Enthalpy Relaxation Studies of Celecoxib Amorphous Mixtures

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Purpose. The purpose of this study was to compare the structural relaxation and molecular mobility of amorphous celecoxib (CEL) with that of CEL amorphous mixtures consisting of various excipients and to study the effect of different excipients on the relaxation of high-energy amorphous systems.

Methods. The measurement of glass transition temperatures (Tg) and enthalpy relaxation were performed using differential scanning calorimetry. The interactions between drug and excipients and the absence of crystalline forms were further confirmed by conducting Fourier transform infrared spectroscopic and X-ray powder diffraction studies on same samples.

Results. All samples exhibited a single Tg value. Polymers had a prominent effect on the lowering of the relaxation rate in amorphous CEL. The lowering of the rate of relaxation was directly dependent on the concentration and type of polymer used. The total enthalpy required for relaxation was same, although additives affected the rate of relaxation.

Conclusions. In absence of any specific interactions during Fourier transform infrared studies, it was concluded that the antiplasticizing activity of polymers is responsible for the stabilization of CEL amorphous systems. Glassy amorphous dispersions of CEL exhibited a complex type of relaxation pattern, which failed to fit in Kohlrausch-Williams-Watts equation with respect to calculation of relaxation time constants.

KEY WORDS: celecoxib; glass transition temperature; molecular dispersion; enthalpy relaxation; molecular mobility.

INTRODUCTION

Amorphous systems offer a versatile tool to pharmaceutical scientists in improving aqueous solubility, bioavailability, and performance characteristics (1–6) of drugs and excipients. Such advantages are offered because of excess properties of amorphous systems in terms of enthalpy, entropy, and free energy. These high-energy systems are unstable and tend to spontaneously revert back to the thermodynamically stable crystalline state (7–10). This metastability is caused by a high degree of molecular mobility existing in them, which is highest near melting point and reaches zero at glass transition temperature (Tg). However, there are reports showing the existence of molecular mobility even below Tg (8,11). The functional advantages of the amorphous state can be beneficially exploited if their instability can be retarded over meaningful time scales for pharmaceutically important products. A useful approach in stabilizing the amorphous systems is the preparation of molecular dispersion of drug with polymers having a higher Tg. The resultant mixture has a higher Tg as compared with drug alone, thereby reducing its molecular mobility and crystallization tendency. The stability of amorphous pharmaceuticals can be evaluated and predicted most conveniently by determining molecular mobility. A variety of techniques have been used for the characterization of molecular motions in amorphous materials, such as dielectric relaxation, dynamic mechanical analysis (12,13), along with thermal methods (11). Of these, differential scanning calorimetry (DSC) is frequently used because of ease of analysis and small sample requirement.

The purpose of present investigation is to compare the molecular mobility of amorphous celecoxib (CEL) with that of amorphous CEL mixtures consisting of various excipients and to study the effect of the latter on the structural relaxation of the high-energy amorphous state. The study was performed using DSC to measure the enthalpy changes accompanying the structural relaxation of CEL alone and in dispersions with time. The enthalpy relaxation of amorphous CEL alone and CEL-excipient dispersions in different concentrations were measured for aging up to 16 h. The aging temperature (Ta) selected was 25°C, which is nearly 30°C less than the Tg of CEL. The degree of undercooling (Tg – Ta) varied for different dispersions depending on their composition. That particular degree of undercooling was selected because it represents the ambient temperature where substances are usually stored.

MATERIALS AND METHODS

Materials

CEL was obtained as a gift sample from Unichem Laboratories Ltd., (Raigod, India). Poly(vinylpyrrolidone) (PVP) K30 (molecular weight 44,000–54,000), and PVP K17 (molecular weight 7,000–11,000) were obtained from BASF Corporation Ltd., (Ludwigshafen, Germany). Hydoxypropylmethylcellulose (HPMC) K100LV was obtained from Colorcon Asia Pvt. Ltd., (Mumbai, India). Anhydrous α,α-trehalose (α-D-glucopyranosyl-α-D-glucopyranoside) was purchased form Fluka Chemicals, (Buchs, Switzerland). All materials were used as obtained without further purification, and stored in chambers containing phosphorus pentoxide (P_2O_5) at room temperatures to prevent them from exposure to moisture.

