Drug Development and Industrial Pharmacy, 2010; 36(11): 1271–1280

informa
healthcare

ORIGINAL ARTICLE

Enthalpy relaxation studies of two structurally related amorphous drugs and their binary dispersions

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Abstract

Objective: The purpose of the current study was to evaluate the enthalpy relaxation behavior of valdecoxib (VLB) and etoricoxib (ETB) and their binary dispersions to derive relaxation constants and to understand their molecular mobilities. *Methods*: Solid dispersions of VLB and ETB were prepared with 1%, 2%, 5%, 10%, 15%, and 20% (w/w) concentrations of polyvinylpyrrolidone (PVP) in situ using differential scanning calorimetry (DSC). Enthalpy relaxation studies were carried out with isothermal storage periods of 1, 2, 4, 6, 16, and 24 hours at 40°C and 0% relative humidity (RH). *Results*: PVP increased the glass transition temperature (T_g) and decreased the enthalpy relaxation. Significant differences between two drugs were observed with respect to their relaxation behavior which may be due to differences in intermolecular interactions as predicted by Couchman–Karasz equation and molecular mobility. Kohlrausch–Williams–Watts equation was found to be inadequate in describing complex molecular relaxations in binary dispersions. The enthalpy relaxation behavior of VLB and ETB was found to be significantly different. PVP stabilized VLB significantly; however, its effect on ETB was negligible. The extent of enthalpy relaxation was found to correlate with hydrogen bonding tendency of the drug molecules. Conclusion: The outcome can help in rational designing of amorphous systems with optimal performance.

Key words: *Amorphous; binary dispersions; enthalpy relaxation; glass transition temperature; molecular mobility*

Introduction

Amorphous pharmaceuticals owing to their high energy state are often associated with high solubility and dissolution rate[1]. These properties make them preferred dosage forms, especially for Biopharmaceutics classification system (BCS) class II drugs, having low aqueous solubility and high permeability[2]. However, amorphous forms are kinetically and thermodynamically unstable because of their high molecular mobility and free energy, respectively[3,4]. Amorphous systems lack long range order associated with crystalline form and this disorderliness is manifested as excess enthalpy, increased entropy, increased volume, and high specific heat capacity[5]. Hence these systems tend to revert to low energy crystalline state by devitrification, often manifested as altered physical, chemical, and mechanical properties[1,6]. The difference in the properties of amorphous and crystalline forms mainly arises because of varied molecular level arrangements like intra- and inter-hydrogen bonding tendency, extent of complexity in molecular geometry, interlocking due to structural shape, and conformational flexibility[7]. Investigations have also suggested that other factors such as optimal orientation of molecules, hydrogen bonds, and nonhydrogen bonds in the crystal lattice in 3D space also play an important role[8].

Because glasses are thermodynamically unstable, they tend to approach equilibrium over extended periods of time when stored at a temperature close to T_g[7]. The excess enthalpy and entropy of amorphous forms present in entrapped frozen molecules is lost gradually on storage at a temperature (T_a) close to T_g for a time (t_a) (Figure 1). As a result there is a decrease in the molecular mobility, enthalpy, entropy, and free volume as a function

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(Received 12 Nov 2009; accepted 5 Mar 2010)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639041003753847

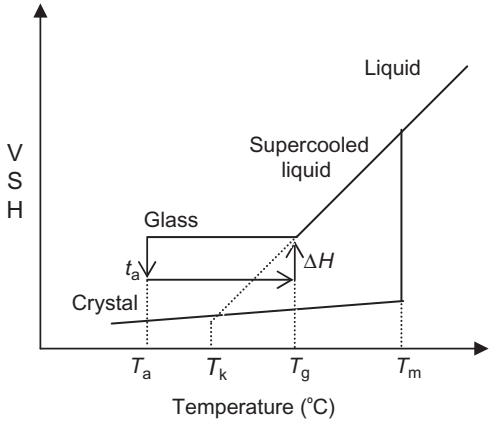

Figure 1. Schematic representation of thermodynamic basis of enthalpy relaxation.

of storage time. This phenomenon is known as either structural relaxation, enthalpy relaxation, or entropy relaxation, according to the parameter measured[9].

In a previous publication using celecoxib, we had demonstrated that the enthalpy relaxation measurements at T_g can be used as a predictor of relative molecular mobilities of amorphous drugs and their binary dispersions[10]. Subsequently, enthalpy relaxation was correlated to aqueous solubility[11] and physical 'stability'[12]. We have also reported the solubility advantage from solid dispersions of valdecoxib (VLB) and etoricoxib (ETB) and assessed intermolecular interactions in the amorphous solid dispersions with polyvinylpyrrolidone (PVP)[13]. Both VLB and ETB structurally related nonsteroidal anti-inflammatory drugs (Figure 2) and act as selective cyclooxygenase - 2 (COX-2) inhibitors. Chemically, VLB possesses a sulfonamide group that can act as H donor, whereas ETB does not have an H donor group. By virtue of this, VLB was found to have stronger interactions with –C=O group of PVP as compared to ETB[13]. Both drugs have reasonably similar T_g values (56.4°C and 58.7°C for VLB and ETB, respectively). This work investigates the enthalpy relaxation behavior of solid dispersions of VLB and ETB and correlates it to their intermolecular interactions. This work

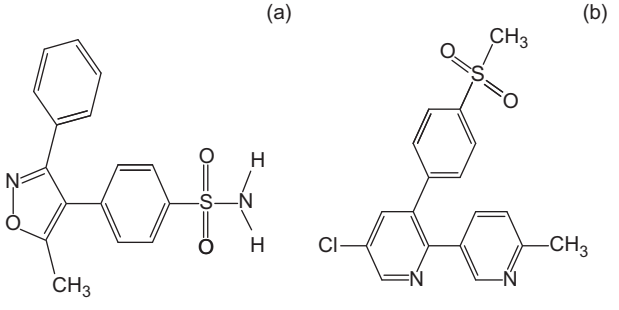

Figure 2. Structure of VLB (a) and ETB (b).

can form the basis of development of an enthalpy relaxation-based experimental protocol for rapid screening of 'stabilizers' for amorphous solid dispersions.

