Stability and Solubility of Celecoxib–PVP Amorphous Dispersions: A Molecular Perspective

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Purpose. The purpose of the current study is to evaluate the solubility advantage offered by celecoxib (CEL) amorphous systems and to characterize and correlate the physical and thermodynamic properties of CEL and its amorphous molecular dispersions containing poly(vinylpyrrolidone) (PVP).

Methods. The measurement of crystalline content, glass transition temperatures, and enthalpy relaxation was performed using differential scanning calorimetry. Solubility and dissolutions studies were conducted at 37°C to elucidate release mechanisms. Further, the amorphous systems were characterized by polarized light microscopy and X-ray powder diffraction studies.

Results. The PVP content has a prominent effect on the stability and solubility profiles of amorphous systems. A dispersion of 20% w/w PVP with CEL resulted in a maxima in terms of solubility enhancement and lowering of relaxation enthalpy. The release of drug from amorphous molecular dispersions was found to be drug-dependent and independent of the carrier.

Conclusions. The solubility enhancement and enthalpy relaxation studies with respect to PVP concentration helped in a better prediction of role of carrier and optimization of concentration in the use of solid dispersions or amorphous systems. The drug release mechanism is drug-controlled rather than carrier-controlled.

KEY WORDS: celecoxib; characterization; enthalpy relaxation; molecular dispersion; release mechanisms.

INTRODUCTION

The enhancement of oral bioavailability of poorly water soluble drugs remains as one of the major hurdles to a drug development scientist. Salt formation and particle size reduction (1) are the most common techniques to improve solubility, but there are practical limitations to these techniques (2). As an alternative, amorphous systems in the form of solid dispersions have extensively been researched and exploited (3–5). Despite decades of research, there still remain many unanswered questions regarding their performance, primarily due to their complex thermodynamic behavior. This has also resulted in an abysmally low number of amorphous systems being commercialized. The main reason for the poor understanding of amorphous systems is due to limited knowledge on i) complicated thermodynamic behavior in solid state (6–10), ii) release mechanisms in solution (11), and iii) stability kinetics during storage. Some of the literature has compiled information needed for basic understanding of physical, chemical, and thermodynamic behavior of amorphous systems (2,11–13).

In the current study, the amorphous systems of a selective cyclooxygenase-2 (COX-2) inhibitor, celecoxib (CEL), and its molecular dispersions with poly(vinylpyrrolidone) (PVP) were studied for their physical and thermodynamic behavior. Amorphous form of CEL has already shown promising results with regard to solubility enhancement (14,15). Molecular mobility studies of various CEL amorphous mixtures at 25°C were also performed, and those mixtures containing PVP K30 showed minimal enthalpy relaxation thus offering stabilization of the high-energy amorphous CEL systems (16). But the processes that occur during the solubilization or dissolution were not completely elucidated. Apart from the solid-state stability of amorphous solid dispersions, its crystallization tendency in a solvent or dissolution medium also crucially affects its performance. The current work attempts to further understand the stability and solubility behavior of CEL–PVP dispersions and correlates it with the molecular events.

MATERIALS AND METHODS

Materials

CEL was purchased from Unichem Laboratories Ltd. (Raigad, India). PVP (K29/32) was obtained from ISP Technologies (Wayne, NJ, USA). All the materials were used as obtained without further purification and were stored in desiccators containing phosphorus pentoxide (P_2O_5) at room temperature to prevent exposure to moisture.

Methods

Preparation of Glassy Molecular Dispersions

Various molecular dispersions of CEL were prepared in the concentration range of 1–60% w/w of PVP. Amorphous CEL and its molecular dispersions with PVP for solubility and isothermal recrystallization studies were prepared by quench cooling of melt, using liquid nitrogen. The chemical stability of the quench-cooled product was assessed by High Performance Liquid Chromatography (HPLC) analysis. The amorphous systems for enthalpy relaxation studies were prepared in the differential scanning calorimetry (DSC) instrument itself as described earlier (16). Samples of about 9–15 mg were taken in standard aluminum pans, hermetically 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 and were stored at 25 ± 0.5°C at 0% relative humidity (RH) for specified time periods.

Prior to glass preparation in both cases, all 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 dichloromethane, 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

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and the poor mixing properties of CEL. Any residual solvent was removed by vacuum drying at temperatures of 40–50°C for 2–3 h.

Preparation of Physical Mixtures

Crystalline or amorphous CEL fractions were physically mixed, in geometric progression, with weighed proportions of PVP, for use in solubility studies.