Methods

Preparing Glassy Mixtures of CEL

All glassy systems studied for relaxation enthalpy were prepared in the DSC instrument itself. Dispersions of CEL with various excipients were prepared by solvent evaporation technique. The technique involved the solubilization of about 1 g of appropriate ratios of both the components, CEL and excipient, in methanol (methanol:dichloromethane in 1:1 ratio for sample III), followed by evaporation under vacuum. This step was necessary to ensure the homogeneous mixing of excipients with CEL, which as such was difficult to achieve because of low excipient concentration and the poor mixing properties of CEL. It was observed in all the cases (except higher concentrations of PVP), before the glass was prepared, that the mixture was present in crystalline form and free from

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amorphous nature. Any residual solvent was removed by vacuum drying at temperatures of 40–50°C for 2–3 h. The dispersions prepared were powdered in a mortar and pestle, passed through a sieve (BSS # 60), and stored over P_2O_5 desiccant at room temperature.

X-Ray Powder Diffraction

A Phillips (PW1729) powder X-ray diffractometer (Holland) attached to a diffractometer control (PW1710) and an online recorder (PM8203A) were used to confirm the absence of the crystalline CEL in various molecular dispersions. The radiation used was generated by a copper Kα source fitted with Ni filter at a 0.154-nm wavelength at 20 mA and 35 kV. Samples were scanned over a range of 2θ values from 5° to 40° at a scan rate of 1.5°/min.

Fourier-Transform Infrared (FTIR) Spectroscopy

FTIR spectroscopy was performed on Impact-410 (Nicolet, Madison, WI, USA) spectrophotometer that was equipped with OMNIC analyzing software. The spectra were collected with powder samples dispersed as 0.5–1% mix in potassium bromide and scanned immediately after mixing. The analyses were performed with samples from two batches and in duplicate.

DSC

Samples prepared by solvent evaporation technique were used for preparation of glassy amorphous systems in the DSC instrument. The samples were analyzed under dry nitrogen purge with a heating/cooling rate of 20°C/min using Mettler Toledo DSC 821 (Switzerland) that was operated with Star software version Solaris 2.5.1 and equipped with automated cooling accessory. The DSC instrument was calibrated for temperature and heat flow with indium. Samples of about 9–15 mg were taken in standard aluminum pans, sealed with a pin-hole, and then heated to 3°C above the melting point of CEL, and this temperature was maintained for about 1 min to standardize the thermal history of sample. The samples were then cooled immediately in the DSC instrument itself to the aging temperature to form the glass, which were stored at 25 ± 0.5°C at 0% relative humidity (RH) for specified time periods. At various time intervals, samples were analyzed by measuring the enthalpy relaxation at Tg. The heating run was continued until melting temperature to confirm for any crystallization. The area of the endothermic peak at Tg at different times was measured by constructing a tangent to the line of heat flow after Tg and extrapolating it to other side to enable measurement of accurate enthalpy changes over the phase transformation.

RESULTS AND DISCUSSION

Glass Transition Temperatures

The onset Tg and Cp values for CEL and various dispersions were measured by DSC. Table I shows an increase in onset Tg values in proportion to the concentration of excipients. But the Tg values of dispersions at 10% concentration were similar to that of CEL and with each other. Before measuring the relaxation, the extent of mixing of excipient with the drug under investigation has to be studied because it causes considerable variation in the Tg and, in turn, relaxation of enthalpy. As a measure of determining goodness of mixing, measured Tg values were compared with those of predicted Tg values obtained with Couchman-Karasz equation (C-K equation, Eq. 1) (14).

$$Tg = \frac{w_1 Tg_1 + K w_2 Tg_2}{w_1 + K w_2} \quad (1)$$

where w_1 and w_2 are weight fractions of each component and Tg_1 and Tg_2 are their corresponding Tg values. K, in C-K equation, a thermodynamic model, is defined as follows:

$$K = \frac{\Delta Cp_2}{\Delta Cp_1} \quad (2)$$

where ΔCp is the difference in heat capacity at Tg. The Tg values can also be calculated from Gordan-Taylor equation (Eq. 3), where K is defined with the help of densities (ρ_1 and ρ_2 are densities of each of the two compounds). These two theoretical models produce almost similar predicted values (15).