Ambike et al.[14] and Shimpi et al.[15] reported stabilized amorphous formulations of VLB and ETB using PVP and Gelucire, respectively. These studies showed that although PVP was able to blunt devitrification of VLB[14], but it failed to improve the stability of ETB[15]. Moreover, ETB could be stabilized by using Gelucire as the formulation additive. Instead of the fact that both the drugs were structurally similar, their amorphous forms behaved differently; however, authors did not provide a detailed mechanistic understanding of their behavior. This work shall support the hypothesis that molecular interactions in amorphous solid dispersions impact the enthalpy relaxation, which in turn determines their physical stability and solubility advantage.

Materials and methods

Materials

VLB and ETB were kind gifts from Aarti drugs Ltd. (Mumbai, India), and PVP K-29/32 was purchased from ISP Technologies Inc. (Wayne, NJ, USA). All solvents used were of analytical grade and were used as obtained without further purification. To avoid exposure to environmental moisture, all materials were stored in desiccators containing anhydrous phosphorus pentoxide (P_2O_5) at room temperature.

Preparation of preliminary solid dispersions of drugs

All amorphous systems for enthalpy relaxation studies were prepared in situ using differential scanning calorimetry (DSC). However, preliminary homogenous dispersions of VLB and ETB with PVP were prepared by solvent evaporation technique using rotary evaporator, R-200 (Buchi Labortechnik AG, Flawil, Switzerland). About 800 mg of drug and PVP in the w/w ratios (drug : PVP) of 99:1, 98:2, 95:5, 90:10, 85:15, and 80:20 were solubilized in dichloromethane : methanol (2:1) cosolvent and evaporated under vacuum. This step was necessary to ensure the homogenous mixing of PVP with VLB because of low polymer concentration.

Differential scanning calorimetry

Homogenous drug polymer mixtures prepared by solvent evaporation technique were used for the preparation of amorphous systems in the DSC instrument. The samples were analyzed under dry nitrogen purge by Perkin Elmer Diamond DSC (Shelton, CT, USA) using Pyris Manager version 7 software, equipped with intracooler

facility. The DSC instrument was calibrated for temperature and heat flow with indium and zinc. Samples of about 9–15 mg were sealed in standard aluminum pans with a pin hole and then heated to 10°C above the melting point of the drug (VLB and ETB) at a rate of 100°C/min. The samples were isothermally held at this temperature for 1 minute to standardize the thermal history and cooled immediately to the aging temperature at 20°C/min to form glass.

Enthalpy relaxation studies

At various time intervals, samples were analyzed by heating the aged samples at 20°C/min and by measuring the enthalpy relaxed at T_g. The heating run was continued until melting temperature to confirm for any crystallization.

Results and discussion

Glass transition temperature

All the solid dispersions of VLB and ETB prepared with PVP exhibited a single glass transition peak in all DSC analyses indicating the presence of a single amorphous phase and a uniform mixing of the drug and the carrier[16,17]. Furthermore, the efficiency of mixing of both the components was evaluated using the following equation[10,18]:

$$T_g = \frac{W_1 T_{g1} + K W_2 T_{g2}}{W_1 + K W_2} \quad (1)$$

where W_1 and W_2 are the weight fractions of polymer and drug, and T_{g1} and T_{g2} are their T_g values, respectively. The simplified value of K in the above equation can be given by Couchman–Karasz equation, given as[19]

$$K = \frac{\Delta C_{p2}}{\Delta C_{p1}} \quad (2)$$

where ΔC_p is the difference in heat capacity at T_g for corresponding components. T_g values observed experimentally and those obtained by using these equations for both the drugs are shown in Figure 3. However, Couchman–Karasz equation does not take into consideration the entropy of mixing of the constituents. Hence, the term K can be considered as an oversimplification of the events involved in the formation of amorphous mixtures[20].

In case of VLB, at low polymer concentrations, experimentally determined values showed negative deviation

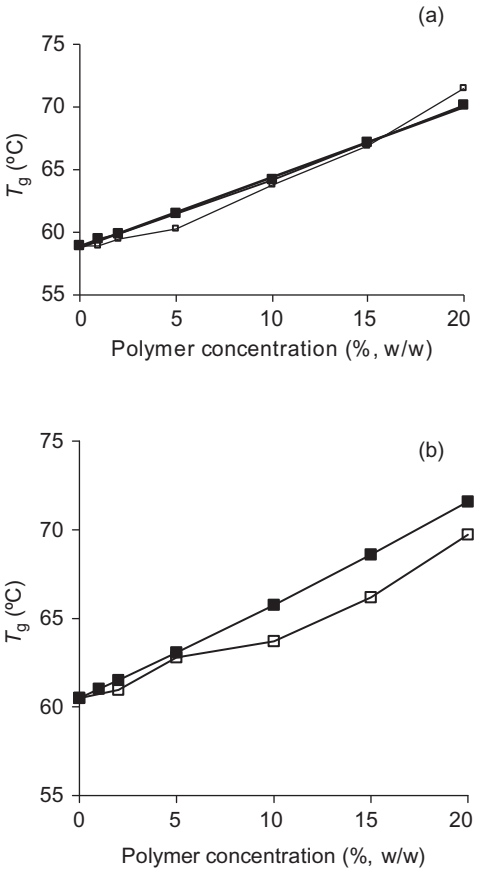

Figure 3. Comparison of experimentally determined T_g values (□) with those predicted (■) by Couchman–Karasz equation for VLB (a), and ETB (b).

