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Co-relationship of physical stability of amorphous dispersions with enthalpy relaxation

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Physical stability studies of valdecoxib (VLB) and its solid dispersions with PVP (1, 2, 5, 10, 15 and 20% w/w) were carried out by Differential Scanning Calorimetry (DSC). Change in specific heat with time was measured to determine the degree of crystallinity of amorphous drug and its binary dispersions after storage at 40 °C and 75% RH. The rate of crystallization was found to decrease with increasing PVP concentration and time for 10% crystallization ($t_{90\%}$) was found to increase significantly for the amorphous drug when formulated as PVP dispersions. Enthalpy relaxation was found to be inversely correlated with $t_{90\%}$ (min) values and was found to be a good predictor of devitrification tendency and hence stability of amorphous VLB.

1. Introduction

Amorphous pharmaceuticals are often preferred for delivery of insoluble drugs due to their solubility and bioavailability advantages (Leuner and Dressman 2000). These advantages are due to a lack of ordered molecular arrangement where molecules are kinetically trapped in a high energy non-crystalline frozen state (Hancock 2002). Amorphous drugs represent the highest level of particle size reduction due to molecular level of particle sub-division and hence the energy required to break the crystal lattice of drugs becomes negligible and the drug dissolution rate hastens (Gupta et al. 2004a). These glassy pharmaceuticals, therefore, represent a solid with the structure of a liquid having high molecular mobility (Hancock 2002). This high molecular mobility of amorphous forms also confers a high degree of thermodynamic and kinetic instability (Surana et al. 2005).

The molecular disorderliness of amorphous pharmaceuticals is often manifested as excess entropy, volume, specific heat capacity and enthalpy (Kaushal et al. 2004). Storage of these glasses at a temperature T_a close to their T_g leads to attainment of equilibrium supercooled liquid state by loss of excess enthalpy, termed as enthalpy relaxation. This aging leads to an increase in density with a concomitant decrease in entropy and free volume. During reheating, the lost enthalpy is regained at T_g and is observed as an endotherm known as enthalpy recovery (Surana et al. 2005). Quantitative measurement of this enthalpy recovery thus gives the enthalpy relaxed during storage. This relaxation rate is an indication of molecular mobility at T_a which along with relaxation phenomena are also responsible for physical and chemical processes leading to unwanted changes like chemical reactivity and devitrification (Byrn et al. 2001).

The enhanced stabilization by solid dispersions has been postulated either due to an antiplasticization effect or specific drug carrier interactions (Weuts et al. 2003). In these dispersions, the drug can exist either in crystalline, amorphous or partially crystalline state each having a distinct dissolution profile. It is therefore critical to quantify the amorphous content to predict crystallization kinetics for ensuring predictable product behavior during the intended shelf life (Hancock 2002).

However, it is often difficult to study crystallization kinetics under real time conditions owing to their highly unstable and unpredictable nature. And there is no method available for predicting the relative stability of different polymeric dispersions of amorphous drugs. This makes development and commercialization of amorphous pharmaceuticals very challenging. Keeping in view the interdependency of storage temperature, molecular mobility, enthalpy relaxation and devitrification, we hypothesized that molecular mobility and hence enthalpy relaxation could be used as a predictor of devitrification tendency of amorphous pharmaceuticals. Since enthalpy relaxation studies are short term studies, its correlation with crystallization tendency could provide a rapid means for screening and selecting the optimum polymers for development and study of binary dispersions. With this aim, we determined the degree of crystallization of VLB at different time intervals as a function of polymer concentration at accelerated stability conditions (40 °C and 75% RH). The $t_{90\%}$ (min) values were determined using Avrami Erofeev equation and were correlated with enthalpy relaxation values to assess the use of latter, as a predictive tool for devitrification.

2. Investigations, results and discussion

2.1. Isothermal recrystallization studies

Amorphous drugs tend to devitrify during storage due to their kinetic and thermodynamic instability. A reduction in devitrification tendency can serve as a practical measure of 'stabilization' of amorphous drugs by high T_g polymers. Therefore, the dispersions of VLB were analyzed for differences in devitrification tendency and stability at accelerated stability conditions (40 °C and 75% RH). Water being a strong plasticizing agent (T_g – 135 K (Johari et al. 1987)) reduces the T_g of amorphous drugs and their binary dispersions and accelerates recrystallization. Quantitative analysis of amorphous fraction present in solid dispersions with various PVP concentrations was done by analyzing changes in heat capacity at T_g. Changes in the heat capacity at T_g are proportional to the amount of amorphous component in partially crystallized samples, it could be used as a measure of amorphous fraction in such samples (Miyazaki et al. 2006). Therefore, to measure the degree of crystallinity at high temperature and humidity conditions, ΔCp values of partially crystallized samples were determined and the fraction of amorphous form remaining at time t, X(t), was calculated by equation