Table I. Sample Composition in Various Dispersions, with Their Onset Tg Values, Degree of Undercooling and ΔH Values Measured after 170 Hours in Comparison to the Calculated ΔH_∞ Values as Measured by DSC

Sample code	Sample components	Additive concentration	Onset Tg (°C)	Tg – Ta	ΔH_{170} (J/gm)[a]	ΔH_∞ (J/gm)
CEL	Celecoxib	—	54.45	29.45	14.57	15.34
—	PVP K30	—	154.50	—	—	—
—	PVP K17	—	152.23	—	—	—
—	HPMC K100LV	—	163.35	—	—	—
—	Trehalose	—	117.05	—	—	—
Ia	CEL + PVP K30	5%	57.30	—	—	—
Ib	CEL + PVP K30	10%	59.21	34.21	15.29	18.54
Ic	CEL + PVP K30	25%	70.98	—	—	—
Id	CEL + PVP K30	50%	106.31	—	—	—
II	CEL + PVP K17	10%	58.57	33.57	15.42	17.96
III	CEL + HPMC	10%	57.05	32.05	15.83	17.40
IV	CEL + Trehalose	10%	57.72	32.72	15.91	17.30

[a] Reported values are within ± 0.8 standard deviation.

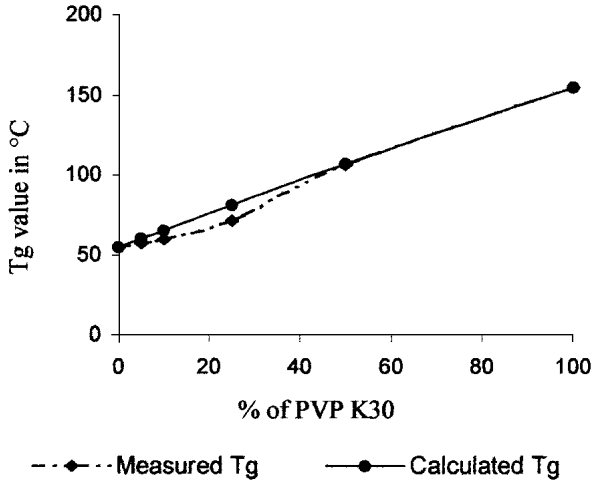

Fig. 1. Plot showing Tg values as a function of PVP K30 concentration and association of measured Tg values with calculated for dispersions.

$$K \approx \frac{\rho_1 Tg_1}{\rho_2 Tg_2} \tag{3}$$

The observed Tg values are in close agreement with the predicted values. Figure 1 shows the plot of onset Tg values vs. the weight fraction of PVP K30. Also, there was only a single Tg observed in the entire concentration range for PVP and other dispersions, indicating the presence of a single amorphous phase. This shows a good level of mixing in the samples. Thus, the effect of polymer on thermodynamic behavior was maximally observed in these studies.