X-ray Powder Diffraction

A Phillips (PW1729) powder X-ray diffractometer (Phillips, Almelo, Holland) attached to a diffractometer control (PW1710) and an online recorder (PM8203A) was used to study the solid-state of CEL. The radiation used was generated by a Cu Kα source fitted with Ni filter at 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.

Polarized Light Microscopy

Polarized light microscopy was carried out using Leica DMLP microscope (Leica Microsystems, Wetzlar, Germany) equipped with online camera Leica DC 300. Acquired images were analyzed using Leica IM 50, version 1.20, release-19 image management software.

Differential Scanning Calorimetry

The DSC analyses of samples, 9–15 mg in hermetically sealed standard aluminum pans with single pin-hole, were performed under dry nitrogen purge (80 ml/min) using Mettler Toledo DSC 821^e (Switzerland) instrument, operating with STAR^e software version 5.1 and equipped with automated cooling accessory. The instrument was calibrated to specifications for temperature and heat flow using 4-Nitro toluene, Naphthalene, and Indium. The samples for measuring relaxation enthalpy at time point of 16 h were analyzed from 25°C to 200°C with a heating rate of 20°C/min as explained earlier (16). Samples were run from 25°C to 200°C with a heating rate of 5°C/min for calculation of crystalline content, as described by Mooter *et al.* (17).

Solubility Measurements

Aqueous solubility of various CEL–PVP dispersions and physical mixtures at 37 ± 0.1°C was determined by placing an excess quantity of about 10 mg of freshly prepared, powdered, and sieved (BSS no. 60) sample in a 15-ml screw-capped glass vial containing 5 ml of distilled water, pre-equilibrated to required temperature. The vials were mechanically shaken in a shaker water bath (Julabo SW 23, Seelbach, Germany), at 200 rpm. At specified time periods, samples were withdrawn (n = 3), filtered through a 0.22-μm nylon membrane filter, and analyzed for drug content at 252 nm spectrophotometrically, after suitable dilution.

Isothermal Recrystallization Studies

About 100 mg of freshly prepared quench-cooled glassy dispersions were distributed into glass vials and stored at 25 ± 0.3°C with various humidity conditions 0%, 35%, 60%, and 80% RH achieved by use of P_2O_5, saturated solutions of calcium chloride, zinc sulfate, and sodium nitrite, respectively, in closed containers. At specified time periods, samples were removed and analyzed by DSC for quantifying the crystalline content.

RESULTS AND DISCUSSION

Amorphous CEL and Its Dispersions

All samples prepared by quench cooling of the melt were found to be stable and showed absence of crystallinity as evident by X-ray diffractometry (XRD) and DSC recordings. The Tg values obtained for samples prepared by the two methods (i.e. quench cooling and preparation in the DSC instrument itself) are in the range of 51.6–53.9°C and 53.4–54.7°C, respectively, which indicates amorphous systems obtained by both methods are thermodynamically similar. A single glass transition peak appeared in all DSC analyses, representing the presence of a single phase and uniform mixing of the drug and the carrier. The efficiency of mixing of excipient with the drug under investigation was evaluated as explained by Kakumanu *et al.* (16), using the Gordan–Taylor equation (G–T equation, Eq. 1) (18).

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

where w_1 and w_2 are weight fractions of each component, and Tg_1 and Tg_2 are corresponding Tg values. K value in G–T equation, a thermodynamic model, is defined as

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

where ΔCp is the difference in heat capacity at Tg.

A close agreement between the observed and predicted Tg values (Fig. 1) and a single Tg in the entire concentration range indicated a good level of mixing in the samples. This enabled maximal and reliable study for physical and thermodynamic behavior of the amorphous dispersions.

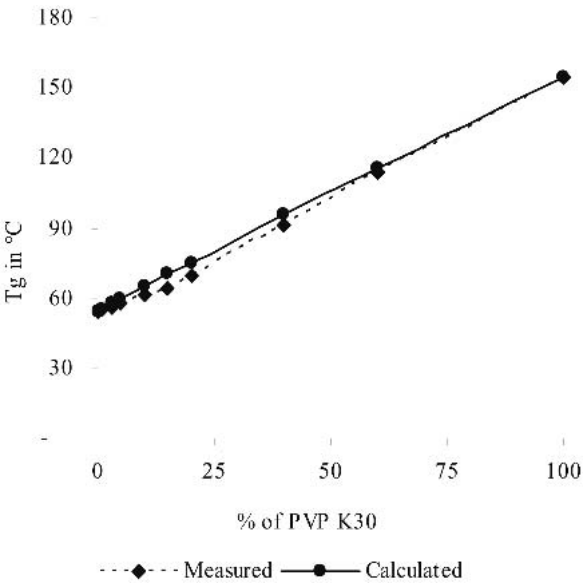

Fig. 1. Plot showing association of measured Tg values with calculated values as a function of PVP concentration.