from predicted values and at polymer concentrations >15% (w/w), a positive deviation was observed, thus indicating concentration-dependent interactions between VLB and PVP[21]. However, in case of ETB, experimentally observed values were always less than those predicted values using Equation (1). The difference between the two values for ETB increased with increase in the polymer concentration. It indicates the absence of significant interactions between the drug and polymer molecules[22].

To gain insights into this phenomenon, molecular stoichiometries of VLB and PVP were deduced. The molar ratios calculated for both the drugs and a PVP monomer (molecular weight 111.14) in all binary dispersions are presented in Table 1. Table 1 shows that up to a polymer concentration of 15% (w/w), the number of PVP monomer units was considerably less than VLB molecules. At such a low concentration, PVP monomers were probably insufficient to interact and stabilize all the VLB molecules. At 15% (w/w) PVP concentration, a stoichiometry ratio of 2:1 is obtained allowing interactions as strong as those existing between the individual

Table 1. Calculated molar ratios of drug: monomer (polymer) in different binary dispersions.

Weight ratio (%, w/w)	Molar ratio	
Drug: polymer	VLB	ETB
99:1	35.00:1	30.00:1
98:2	17.34:1	15.17:1
95:5	6.72:1	5.88:1
90:10	3.18:1	2.78:1
85:15	2.00:1	1.75:1
80:20	1.41:1	1.23:1

components. The interactions become further strong as the drug:polymer approaches 1:1 and is manifested as positive deviations in T_g.

Enthalpy relaxation studies

The extent of instability and hence the rate of devitrification of an amorphous substance can be measured in terms of enthalpy relaxed during storage[23]. High molecular mobility of amorphous drugs drives it toward equilibrium supercooled liquid state through gradual enthalpy loss, when it is stored at a temperature (T_a) below T_g for a time (t_a) (Figure 1)[9]. This lost enthalpy is regained back by the sample during the heating run in DSC and is observed as an endothermic peak at T_g. The extent of enthalpy lost/regained is a direct measure of molecular mobility of the substance[9]. To assess the effect of polymer on enthalpy relaxation with time, solid dispersions containing 1%, 2%, 5%, 10%, 15%, and 20% PVP for both the drugs were prepared and analyzed in DSC after storage at 40°C. The thermograms obtained for VLB and ETB after aging at 40°C for different storage times are shown in Figure 4.

As indicated in Figure 4, the endothermic peak for both the drugs gradually enhanced indicating an increase in enthalpy relaxation leading to equilibrium supercooled liquid state. Similar trend was observed with all the solid dispersions of both the drugs prepared with different concentrations of PVP. However, with an increase in polymer concentration, the enthalpy relaxation was found to decrease (Figure 5). The enthalpy relaxation was found to be low for both the drugs; however, the decrease was higher in case of VLB and significantly less in case of ETB. Amorphous VLB showed enthalpy relaxation of 7.95 J/g and with 20% (w/w) PVP it decreased to only 3.32 J/g after 24 hours. In case of ETB, the enthalpy relaxed with 20% (w/w) PVP in 24 hours was 4.91 J/g as compared to 6.38 J/g in ETB alone. Because both the drugs possess almost similar structure, such a difference in their enthalpy relaxation behavior with similar PVP concentrations was striking.

Although the presence of PVP lowered enthalpy relaxation, a gradual enthalpy loss continued with time.

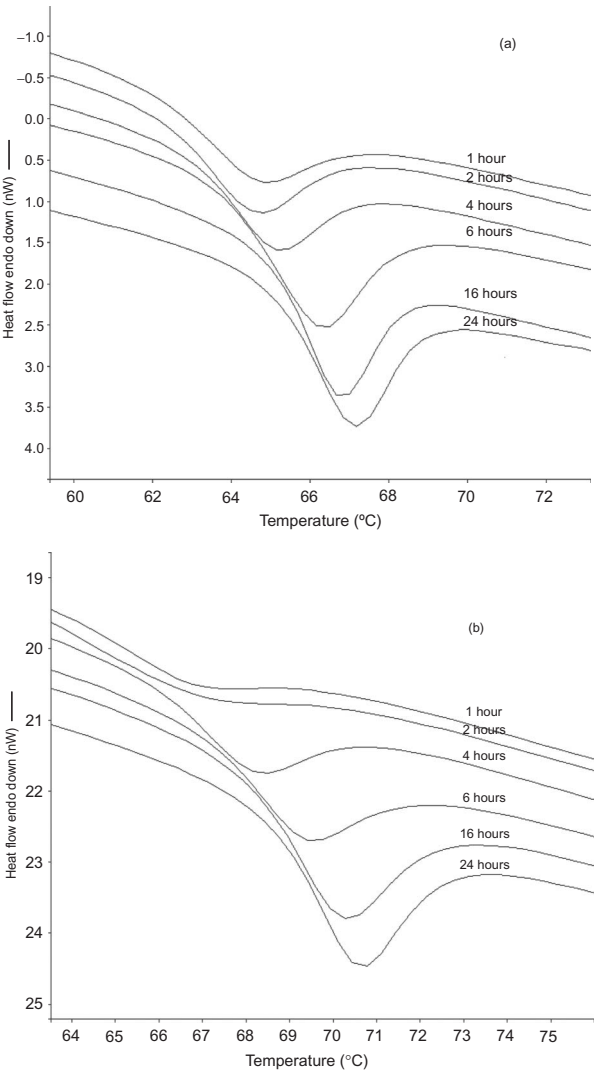

Figure 4. Gradual enhancement in enthalpy recovery with time observed for amorphous VLB (a), and ETB (b).