Enthalpy Relaxation Studies

Amorphous substances aging at a particular temperature below Tg shows the crystallization of the glassy state via the equilibrium supercooled liquid state. The material experiences a gradual loss in energy in terms of enthalpy because of the effect of molecular motions occurring at prevailing conditions, which drive it toward a more stable crystalline state. The amount of enthalpy lost during storage is recovered by the sample during its heating run in DSC to reach same equilibrium supercooled liquid state. The enthalpy lost or relaxed can be measured with time, and it reflects the molecular mobility and, in other words, the crystallization rate of unstable glassy amorphous system, provided the amorphous systems are prepared in a consistent manner. This recovery of enthalpy at Tg can be quantified easily with the standard DSC acquisition software. A comparative assessment of stabilization capacity of various polymers was obtained by measuring the structural relaxation of the amorphous drug in their presence. An evaluation was performed on dispersions containing 10% excipients, Ib, II, III, and IV and dispersions containing PVP K30 in different concentrations, Ia, Ib, Ic, and Id (refer to Table I). The present work was similar to techniques used previously in characterizing the molecular mobility of solids of pharmaceutical interest, such as drugs (11), carbohydrates (14), polymers (16), and also proteins (17) alone and in amorphous dispersion forms. The DSC observations for CEL after aging at 30°C undercooling of Tg at different time points are shown in Fig. 2. The size of the endothermic peak accompanying Tg experienced gradual enhancement with time, reflecting an increase in enthalpy recovery and structural relaxation of glass toward the supercooled liquid region. The enthalpy changes observed for various dispersions of CEL are qualitatively similar to the observations in Fig. 2. The observations showed that all the dispersions exhibited a considerable reduction in enthalpy recovery compared with CEL alone (Figs. 3 and 4). The reduced enthalpy relaxation with time was attributed to following three reasons: 1) dilution effect, because dispersions constitute some quantity of additives. This assumes no significant contribution of additives added to dispersions in total relaxation of the mixture at that particular temperature. 2) Nonspecific effect i.e., antiplasticizing effect or raising of Tg of system, which is commonly observed with polymers. 3) Interactions occurring at the molecular level, like hydrogen bonding or any other weak electrostatic bonding between the two components. Thus, any of the above factors mentioned in combination or alone may have contributed to the overall effect of reduced structural relaxation of CEL dispersions with time. The dilution effect was evaluated by comparing the enthalpy values of disper-

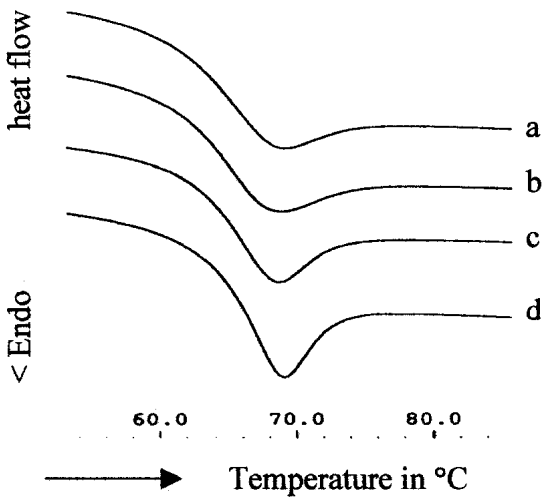

Fig. 2. Typical representation of DSC scans of amorphous CEL dispersion aged at 25°C; (a) 2 h, (b) 4 h, (c) 8 h, and (d) 16 h.

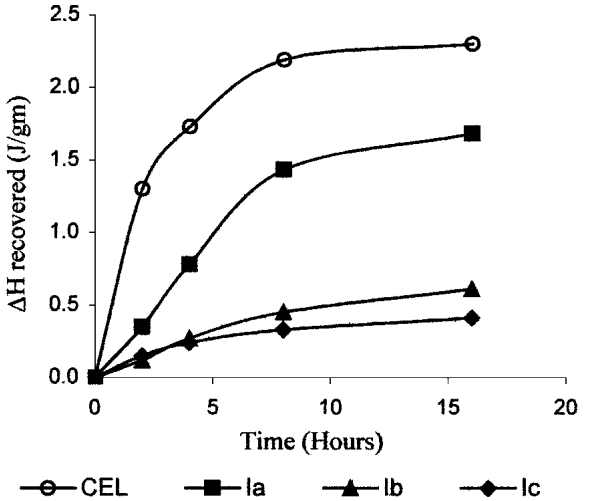

Fig. 3. Relaxed enthalpy values for CEL-PVP K30 dispersions aged at 25°C for up to 16 h.