Solubility Measurements

CEL in the crystalline state is very hydrophobic in nature and achieved an equilibrium aqueous solubility of 3.46 μg/ml in about 60 min. Glassy CEL and its molecular dispersions enhanced solubility to a considerable extent with all samples exhibiting a trend of attaining a peak solubility in the initial period, followed by a drop and achievement of a plateau phase afterward. The plateau phase is achieved in a time period of 30 min to 60 min, depending on the type of the sample studied. Glassy CEL in pure form exhibited 1.32-fold enhancement in peak solubility over crystalline form, which decreased with time and attained an equilibrium value similar to that of crystalline form, in a time period of about 30 min. The experimentally determined solubility vs. time profiles for CEL and its PVP dispersions are depicted in Fig. 2. As discussed in the preceeding section, this behavior of glassy systems is attributed to reversion to stable crystalline form, due to water induced plasticization of the amorphous system (19). The peak solubility achieved ranged from 4.57 μg/ml to 24.35 μg/ml, with pure amorphous CEL exhibiting the minimum and 60% w/w PVP dispersion exhibiting the maximum values, respectively. The time required to achieve the peak solubility was also affected by the polymer concentration in the dispersion, with 5% w/w PVP dispersion requiring 45 min and 60% w/w PVP dispersion requiring 5 min, respectively. The plateau phase solubility for crystalline CEL, amorphous CEL, 5%, 10%, 20%, 40%, and 60% w/w PVP dispersions was found to be 3.46 ± 0.17, 3.50 ± 0.14, 7.70 ± 0.57, 12.10 ± 0.22, 12.54 ± 0.36, 12.67 ± 0.51, and 12.59 ± 0.17 μg/ml, respectively, as observed at 6 h time point. These plateau solubility values are observed values only, as with time the equilibrium solubility for all cases will become equal to the solubility of crystalline form, as has been observed in case of amorphous CEL. However, the time of achievement of equilibrium may extend from hours to days depending on content of PVP in the dispersions.

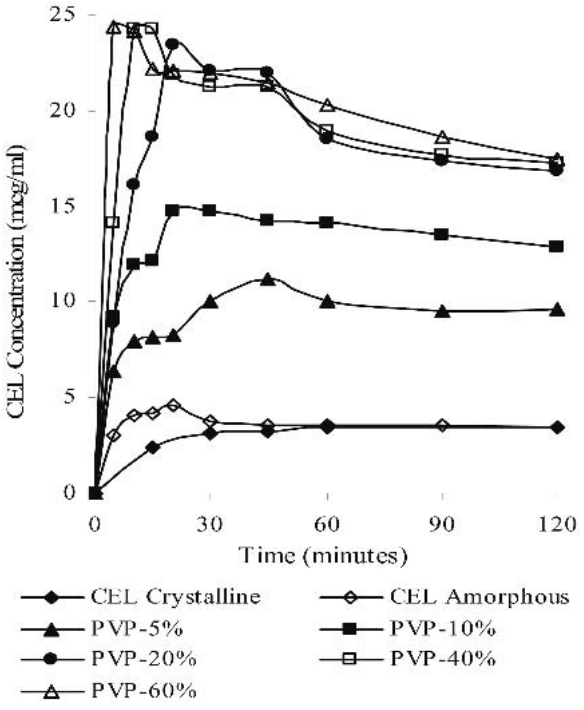

Fig. 2. Aqueous solubility of CEL–PVP dispersions containing varying concentrations of PVP (reported values are within ±5% standard deviation).

The value of peak solubility and decrease in time taken to achieve peak solubility are affected by the concentration of polymer. The increase in peak solubility values and decrease in time taken to reach peak solubility is more pronounced till 20% w/w PVP concentration, after which only a slight change in the values is observed. The benefits observed in plateau phase solubility values were obtained for certain time period only and were gradually lost as the system gradually progresses toward the equilibrium state. Residual solid samples recovered at various time points during solubility study of glassy CEL and its dispersions were analyzed instantaneously by powder XRD and polarized light microscopy after quick drying. Qualitative results confirmed presence of partially crystallized drug in the pre-plateau and almost complete conversion to crystalline form in the post-plateau phase, thus indicating complete reversion of the amorphous drug to crystalline state during the course of solubility study.

