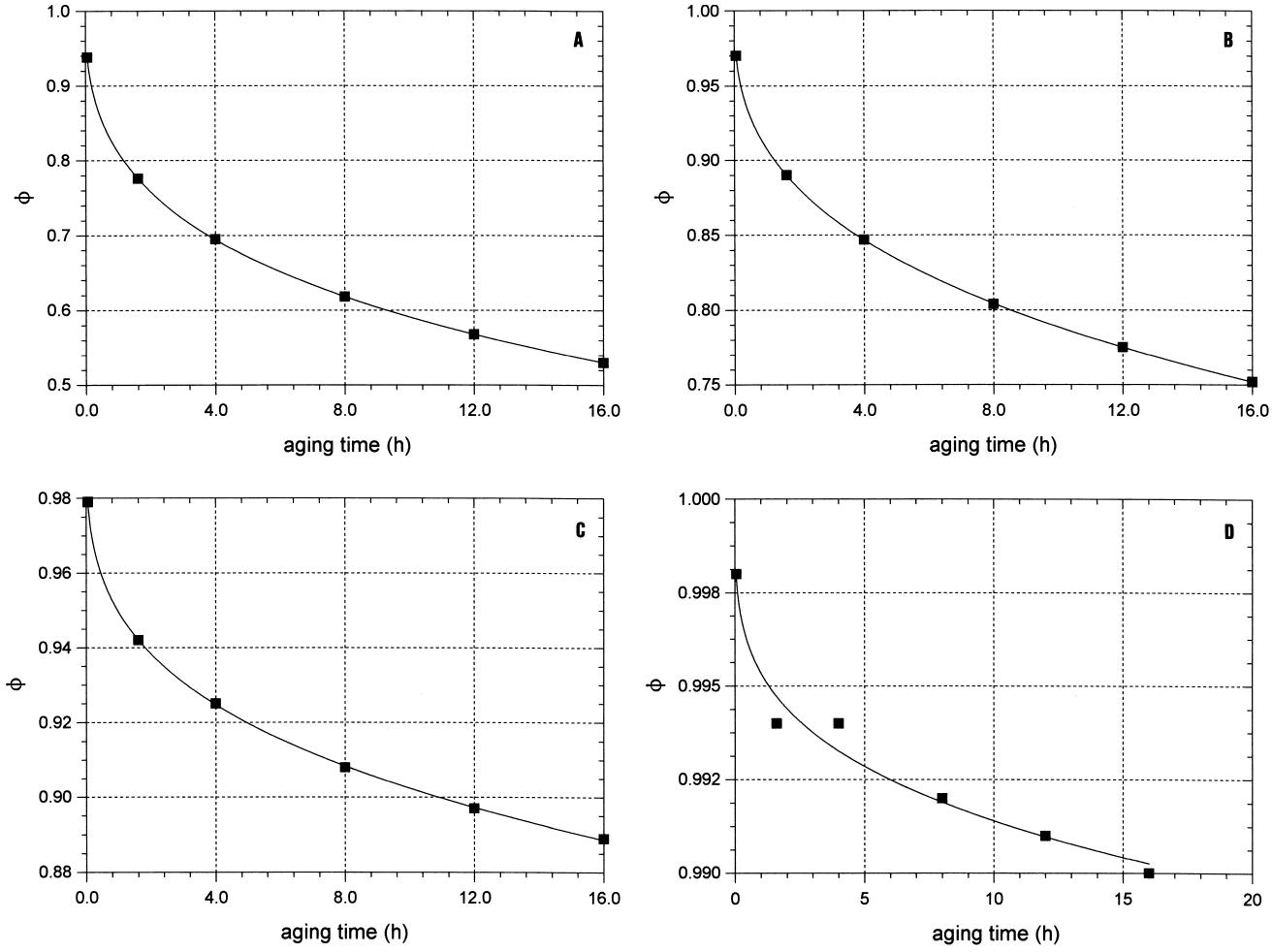

Fig. 4. Plot of the relaxation function of temazepam at Tg-16 K (A), Tg-25 K (B); Tg-46 K (C); Tg-66 K (D).

hence to anticipate possible stability problems. One can see from Fig. 5 that the stability of glassy diazepam, temazepam and triazolam will not be jeopardized if they are stored at temperatures which are approximately 50 K below their glass transition temperature. It was very interesting to note that this temperature was also calculated for pharmaceuticals which are structurally different from the studied benzodiazepines [2], since this might indicate that the value of 50 K below the glass transition temperature is a general 'threshold value' below which molecular mobility is too low to cause problems within the expected life time of glassy pharmaceutical products. Nevertheless, additional experiments are necessary to confirm this hypothesis; it may therefore be of interest to also test other drugs which are structurally unrelated.

Table 1

Calculated b parameters of the Williams–Watts function for diazepam, temazepam and triazolam

Drug	Ageing conditions			
	Tg-16 K	Tg-25 K	Tg-46 K	Tg-66 K
Diazepam	0.35 (±0.05)	0.34 (±0.05)	0.35 (±0.06)	0.30 (±0.03)
Temazepam	0.40 (± 0.06)	0.39 (±0.04)	0.30 (±0.03)	0.27 (±0.09)
Triazolam	0.55 (±0.07)	0.50 (±0.07)	0.40 (± 0.06)	0.35 (±0.05)

4. Conclusion

The use of the empirical Williams–Watts decay function enabled us to calculate two important parameters in the characterisation of amorphous drugs: the mean relaxation time constant and the molecular relaxation time distribution parameter. The mean relaxation time constants for the three drugs increased from approximately 10 h at the glass transition temperature with more than eight orders of magnitude at 66 K below the glass transition temperature. The results obtained in this study indicate that molecular mobility may be regarded as unimportant from 50 K below the glass transition temperature with respect to shelf life stability of amorphous drugs.

Although the procedure to calculate the molecular mobility may be time consuming, the methodology can be extre-

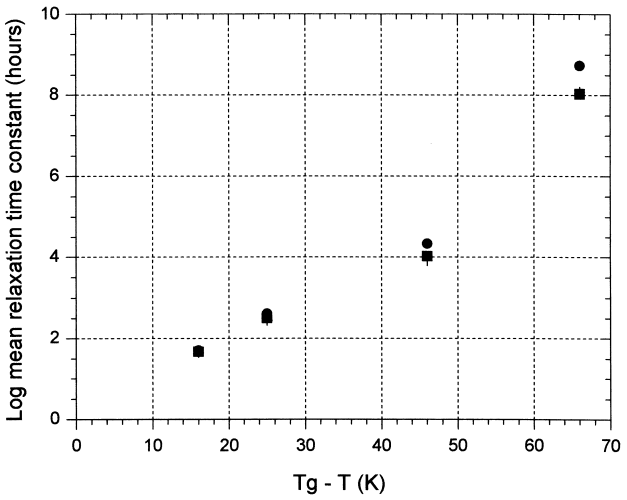

Fig. 5. Plot of log mean relaxation time constant as a function of the scaled temperature for diazepam (B), temazepam (X), and triazolam (+).

mely useful to answer the question of stability of amorphous drugs. It not only provides the formulation scientist with a tool to set storage conditions for amorphous drugs as such, but it may also help to select the right excipients (polymers) for elevating the glass transition temperature (anti-plasticizing effect) of the drug in co-evaporates/spray-dried systems.

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