Because enthalpy relaxation changes as an inverse function of degree of undercooling [difference between the T_g and storage temperature (T_a)][24], hence the maximum enthalpy change that is required to reach supercooled liquid state can be given by equation[25].

$$\Delta H_\infty = \Delta C_p (T_g - T_a) \quad (3)$$

where ΔC_p is the change in heat capacity at T_g, that is, difference in heat capacity between supercooled and glassy states. These calculated ΔH_∞ values represent total enthalpy change required for a glass for phase transition. However, owing to the nonlinear function of relaxation phenomenon, the actual ΔH_∞ values required for complete transformation cannot be determined experimentally[26].

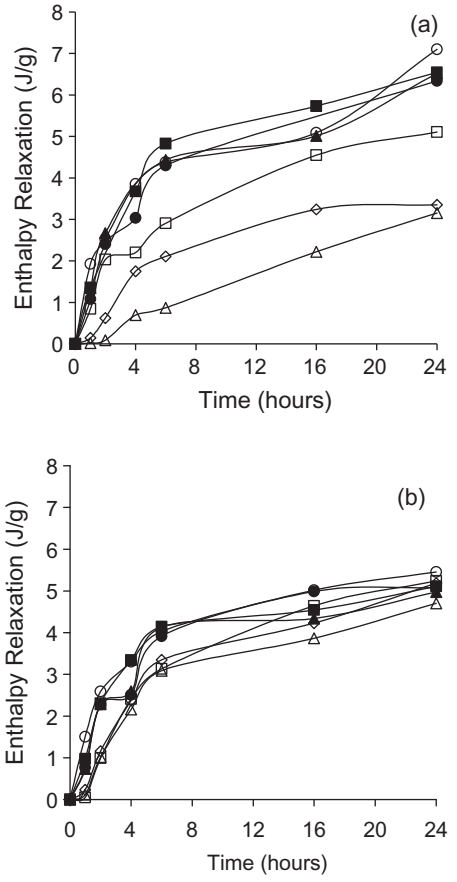

Figure 5. Enthalpy relaxation (J/g) for amorphous drug (○) and its solid dispersions with 1(■), 2(▲), 5 (●), 10 (□), 15 (◇), 20% (△) (w/w) PVP determined after aging for different storage times at 40°C for VLB (a), and ETB (b), (n = 2, SD < 0.5). (Note: The enthalpy relaxation of unaged sample has been subtracted to obtain enthalpy relaxation values at each time point.)

Furthermore, due to the presence of heterogeneity and wide distribution of differing local densities in solid dispersions, the molecular mobility varies from one point to another[27], which prevents objective comparison between different solid dispersions[28]. Therefore, relaxation constants are determined to compare molecular mobility/structural relaxation of different systems. The most commonly used relaxation constants to describe structural relaxation phenomenon are given by Kohlrausch–William–Watts (KWW) equation[10]

$$\phi_t = \exp\left[\frac{-t}{\tau}\right]^{\beta} \tag{4}$$

where ϕ_t represents the extent to which a material relaxes, τ is mean relaxation time, and β is the relaxation time distribution parameter. These time constants represent the average time taken for a single molecular motion of a particular type to occur and can be determined by treating the data with a stretched exponential function using nonlinear regression. The extent to which a material relaxes (ϕ_t) can be calculated for any time (t) and storage temperature (T_a) by following equation[10].

$$\phi_t = 1 - \left(\frac{\Delta H_t}{\Delta H_\infty}\right) \tag{5}$$

It is well known that glasses follow nonlinear relaxation kinetics and relaxation time becomes longer as aging progresses. The kinetics of glass transition can only be described by using a model in which relaxation time is a function of structure or time of aging[29]. This has also been addressed in two recent publications involving polymeric systems[30,31]. We have relied on Cowie and Ferguson's model for comparing molecular mobility of the drug in solid dispersions to obtain rank order of polymers for 'stabilizing' the amorphous state of the drug[32]. Figure 6 shows the amount of drug

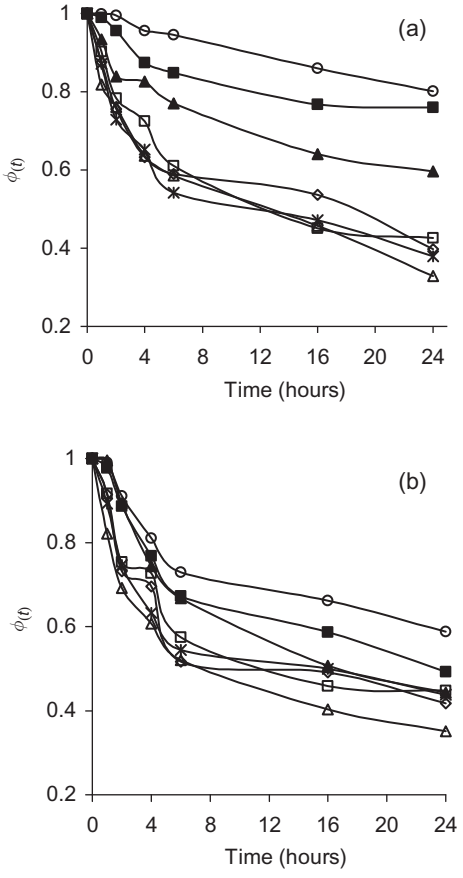

Figure 6. Extent of relaxation with time for amorphous drug (△), 1% (w/w) PVP (ж), 2% (w/w) PVP (◇), 5% (w/w) PVP (□), 10% (w/w) PVP (▲), 15% (w/w) PVP (■) and 20% (w/w) PVP (○) for VLB (a), and ETB (b).