The process of recrystallization was also observed with the online camera attached to polarized light microscope for pure glassy sample and a 10% w/w PVP dispersion suspended in a drop of water. Growth of needle-shaped microcrystals of CEL was observed in both cases, but presence of PVP caused some delay in appearance. The amorphous form of the drug, by virtue of its higher free energy, dissolves rapidly and achieves a supersaturated state, which is reflected as the peak solubility. This triggers crystallization of CEL in the dissolution medium with consequent drop in solubility value, with attainment of the plateau phase. The role of water as a plasticizer in reducing Tg of amorphous systems, accelerating molecular mobility and crystallization, is well documented (19). The kinetics of generation of crystal nuclei is affected by the polymer released from the solid dispersion, which dissolves in the dissolution medium during solubility studies. Depending on the ratio of the drug and polymer in the dispersion, a unique solubility profile is obtained.

van't Hoff Plots

It is evident from the preceding section that the solid-state form of the drug and type and quantity of stabilizing polymer play a crucial role in the overall solubilization process from a solid dispersion. In an attempt to derive more information about the molecular behavior of binary systems, van't Hoff plots were generated by conducting the solubility studies as a function of temperature in the range 35–95°C. By virtue of their higher energy, amorphous systems were found to devitrify to lower energy crystalline form. As reported earlier for amorphous systems (1) and metastable polymorphs (20), the peak solubilities were taken as the estimates of their solubility. Plots were made between natural logarithm of solubility (S_s) and inverse of temperature (T) (Fig. 3).

$$ln\ S_S = -\Delta H_{sol}(RT)^{-1} \quad (3)$$

where R is the gas constant, and the heat of solution, ΔH_{sol}, was derived from the slope of resultant van't Hoff plots. The heat of transition, ΔH_{trans}, for solvent-mediated devitrification was calculated as the difference between ΔH_{sol} of amorphous and crystalline forms. The changes in Gibb's free en-

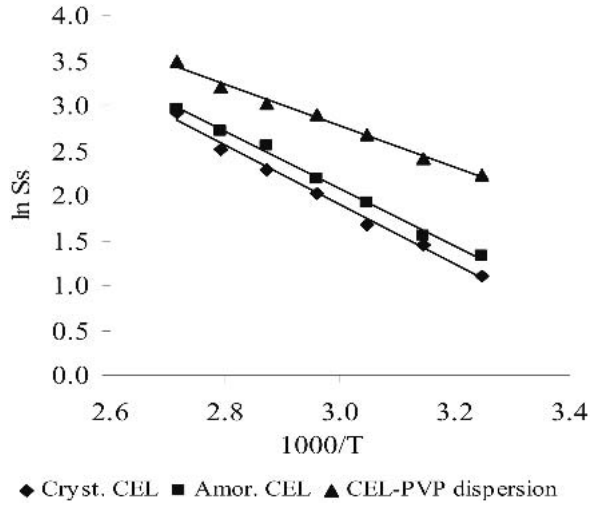

Fig. 3. van't Hoff plots of various forms of CEL.

ergy (ΔG) and entropy (ΔS) of amorphous systems relative to crystalline form were calculated using Eqs. 4 and 5,

$$\Delta G = RT(\ln S_{amor} - \ln S_{crys}) \quad (4)$$

$$\Delta G = \Delta H_{sol} - T\Delta S \quad (5)$$

CEL solubility increased linearly with increase in temperature, signifying the endothermic nature of solubilization process. This increase was higher for amorphous form as compared to crystalline form, and much higher for 20% w/w PVP dispersion, at all temperatures. The thermodynamic parameters calculated are represented in Table I. Amorphous form due to solution-mediated devitrification shows only a minor degree of lowering of ΔH_{sol}. In comparison, PVP dispersion shows a greater decrease in ΔH_{sol} and a higher ΔH_{trans}, due to stabilizing effect of PVP on the amorphous state. The least ΔH_{sol} value of the PVP dispersion signifies the ease and spontaneity of solubilization process. Further, a linear trend in solubility enhancement for 20% w/w PVP dispersion with increase in temperature suggests the solvent properties of PVP for amorphous CEL in the solid state. It also infers the absence of any kind of interaction or hydrogen-bond formation between CEL and PVP in solution state, as an increase in temperature disfavors hydrogen bonding leading to higher solubility values and a nonlinear trend (21).