$$X(t) = \Delta Cp(t)/\Delta Cp(0) \quad (1)$$

where ΔCp(0) and ΔCp(t) are the changes in the ΔCp initially and after time t. The X(t) values for VLB and its dispersions are shown in Fig. 1. ΔCp values decreased with time for amorphous drug and its binary dispersions, indicating increased crystallization. SDs of VLB with varying concentrations of PVP (1, 2, 5, 10, 15, 20% w/w) exhibited an increasing stability towards reversion as compared to pure amorphous VLB. PVP due to its high T_g (160 °C) acts as an antiplasticizing agent and hence delayed the recrystallization phenomenon (Gupta et al. 2004b).

Primary crystallization kinetics at initial stages of crystallization of amorphous drugs and their SDs can be best described by the Avrami Erofeev equation as suggested by Aso et al. (2004) due to their nonlinear behavior (Fornes and Paul 2003):

$$X(t) = \exp(-kt^n) \quad (2)$$

where k is the crystallization rate constant and n describes the nucleation and growth process. The parameters n and k were determined by fitting X(t) to the linearized form of this equation (Fornes and Paul 2003):

$$\ln(\ln(1/X(t))) = \ln k + n \ln t \quad (3)$$

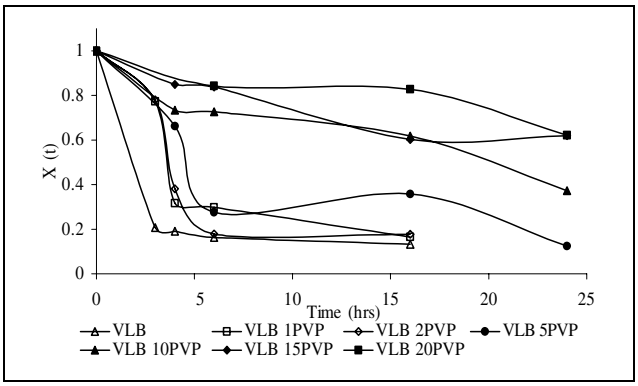

Fig. 1: Amorphous fraction determined by change in specific heat with time on storage for (a) VLB and and its dispersions with 1, 2, 5, 10, 15 and 20% w/w PVP (n = 3, SD ≤ 5%)

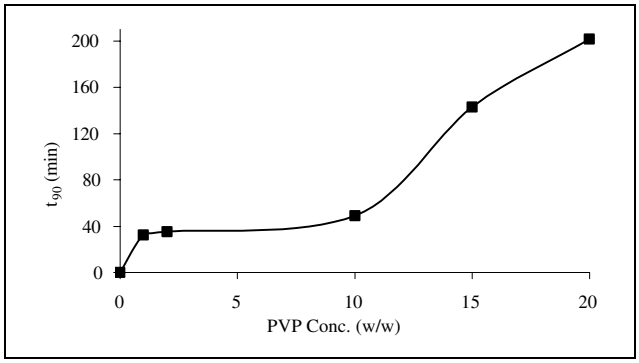

Fig. 2: Time required for 10% crystallization determined by Avrami Erofeev equation for VLB binary dispersions at different PVP concentrations

ln (ln (1/X(t))) values were analyzed against ln t by linear regression and values of k and n were determined. These k and n values were further used to determine t_{90} values for VLB and its SDs (Fig. 2) (Aso et al. 2004). It was found that increasing PVP concentrations increased the time for 10% crystallization to 200 fold (210 min) in presence of 20% w/w PVP and hence improved the stability manifold.

The inhibitory effect of small amounts of PVP against crystallization of VLB was attributed to antiplasticization effect and H bonding interactions between the drug and the polymer molecules (Matsumoto and Zografi 1999). The T_g of amorphous VLB increased from 58 to 71 °C with 20% w/w PVP concentration, showing an increase of 13 °C. This high increase in T_g confers VLB-PVP dispersions with higher stability. Further, Fourier Transform Infra Red based studies in our lab had revealed presence of significant interactions between VLB and PVP molecules (Bansal et al. 2007) may have contributed towards the same.