relaxed against time for different binary dispersions of VLB and ETB with PVP in terms of ϕ_t versus time. Amorphous form of VLB and ETB alone attained ϕ_t values of about 0.45 and 0.4, respectively, after 16 hours from an initial value of 1. However, in the presence of varying concentrations of polymer, the extent of relaxation decreased and with 20% (w/w) PVP, it reached only to 0.86 and 0.66 after 16 hours from an initial value of 1 for VLB and ETB, respectively. It can also be observed that with same polymer concentration, the lowering in the extent of relaxation for VLB was very high as compared to ETB. Much less differences could be observed in the dispersions containing 0–5% (w/w) PVP during the experimental time scale. Therefore, it could be said that binary dispersions with relatively high T_g show a significant reduction in the extent of relaxation (higher ϕ_t) relative to low T_g dispersions[25]. Hence, solid dispersions with higher concentration of PVP exhibit a higher T_g (Table 2) and reduced relaxation of the glassy state.

The statistical treatment of Equation (4) gives a mean τ value for all the molecular motions, occurring under a given set of conditions[26]. Because of nonlinearity of function, β can have any value ranging from 0 to 1. A β value equal to 1 describes a single relaxation time occurring in whole of the substance[25]. These relaxation time constants were determined from the enthalpy relaxation data by using Sigmastat® (version 2.0.3.0, SPSS Inc., Chicago, IL, USA) based on Marquardt–Levenberg algorithm. The initial parameters used were τ equal to 100 and β equal to 0.5 for all solid dispersions. τ and β values obtained by nonlinear regression for VLB and ETB with different concentrations of PVP are given in Table 2.

Calculated τ values adequately described the relaxation phenomenon in ETB and its dispersions, but in case of VLB and its dispersions no clear trend is perceptible. However, a generalized increase in τ indicative of reduced molecular mobility is perceptible in solid dispersions containing polymer concentrations beyond 10% (w/w). It is reported that KWW equation is satisfactory for monocomponent amorphous systems but frequently fails to describe the distribution of relaxation times in bicomponent systems, where the complexity increases because of the presence of polymers/excipients[25]. This fact has also been substantiated in literature, involving characterization of amorphous dispersions using dielectric and dynamic mechanical techniques[27].

It, therefore, appears that simply knowing the relaxation time constants from the fit of the KWW equation is not sufficient to characterize and quantify molecular mobility in more complex binary systems[33]. Therefore, to use relaxation time constants for the prediction of physicochemical stability, actual distribution of relaxation times and their effect on relaxation time constants should be considered[34]. In such cases, the time required for each glass to reach a semirelaxed state can be determined for quantitative comparisons[27]. The time to reach semirelaxed state ($\tau_{(\phi(\tau)=0.5)}$) can be calculated by fitting a straight line through the plot of ϕ_t versus log time scale as shown in Figure 7 and solving for ϕ_t = 0.5. The log $t_{((\phi_t)=0.5)}$ values for VLB and ETB for their dispersions are shown in Table 2. These values indicate that the binary mixtures relax slowly than amorphous drugs alone[35]. In case of VLB, the time required to reach semirelaxed state became more than 14 times which increased from 2.72 to 39.65 hours [log(t) = 1 and 3.68] with 20% (w/w) PVP. However, ETB dispersions at a similar concentration of PVP showed only an insignificant increase to 5.42 from 2.46 hours.

Regardless of the type and distribution of relaxation time, it is clear that polymers help in the stabilization of amorphous systems by reducing enthalpy relaxation where the extent of relaxation depends on the drug used. This reduction in enthalpy relaxation can be attributed to (1) dilution effect due to the presence of polymers/excipients, (2) increase in T_g of glassy drug due to the antiplasticizing effect of polymers, and (3) molecular level interactions like H bonding, electrostatic forces of attraction, van der Waals interactions between the molecules of drug and the polymer[8]. To determine the individual effects of each factor on total enthalpy relaxation, their individual contributions were analyzed.

Table 2. Values of relaxation parameters (τ and β), degree of undercooling ($T_g - T_a$), log $t_{(\phi(t)=0.5)}$ for VLB and ETB.