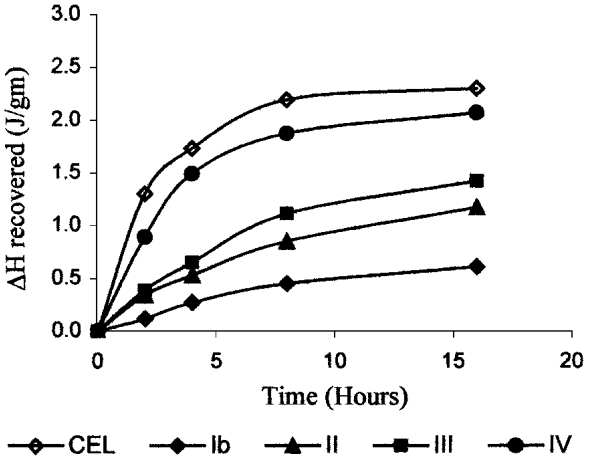

Fig. 4. Effect of various excipients on enthalpy relaxation of CEL amorphous dispersions at 10% concentration.

sions with that of 10% dilution enthalpy values of pure CEL (Fig. 5). It was observed in all cases, except for trehalose, that the enthalpy values were lowered beyond the predicted values of simple additive dilution. In the case of trehalose, the reduced enthalpy values were comparatively nearer to those of the predicted values, considering a 10% additive dilution. This reflects the fact that CEL dispersion with trehalose was devoid of any specific interactions between the components and the antiplasticizing effect of trehalose and that reduced enthalpy recoveries seem to be solely the result of the effect of dilution factor, whereas, in all other dispersions, the reduction in enthalpy recovery values were far from predicted values based on dilution factor. This points toward the antiplasticizing effect of polymer or specific interaction between components at molecular level. FTIR studies revealed that there were no specific identifiable interactions between constituents of dispersions, which supports that net lowering of enthalpy relaxation in all dispersions is caused primarily by the antiplasticizing effect and secondarily by the dilution effect.

From the results, it was observed that in all cases, whether for CEL alone or its dispersions, similar aging phenomena occurs with time and temperature. To better understand the

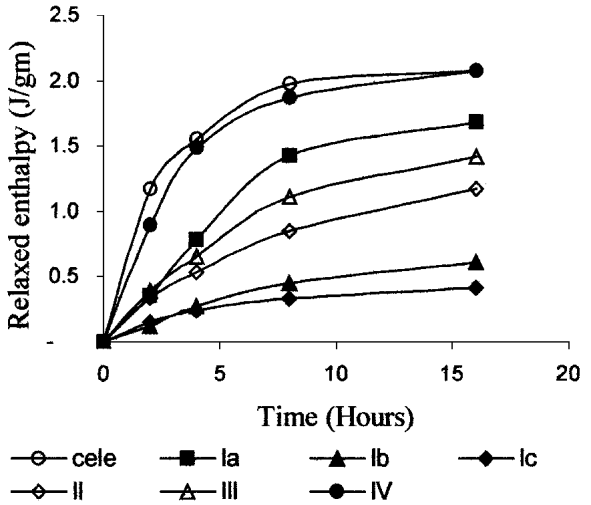

Fig. 5. Relaxed enthalpy values of CEL dispersions in comparison with calculated values of CEL with 10% additive dilution.

relative effects of different additives on mobility of CEL in glassy mixtures, the extent of enthalpy relaxation was calculated for various dispersions. Because the crystalline state is the most stable state having low internal energy, glassy material loses its energy in the form of heat to reach stabilized state via supercooled region, which is assumed to be the state of equilibrium as compared with the nonequilibrium glassy state. The enthalpy change necessary for a glass to reach a supercooled state depends on thermal history of the same and the degree of undercooling or aging temperature below Tg. But the presence of additives is supposed to affect only the rate of enthalpy recovery or structural relaxation. As all samples studied were subjected to same thermal treatment protocol; effectively, enthalpy change depended only on aging temperature. The total or maximum enthalpy change (ΔH_∞) needed for a glass to relax to a supercooled state increases linearly with decrease in degree of undercooling, as explained by Eq. (4):

$$\Delta H_\infty = \Delta Cp\ (Tg - Ta) \tag{4}$$

where ΔCp is the change in heat capacity at Tg, i.e., difference in heat capacity between supercooled and glassy states.