The molecular randomness of amorphous form lead to higher values of ΔG in amorphous systems, as compared to crystalline form. Both ΔG and ΔS, the determinants of degree of disorderliness, were substantially higher for the PVP dispersion inferring a strong positive effect of PVP on the solubilization process, which is mediated by the delay in formation of crystal nucleation. These differences may be a result of differences in van der Waals interaction, the extent of the total energy associated with H-bonding in different solid-state forms, and their vibrational frequencies. Further, DSC results of various compositions of CEL-PVP dispersions have been reported to result in a linear increase in drug's Tg (16). This is due to the anti-plasticizing effect of PVP toward Tg enhancement of amorphous CEL. By increasing the Tg value, PVP minimizes the molecular relaxation and rearrangement responsible for devitrification. A high degree of closeness in measured and theoretical T_g values additionally postulated toward lack of interaction between CEL and PVP. Thus, PVP contributes a dual effect of i) stabilizing the amorphous form in the solid state and ii) delaying nucleation from the supersaturated drug solution. The latter, under *in vivo* conditions could provide a temporal delay, sufficient to facilitate effective removal of the dissolved drug molecules by absorption into the systemic circulation and resulting into sink conditions.

Table I. Thermodynamic Parameters of the Solubility Process of CEL in Water

		Crystalline CEL	Amorphous CEL	20% w/w PVP dispersion
ΔH_{sol}	(KJ/mol)	27.56	26.55	19.06
ΔH_{trans}	(KJ/mol)	—	1.01	8.50
ΔG	(J/mol)[a]	—	569.86	3097.08
ΔS	(J/K/mol)[a]	—	1.48	18.13

CEL, celecoxib; PVP, poly(vinylpyrrolidone).
[a] At 298 K.

Isothermal Recrystallization Studies

As discussed in the previous section, water plays a crucial role by affecting i) the solid-state stability of the amorphous dispersion and ii) recrystallization in the dissolution medium. The role of water in these two processes and effect of polymer concentration was studied by performing isothermal crystallization studies at various humidity conditions. Quantitative analysis of amorphous form present in a sample was done (17) by using the quantity of heat liberated during recrystallization (ΔH_c) and melting (ΔH_f) events. The amount of CEL recrystallized vs. time in various PVP dispersions at specified conditions is shown in Fig. 4. The CEL–PVP dispersions exhib-

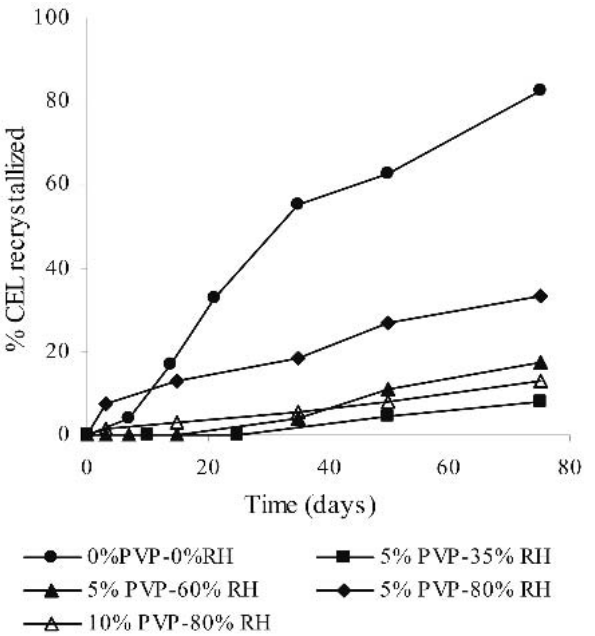

Fig. 4. Percentage CEL recrystallized with time from dispersions containing 5% and 10% w/w of PVP, stored at 25°C and 0%, 35%, 60%, and 80% RH. (The data not shown represent no reversion to crystalline form.)

ited more stability toward reversion to crystalline form, as compared to the pure amorphous CEL at all the experimental conditions studied.

The plasticizing effect of water could be clearly seen with reduction in Tg values to humid conditions. The Tg values of a 10% w/w PVP dispersion stored at 25°C and 0%, 35%, 60%, and 80% RH for 8 h were found to be 69.2, 63.5, 60.1, and 55.4°C, respectively (the SD for all Tg values are within ±1°C). The presence of PVP delayed the recrystallization phenomenon to variable degree, due to its antiplasticizing effect. A comparative assessment of recrystallized CEL in 75 days of storage period clarifies the picture, wherein pure amorphous CEL at 0% RH shows about 80% of recrystallization and inclusion of 3% w/w PVP or more in dispersions completely prevented recrystallization. At all higher humidity storage conditions studied, pure amorphous CEL completely reverted to crystalline form in less than 3 days. At 35% and 60% RH values, 10% PVP was able to prevent crystallization, whereas 5% PVP could arrest crystallization upto 25 days and 15 days, respectively, and the final crystalline content was less than 10% at the end of the storage period (Fig. 4). Storage of 5% and 10% dispersions at 80% RH conditions resulted in a 30% and 10% crystalline content, respectively, at the end of the study.