VLB/ ETB	PVP	$T_g - T_a$ (°C)		τ (hours)		β		log $t_{(\phi(t)=0.5)}$	
(%, w/w)	(%, w/w)	VLB	ETB	VLB	ETB	VLB	ETB	VLB	ETB
100	0	18.90	20.50	24.95	17.12	0.486	0.494	1.00	1.00
99	1	18.92	22.22	22.77	25.16	0.518	0.493	1.04	1.06
98	2	19.51	20.96	35.89	21.10	0.449	0.534	1.12	1.09
95	5	20.24	22.79	23.50	21.40	0.565	0.612	1.30	1.14
90	10	23.78	23.69	65.76	23.36	0.550	0.798	1.79	1.22
85	15	26.89	26.17	99.48	34.76	0.697	0.674	2.64	1.38
80	20	31.46	29.71	106.4	52.07	1.000	0.662	3.68	1.69

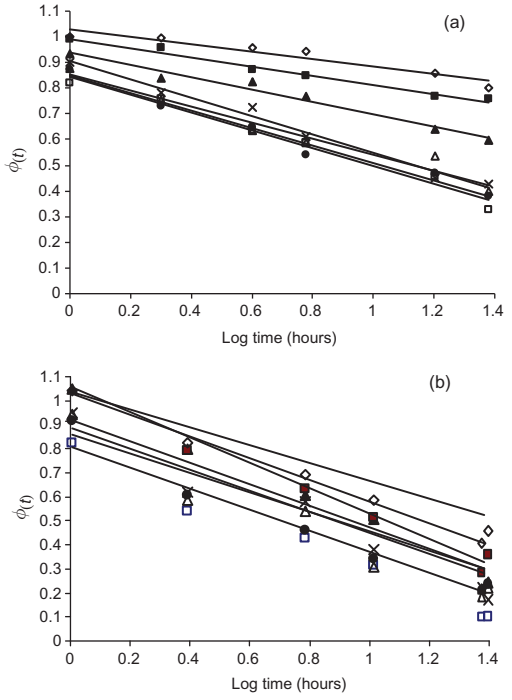

Figure 7. Proportion of glass relaxed with log of aging time for amorphous drug (□) and its solid dispersions with 1 (●), 2 (△), 5 (x), 10 (▲), 15 (■), 20% (w/w) (◇) PVP for VLB (a), and ETB (b). The straight lines represent linear fits to the data using least squares regression.

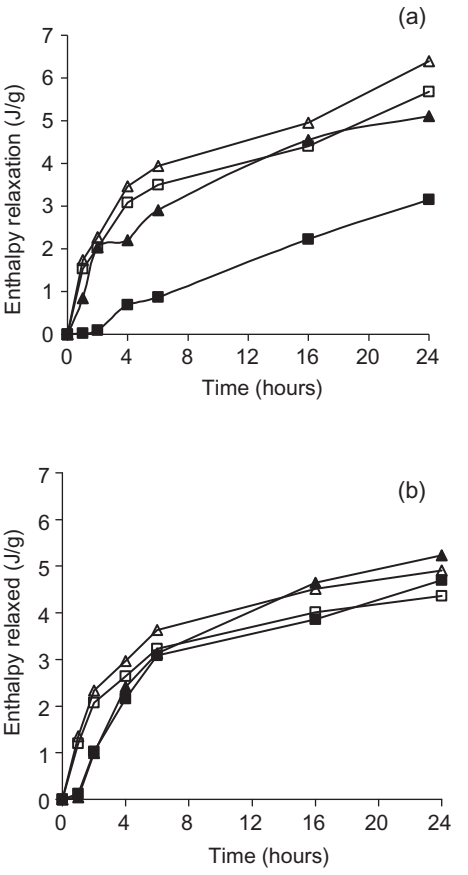

Figure 8. Comparison of experimentally observed enthalpy relaxation values with 10 (▲) and 20% (w/w) (■) PVP with those predicted for the same concentrations (△, □), respectively, according to the dilution effect for VLB (a), and ETB (b).

Dilution effect

Significant dilution of drug molecules occurs because of the addition of a high T_g polymer. As a result, the effective concentration of drug molecules undergoing relaxation will be lower in compositions with high polymer concentrations as compared to pure drug without any polymer. To assess the effect of polymer dilution, reduction in enthalpy relaxation due to the addition of polymer was calculated for both the drugs and was compared to their respective experimentally observed values, in case of 10% and 20% polymer concentrations (Figure 8).

As can be seen in the Figure 8, calculated enthalpy relaxation values on the basis of dilution effect were found to be higher as compared to those actually observed in case of VLB. However, in case of ETB the experimentally observed values were almost similar to those predicted using the dilution effect. The difference between the predicted and the experimental values was found to be highly significant ($P < 0.005$) in case of VLB and insignificant in case of ETB by using *t*-test. It is, therefore, highly likely that factors apart from the dilution effect are contributing critically toward lowering of enthalpy relaxation particularly in case of VLB that are absent in case of ETB.

Antiplasticization effect

Molecular mobility associated with any amorphous system is a direct function of difference between its T_g and storage temperature (T_a). Molecular mobility and hence 'instability' increases, as the difference $T_g - T_a$ decreases[10]. When an amorphous drug forms a miscible solution with polymers having high T_g values, the T_g of the binary mixture increases and the phenomenon is referred as antiplasticization. This results in an increase in degree of undercooling ($T_g - T_a$) and hence decrease the molecular mobility[36].

In case of VLB–PVP dispersions, an increase in T_g from 58°C to 71°C was observed with increasing polymer concentration (Figure 9). Presence of PVP showed a significant increase of 13°C from 0% to 20% PVP concentration. However, in case of ETB dispersions with similar concentrations of PVP, an increase of 9°C from 60°C to 69°C was observed. Similar facts were also demonstrated by Matsumoto et al. for binary mixtures of indomethacin and PVP[26].