The ΔH_∞ values were measured for various dispersions after a long storage period (>170 h) to observe the effect of polymer on it. Also, the ΔH_∞ values were calculated using Eq. (4). The results are tabulated in the Table I. The measured ΔH_∞ values ranged from 14.5 J/g to 16 J/g and calculated values ranged from 15.3 J/g to 18.5 J/g, which were in very close agreement with each other. The results indicate that excipients had no effect on the enthalpy change required for a glass to reach supercooled state, but only rate of enthalpy change was affected. Similar behavior was observed for glassy polymers (18) and sucrose (15), where comparable values of ΔH values were measured after long storage periods with calculated ΔH_∞ values from Eq. (4). This again confirms that the ΔH_∞ values calculated represent total enthalpy change needed for a glass for phase transformation. Predicted ΔH_∞ values were used for further calculations of structural relaxation parameters. From the maximum enthalpy recovery, the extent to which a material relaxes (ϕ_t) can be calculated for any time (t) and temperature (Ta), by Eq. (5), as at each time, a lesser fraction of the mixtures had relaxed as compared to CEL alone (Figs. 6 and 7). Equation (5) normalizes the ΔH values measured for CEL and its dispersions, enabling comparison of rate of structural relaxation.

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

where ΔH_t is the measured enthalpy recovery at particular conditions and ϕ_t reflects the proportion of the glass that has been relaxed over time t. The greater the value of ϕ_t, lesser is the relaxation of glass to the pseudoequilibrium supercooled state. However, the appropriate way to express the extent of relaxation is to describe it in an easiest manner like relaxation time constants, the most common of which is the Kohlrausch–Williams–Watts (KWW) equation. The KWW equation (Eq. 6) assumes that multiple relaxation processes occur simultaneously, with distribution of multiple relaxation times, and enables the data to be fitted to a stretched exponential function using nonlinear regression to obtain a single overall average relaxation time constant (τ).

$$\phi_t = \exp\ (-t/\tau)^\beta \tag{6}$$

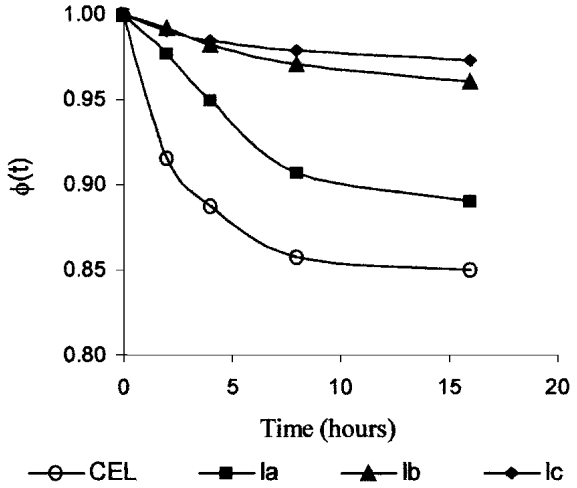

Fig. 6. Proportion of glass relaxed with aging time for CEL- PVP K30 dispersions.

In Eq. (6), a relaxation time parameter (β) represents relaxation behavior, which describes the extent to which it is nonexponential, and is defined with a value between 0 and 1. If the value of β is equal to 1, then there exists only a single relaxation time. As the glass relaxes toward the pseudoequilibrium supercooled state, some changes occur within the substance at molecular level, such as a decrease in free volume and free enthalpy, which affects molecular motions. Thus, the relaxation of glasses is nonexponential and cannot be explained by normal mathematical models. It is also possible to calculate τ by combining Eqs. (5) and (6) and fitting the experimental data to nonlinear regression analysis. In the present experiment, time constants were calculated from enthalpy recovery data using Eqs. (4), (5), and (6) and the curve fit feature of Sigma Plot (version 4.01, Jandel Scientific, USA). The best fit to the data was analyzed by fitting the data to an iterative nonlinear regression by Marquardt algorithm, with initial parameters provided $\tau = 100$ s and $\beta = 0.5$ for all samples studied. But in the results, whereas CEL has shown reasonable fit to the equation with values of $\tau = 2.79$ h and $\beta = 0.274$, data from other samples showed a considerable deviation to fit KWW equation by nonlinear fit method. The errors in measured values of mixtures can be attributed to various reasons. The excipient mixtures might be exhibiting a more complex type of relaxation behavior for which the KWW equation (using two optimized parameters, τ and β) and nonlinear regression approach are not the right tools to explain multiple relaxation behaviors occurring simultaneously.