Storage at higher humidity values required a higher concentration of PVP to arrest recrystallization. However, all samples studied experienced a reduction in physical stability with increasing RH values. Thus, increase in humidity or moisture content had a direct effect on the instability of amorphous system (19). The reason behind the stabilization of amorphous CEL in PVP dispersions has been proposed earlier, wherein a nonspecific antiplasticizing effect of PVP was found to be the predominant factor (16). When used at appropriate concentrations, PVP can provide stability to amorphous form, even in the presence of moisture. This is likely to contribute positively during the solubilization of CEL from CEL–PVP amorphous dispersions.

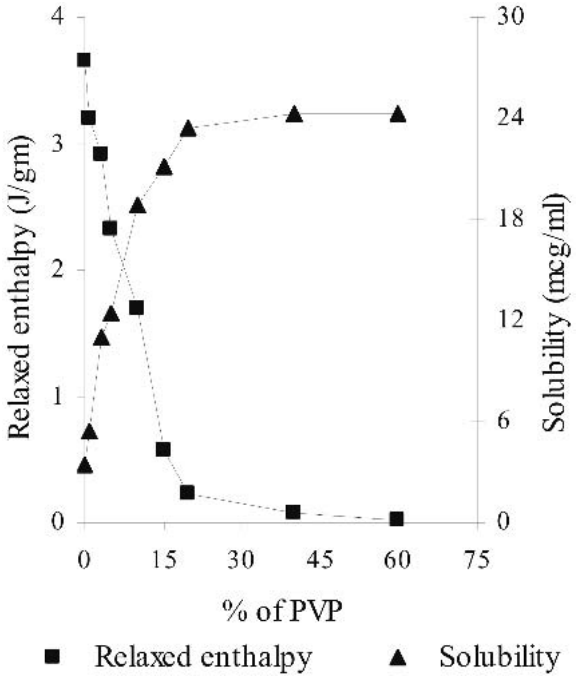

Fig. 5. The correlation between relaxed enthalpy after 16 h of storage at 25°C at 0% RH and CEL solubility as a function of PVP concentration in dispersions.

Enthalpy Relaxation Studies and Correlation with Solubility

Aging of amorphous substances at temperatures below Tg is associated with enthalpy relaxation as the material approaches the equilibrium supercooled liquid state. Molecular motions occurring in a glassy material cause a gradual loss of energy in terms of enthalpy. The amount of energy lost during storage in the form of enthalpy is recovered at Tg during a DSC analysis of the sample, as to reach the supercooled liquid state at same energy level. This enthalpy lost or relaxed can be measured with time, and is an indirect measure of molecular mobility of the glassy system.

The enthalpy relaxed after 16 h of aging at 25°C was measured for CEL and its dispersions containing PVP in the concentrations ranging from 1% to 60% w/w (Fig. 5). The amount of enthalpy relaxed is generally influenced by the type and concentration of additive, which in this case is a polymer. A gradual decrease in relaxed enthalpy was observed as the concentration of PVP increases. As the concentration of PVP reaches to a higher level, the difference in amount of enthalpy relaxed between two successive points considerably decreases. There appears a gradual decrease in relaxation enthalpy value with respect to concentration of polymer, and after a concentration of 20% w/w PVP, a plateau phase appears. As explained in the previous section, CEL–PVP dispersions exhibit an increase in solubility up to 20% w/w PVP concentration, and beyond that, no further increase in solubility is observed. The lowering of relaxation enthalpy was correlated with enhancement in solubility behavior of PVP dispersions with respect to PVP concentration. Enthalpy relaxation studies ideally should be performed at a constant degree of undercooling (Tg – Ta). However, in the real-life situation, different amorphous systems perform at varying degrees of undercooling, as dictated by the temperature of storage or solubility studies. An attempt was made to correlate markers of enthalpy relaxation and aqueous solubility, and a correlation analysis (Spearman correlation test and Pearson correlation test) was performed using Sigma Stat (version 2.03, SPSS Inc., Chicago, IL, USA), wherein a very good inverse corelationship was observed with correlation coefficient values of –1.000 and -0.979, respectively, with a p value of zero in both the cases. Similarly, a linear regression analysis using the same data yielded a definite relation between the two responses with a good correlation coefficient ($r = 0.985$). These statistical analyses show the interrelation between the values inversely. At a macro level, both the parameters seem to be independent of each other, as one is an energy representation in the solid state and the other is related to solubilization process, but both are related to instability of the amorphous systems, in terms of its tendency of continuously transforming to a stabilized lower energy crystalline state.