Because both the drugs have similar concentrations of PVP, they should have shown a similar increase in T_g with

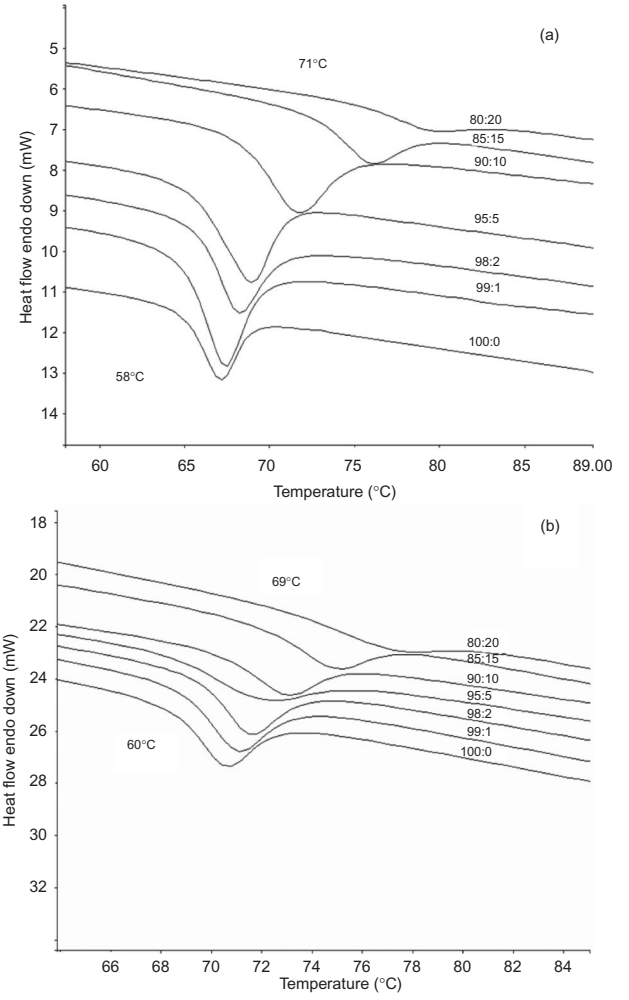

Figure 9. DSC thermograms showing decrease in enthalpy relaxation with increasing polymer concentrations with a concomitant increase in T_g for VLB (a), and ETB (b).

similar concentrations of PVP as their initial T_g values were almost equal. The contribution of miscibility of the drug and polymers to the phenomena could be ruled out, as both VLB–PVP and ETB–PVP dispersions have exhibited a single T_g value, indicating complete miscibility at all the drug–PVP compositions studied. It, therefore, appears that antiplasticization effect does not depend only on the additive property of T_g values and their weight fractions in solid dispersions as given by the Fox equation[37]. These results indicate that as both the drugs differ in the extent of interactions they undergo with PVP molecules, it is highly probable that presence of interactions contribute significantly toward antiplasticization effect[37].

Intermolecular interactions and enthalpy relaxation

It is known that –C=O of PVP can interact and H bond with –H containing functional groups like –OH, –NH[27]. Such an occurrence of molecular interactions could be reflected in the downward shift of vibrational frequency of characteristic functional groups. Therefore, to study differences in H bonding interactions of VLB and ETB with PVP, detailed FTIR studies of both the drugs and their amorphous solid dispersions were carried out[13,38]. These studies showed significant interactions between VLB and PVP molecules that were absent in case of ETB and PVP molecules (reproduced in Figure 10)[13,38]. The sulfonamide group present in VLB was found to participate in H bonding with –C=O group of PVP, which can lead to enhanced stability toward enthalpy relaxation and solubility[13,38].

In amorphous VLB and its PVP dispersions, –NH stretching band of sulfonamide broadened and shifted to 3256 from 3249 cm^{-1} as compared to crystalline VLB. Both asymmetric and symmetric bands of –S=O also shifted to 1338 and 1164 cm^{-1} from 1334 and 1150 cm^{-1}, respectively (Figure 10b)[38]. Above 15% PVP concentration, only one broadband was evident. These results showed that there was an increase in the extent and strength of H bonding between –C=O of PVP and –N–H of VLB with increasing PVP concentrations[23]. However, such interactions were not found between ETB and PVP molecules (Figure 10c). A similar trend was also observed in –C=O stretching frequency of PVP (Figure 10d). Stretching frequency of –C=O group shifted from 1675 to 1660 cm^{-1} in VLB–PVP dispersions. This shift was also absent in ETB–PVP dispersions.

These results show that differences in enthalpy relaxation (ER) behavior of both the drugs can be attributed to differences in their H bonding tendencies. H bonding has been postulated to be the major interacting force at the molecular level, with some contribution from nonpolar dispersion forces, for reduction in molecular mobility and enthalpy relaxation[39]. It appears that due to strong H bonding interactions between VLB and PVP molecules, molecular mobility slows down which results in a significant reduction in ER. Because cooperative motions in the supercooled state are micro-Brownian in nature that leads to α and αβ relaxations[40], it is quite probable that presence of polymers can lead to chain entanglements by intermolecular interactions thus hindering these motions. Because such interactions between the drug and the polymers can occur only when they are in a specific conformation, the configurational entropy of cooperatively rearranging regions will decrease significantly in the presence of polymers blunting ER[33]. These results suggest that structural characteristics (H bonding tendencies) of drug molecules play a significant role in determining the ER and hence the stability of amorphous dispersions[8]. Our findings provide a rational approach for the selection of drugs and polymers that can favorably interact to give 'stabilized' amorphous dispersions.