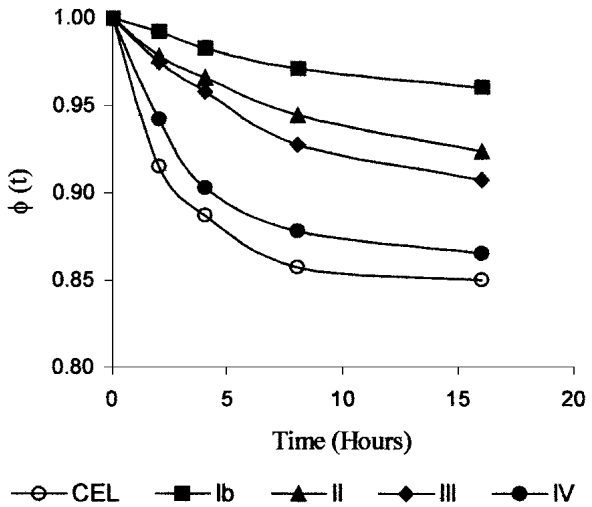

Fig. 7. Effect of various excipients on proportion of glass relaxed from CEL dispersions with time at 10% concentration.

The existence of complex relaxation processes in case of mixtures as compared with a single component was proven by dielectric and dynamic mechanical analysis techniques (19,20). As it is well known that in glassy systems there exist different regions at the microlevel with varying densities and viscosities (21–23), especially when two components of different nature, such as a small organic molecule and a large high molecular weight polymer are present. This leads to more structural relaxation in areas having less local densities and viscosities. This may reflect considerable varying rates of relaxation below Tg, leading to unusual behaviors and the analytical techniques used capture only an average of Tg value and other thermodynamic processes. The β value obtained for CEL also infers about complexity of the relaxation process because the value of β is far from the value of unity, which is a single relaxation time model. A similar type of observation was obtained in case of sucrose, a highly water-soluble compound, where the KWW equation has failed to deduce the true quantitative relaxation time constants (15). In such cases, more sophisticated tools or a combination of analytical techniques are needed to measure the contribution of individual processes. Besides, the KWW equation is more suitable for studying a single component rather than comparisons because the calculations involve simple parameters such as Tg, which is not sensitive to minute changes in composition. A small observable change in Tg value for 5% and 10% of PVP K30 further illustrates this point. A small error in measuring these values can lead to magnified error because of the sensitivity of the nonlinear regression algorithm. Further, the contribution of polyamorphism in these processes needs to be aggressively researched (24).

CONCLUSIONS

The structural relaxation of amorphous CEL dispersions from glassy state was significantly less as compared with pure amorphous CEL when studied using enthalpy relaxation at single temperature below Tg measured through DSC. The addition of high molecular weight polymers seems to stabilize the amorphous system in best way. Even though all samples need same enthalpy change for reaching a supercooled liquid state, the rate of enthalpy change is affected by the addition of excipients to the amorphous substance under study. In the present investigation, the reason for reduction in enthalpy relaxation of CEL dispersions was caused by the antiplasticizing effect of excipients and, to a small extent, the dilution effect. No specific interactions between CEL and stabilizing excipients could be identified by FTIR. The presence of such specific interactions effectively retard the rate of structural relaxation, as was observed in case of indomethacin (25) and sucrose (14,15) mixtures. The relaxation time constant for CEL was determined, but the data generated for various mixtures of CEL were unable to fit into the KWW equation using nonlinear regression analysis, which might be attributed to

complex type of relaxation patterns existing in them and failure of the equation to explain those. To elucidate such situations more critically, more sophisticated or combination of tools have to be used that can be able to resolve and study the individual processes occurring in different regions at the molecular level. Structural relaxation studies can be conveniently and effectively used to compare potential of various excipients in stabilizing the high-energy amorphous state.

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