The solubility of a solid solute is governed by the following equation (22),

$$S = f[\text{Crystal packing energy} + \text{cavitation energy} + \text{solvation energy}] \quad (6)$$

The first two are endoergic processes, requiring disruption of i) crystal lattice of the solid and ii) water molecules, respectively. Solvation energy represents the exoergic process due to favorable solute–solvent interactions. Amorphous systems enhance solubility by affecting the "crystal packing energy" by formation of molecularly disordered structures, which are devoid of characteristic long-range order of the crystalline state. This lowers the energy requirement for the "escape" of the molecule from the crystal lattice, leading to solubility benefits. The process of devitrification of the amorphous state, either during solid-state stability or solubilization process, pushes it toward the ordered crystalline form with consequent loss of the solubility advantage. This can be prevented by judicious qualitative and quantitative selection of stabilizing excipients for formulating the solid dispersion.

In the current context, both solubility and stability advantages are maximally derived at 20% PVP concentration, and using a concentration higher than 20% will lead to excipient load in the final formulation. This becomes especially crucial in high-dose drugs and is reported to have caused failure during formulation development and processing (2).

The current study is an interesting example where 20% PVP concentration performs optimally for stability i) in the solid state and ii) during the solubilization process. This could be observed in cases where the mechanism of contribution of the polymer during both the processes is similar and no other significant phenomenon, such as specific molecular interactions between the drug and the polymer, is at play. It would be interesting to identify and explore cases where only specific interactions are observed during one of the two processes, wherein a deviation from the inverse relationship is expected to occur.

Mechanism of Drug Release from Molecular Dispersions

The mechanism underlying the drug release from its molecular dispersions needs to be understood to enable rational dosage form development. Few of the experts in the field have reviewed the mechanisms of drug release from solid dispersions containing water-soluble additives (4,11,12), and two mechanisms, that is, carrier-controlled and drug-controlled dissolutions, have been suggested. The CEL–PVP dispersion studied in the current investigation is a molecular-level amorphous dispersion, as has been conclusively demonstrated with the help of DSC, XRD, and mixing efficiency studies. In an attempt to elucidate the release mechanisms, a series of experiments, involving molecular dispersions of CEL at 20% PVP concentration, were performed, and the following observations were recorded.

1. Solubilization of crystalline CEL in an aqueous medium containing PVP in quantity equivalent to that obtained with 20% w/w CEL-PVP dispersion did not show any enhancement in solubility over the value achieved with CEL in an aqueous medium. This proves that PVP as such does not contribute toward enhanced aqueous solubility of CEL (Table II).

2. Pure amorphous CEL, when dispersed in the above described PVP aqueous solution, gave a solubility of 20.43 μg/ml. This value is close to the value obtained for solubility of 20% w/w PVP dispersion in water. This indicates that aqueous solubility and mechanism of drug release is dependent on its solid-state characteristics (i.e., amorphous nature of CEL). The polymeric carrier, PVP, only contributes in stabilization of the amorphous form and is equally effective in solubility enhancement, even if it is predispersed in the aqueous medium.

Table II. Solubility of CEL Samples in Water and Aqueous Solutions of PVP

Sample	CEL solubility (μg/ml)	
	Water	PVP aqueous solution[a]
Crystalline CEL	3.46 ± 0.17	2.51 ± 0.61
Amorphous CEL	4.57 ± 0.62	20.43 ± 0.03
Crystalline CEL–PVP physical mix[b]	3.26 ± 0.67	—
Amorphous CEL–PVP physical mix[b]	19.87 ± 1.49	—
CEL–PVP dispersion†	23.45 ± 0.52	—

CEL, celecoxib; PVP, poly(vinylpyrrolidone).
[a] Equivalent to amount of PVP when 10 mg of 20% w/w CEL–PVP dissolves
[b] 20% w/w PVP.

3. A lack of carrier-controlled drug release is also indicated by the fact that no solubility increase beyond 20% PVP concentration is observed from CEL–PVP molecular dispersions.

The primary role of a polymeric component in a molecular dispersion is anticipated to be toward stabilization of the amorphous form both in solid state as well as during dissolution in the aqueous media.