2.2. Correlation between enthalpy relaxation and stability

Enthalpy relaxation is a measure of molecular mobility which determines the physical stability of amorphous dispersions. Enthalpy relaxation studies for both the drugs and their PVP SDs were performed (results communicated elsewhere). Enthalpy relaxation values observed at various PVP concentrations were correlated with stability enhancement. For this purpose, the values of enthalpy relaxed at 24 h and $t_{90\%}$ (min) values determined by Avrami Erofeev equation were analyzed and are shown in Fig. 3. The results obtained clearly showed that in case of VLB, with

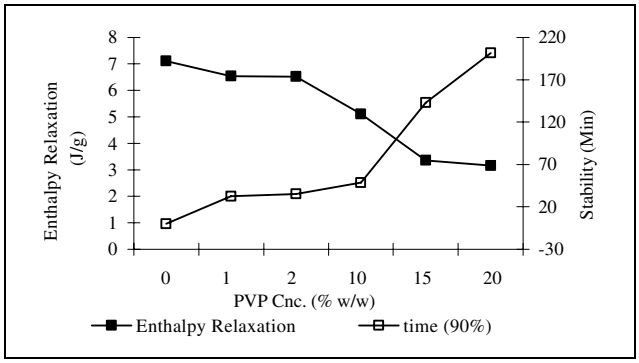

Fig. 3: Correlation between enthalpy relaxation and stability enhancement of VLB

increasing polymer concentration, reduction in enthalpy relaxation and increase in stability were observed. Karl Pearson's correlation function was used to analyze the results statistically by using Sigma Stat (version 2.0.3.0, SPSS Inc., Chicago, IL, USA) (Fig. 3). Karl Pearson's correlation function showed an inverse correlation between the two with increasing PVP concentration in case of VLB having $r^2 = 0.95$ with P value less than 0.002. It shows that ER could be used as a measure of stability for VLB and its dispersions and could provide useful insights for preliminary screening of drug polymer dispersions for stability enhancement. However, extensive studies with a number of drugs and polymers are required to substantiate this correlation for other drugs as well.

Previously our lab had demonstrated the usefulness of enthalpy relaxation studies for screening of stabilizers for amorphous solid dispersions (Kakumanu and Bansal 2002). Thereafter in separate publication we had demonstrated a inverse correlation between enthalpy relaxation and aqueous solubility advantage in two model drugs celecoxib (Gupta et al. 2004b) and VLB (Bansal et al. 2007). This part of the work has demonstrated the importance of enthalpy relaxation for devitrification kinetics, thus establishing overall significance and utility of enthalpy relaxation studies for designing amorphous solid dispersions. The concept however requires further validation by incorporating drugs having varying molecular mobility in their amorphous state.

In conclusions the stability of VLB and its dispersions was found to increase with increasing PVP concentration. The degree of crystallization was found to decrease significantly with increasing PVP concentration at accelerated conditions of temperature and humidity. $t_{90\%}$ values were found to increase significantly for VLB-PVP dispersions. An inverse correlation was observed between enthalpy relaxation and stability with increasing PVP concentrations. Solubility enhancement was found to be directly correlated with increased physical stability.

3. Experimental

3.1. Materials

Valdecoxib (VLB) was a generous gift from Aarti drugs limited (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.

3.2. Isothermal crystallization studies

Preliminary amorphous dispersions of VLB were prepared using solvent evaporation technique to ensure the homogenous mixing of drug and the polymer at the molecular level. The technique involved the solubilization of drug and the polymer in appropriate ratios in methanol dichloromethane cosolvent (1 : 1), followed by evaporation under vacuum. These binary dispersions were again amorphized in DSC instrument (Diamond DSC, Perkin Elmer, Shelton, USA) at a controlled rate under nitrogen purge (20 ml/min). Samples of about 7–8 mg were taken in standard aluminium pans and heated to 10 °C above their melting point at 100 °C/min without sealing the pans. This temperature was maintained for 1 min to standardize the thermal history of sample and was cooled to room temperature at 20 °C/min. These open DSC pans were then placed in desiccators maintained at 75% RH by using saturated NaCl solution under vacuum and they were placed in an oven maintained at 40 ± 1 °C. Samples were removed at specific time intervals and analyzed by the 'Iso-Step-Iso' method of Perkin Elmer Diamond DSC. The method involved an isothermal hold for 1 min at room temperature, followed by a linear heating at a rate of 20 °C/min and again an isothermal hold of 1 min at final temperature. The thermograms obtained were analyzed for changes in heat capacity and T_g.

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