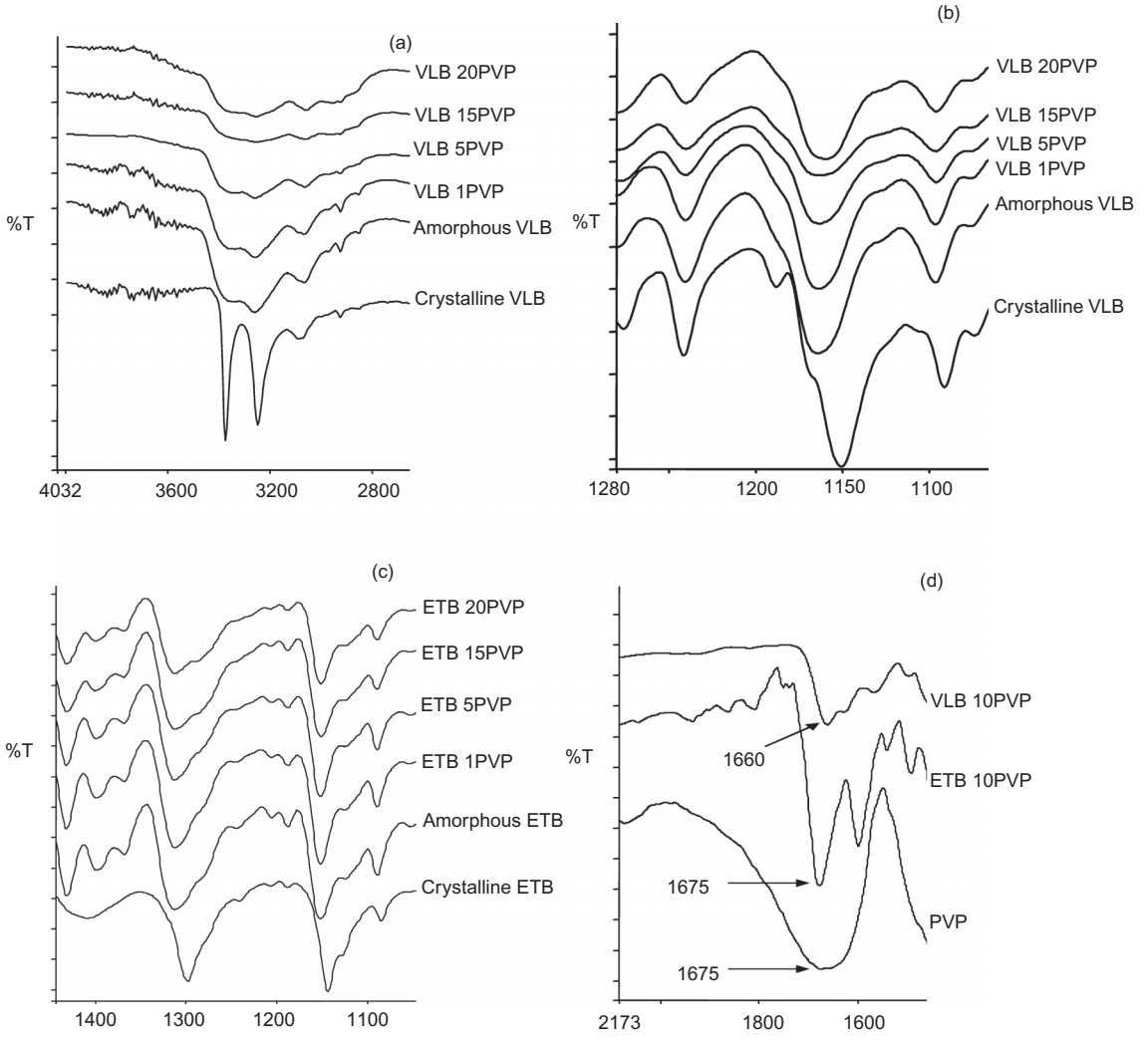

Figure 10. FTIR spectrum of (a) –N–H region of VLB, (b) –S=O region of VLB, (c) –S=O region of ETB; and their dispersions prepared with 1 (VLB 1PVP), 5 (VLB 5PVP), 15 (VLB 15PVP) and 20 (VLB 20PVP) % (w/w) PVP and (d) –C=O region of PVP and its dispersions with VLB and ETB containing 10% (w/w) PVP (From Bansal et al.,[13] reproduced with permission).

Conclusions

The structural relaxation of amorphous binary dispersions was found to be significantly low as compared to pure amorphous drugs. This structural relaxation was found to be significantly lower in case of VLB as compared to ETB which means that it varies widely with the chemical nature of the drugs. Presence of polymers in amorphous dispersions significantly affects the stability and stabilizes them toward devitrification. Polymers with high T_g increase the kinetic stability of amorphous drugs by decreasing their molecular mobility and enthalpy relaxation. The relaxation time constants determined through KWW equation failed to exhibit any trend, showing its inability to describe systems with varying local viscosities and structural heterogeneity, which gives rise to complex relaxation patterns. These polymers exert such effects either due to dilution effect, antiplasticization effect, or through the development of specific molecular interactions with the drug molecules.

This study additionally underlines the utility of enthalpy relaxation as an effective tool for the development of binary dispersions of amorphous drugs. Experimental protocols based on enthalpy relaxation can help in objective selection of polymers for the stabilization of high energy amorphous drugs. The rapidity of the experiments can help in reducing time and cost of formulation development. Therefore, this study shows that ER can provide a simplified experimental tool for rational selection of 'stabilizers' for amorphous dispersions.

Acknowledgments

The authors acknowledge Aarti drugs Ltd., Mumbai, India, for providing gift sample of VLB. Aditya Mohan Kaushal would like to acknowledge the Council of Scientific and Industrial Research (CSIR), New Delhi, India for providing senior research fellowship.

Declaration of interest

The authors report no declarations of interest. The authors alone are responsible for the content and writing of this paper.

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