Modeling of Drug Dissolution from PVP Molecular Dispersions

The overall dissolution rate at time t $[G_T(t)]$ is a function of mean dissolution rate from each individual particle $[G_p(t)]$ and the number of particles available $[N(t)]$ (11)

$$G_T(t) = \Sigma G_p'(t) \approx G_p(t)N(t) \tag{7}$$

where G_p' is the dissolution rate at time t of the individual particles. In case of amorphous molecular dispersions, like in the current case, this expression reduces to

$$G_T(t) \approx N(t) \tag{8}$$

where $N(t)$, instead of number of particles, is the number of drug molecules.

The time t_p required for release of one molecule will be given by

$$t_p = 2r\rho/P_A \tag{9}$$

where r is the molecular radius, P_A is the intrinsic polymer dissolution rate, and ρ is the polymer density, which would be very low, indicating that the lag time for drug release from molecular amorphous dispersions does not contribute significantly toward the dissolution process. This is also evident from the overlapping dissolution profiles for i) molecular dispersion in water and ii) amorphous CEL in water containing equivalent amount of predissolved PVP.

Drug Release Modeling

To get a better understanding of the drug release mechanism from the solid dispersion, the solubility data from the 20% w/w PVP dispersion was fitted to various appropriate drug release models such as zero-order (23), first-order (24), Hixson–Crowell (HC) model (25), and Baker–Lansdale (BL) model (26). HC model is applicable in powder dissolution studies, where surface area changes uniformly with time, maintaining the initial geometric form, whereas BL model best describes the drug release from spherical matrices. The selection criterion for the most appropriate model was based on the best goodness of fit and smallest sum of squared residuals (SSR). Table III comprises the model fitting data for drug release from solid dispersion upto the attainment of peak solubility. Highest correlation coefficient (r) values were obtained with zero-order and HC models. A lower SSR value indicates that the HC model fits best for CEL–PVP dispersions. As reported in earlier sections, this signifies the presence of uniform homogeneous matrix system for the first 20 min, till a peak solubility is achieved with a near constant release rate. As the drug release from amorphous dispersion is accompanied with devitrification to crystalline form, it leads to generation of multiparticulate heterogeneous system characterized by numerous crystal nuclei in the matrix. This is evidenced by a nonlinear response to model fitting after 20 min of solubility study. Also, a nearly good correlation of drug release according to zero-order kinetics further strengthens the drug release to be independent of drug concentration and purely limited to the physical state of drug molecule, as detailed earlier.

The overall dissolution from an amorphous molecular dispersion is a complex phenomenon dependent on i) supersaturation of solvent with solute molecules followed by precipitation/recrystallization of dissolved drug; ii) kinetics of recrystallization of the drug in molecular dispersion during solubilization; and iii) capacity of stabilizing carrier to alter penetration of dissolution medium to the inner core of molecular dispersion.

CONCLUSIONS

Qualitative and quantitative choice of the carrier/additive in an amorphous dispersion contributes crucially to enhancement of solubility and optimal shelf life. The additives used should help in maintaining the drug in amorphous form for sufficient time to enable harnessing of their special properties both in solid and solution states. In case of CEL, molecular dispersions of PVP showed maximum enhancement in solubility, up to 20% of PVP content. A similar behavior was observed in relaxation enthalpy studies of CEL–PVP dispersions, where an apparent plateau phase appeared after 20% of PVP content. The results of both solubility and enthalpy relaxation studies were found to have an inverse correlation. This helps in the selection of appropriate concentration of PVP, which will perform optimally in terms of solubility and stability. The mechanism of drug release from CEL amorphous dispersions was characterized as dominantly drug-controlled type and independent of carrier.

The molecular mechanism of drug–polymer interaction holds the key for design of a successful product. However, this needs to be viewed from two angles: i) stability in the predissolution solid state and ii) during dissolution process. The role of increase in Tg, H-bonding, physical entrapment of the drug in polymer network, and other specific drug–polymer interactions needs to be explored further to understand the overall phenomenon. The fact that PVP provides benefits both in the solid state and dissolution phase indicates towards a role of PVP, in addition to the polymer-induced rise in the Tg value. FTIR studies reported previously (16) were probably insensitive to unravel the intermolecular interactions. A deeper understanding using more sensitive methodologies and techniques will help in designing amorphous systems that can provide solubility benefits over meaningful shelf-life.

Table III. Statistical Results of Drug Release Data from CEL–PVP Dispersions as Fitted to Various Kinetic Models

Release model	r Value	Mean sum of squares	Release rate constant (k)
Zero order	0.9984	2.15×10^{-4}	0.0377
First order	0.9950	7.92×10^{-4}	0.0355
HC model	0.9984	1.50×10^{-9}	6.40×10^{-5}
BL model	0.9682	11.60×10^{-4}	0.0167

CEL, celecoxib; PVP, poly(vinylpyrrolidone).

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