Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), S.A.S. Nagar, Punjab, India

Ternary amorphous composites of celecoxib, poly(vinyl pyrrolidone) and meglumine with enhanced solubility

P. GUPTA, A. K. BANSAL

Received November 15, 2004, accepted February 16, 2004

Dr. Arvind K. Bansal, Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, Phase X, S.A.S. Nagar, Punjab – 160 062, India
akbansal@niper.ac.in

Pharmazie 60: 830–836 (2005)

The present study highlights the development of ternary amorphous composites to enhance the solubility of a poorly soluble crystalline drug, celecoxib (CEL). These systems comprised of an 'amorphous drug,' and its 'stabilizer' and 'solubilizer.' The ternary amorphous system of CEL, poly(vinyl pyrrolidone) (PVP) and meglumine (MEG) (7 : 2 : 1 w/w) enhanced CEL solubility by ≅ 10.2-fold over that for the crystalline drug, and maintained the thermodynamic stability of the amorphous drug. However, MEG alone was unable to stabilize the amorphous CEL against thermally-induced crystallization, and so gave no solubility advantage. The PVP-MEG combination provided a 'synergistic' enhancement of CEL solubility, as compared to their use alone in the amorphous systems. Phase-solubility studies provided greater insight into molecular mechanisms underlying stability and solubility of these amorphous systems. MEG exhibited phase-specific interaction with CEL molecules, when stabilized by PVP in the amorphous state. The higher solubility of CEL from ternary amorphous systems was also thermodynamically favored, as analyzed by van't Hoff plots. A possible molecular level interaction of MEG with PVP-stabilized amorphous CEL seems to be responsible for the solubility advantage of the CEL-PVP-MEG ternary amorphous system.

1. Introduction

Celecoxib (CEL), a drug belonging to class II of the biopharmaceutics classification system (BCS), has been reported (Paulson et al. 2001) to exhibit dissolution-limited absorption. The absolute bioavailability (BA) of CEL was higher when given as a solution (64–88%) than as a capsule (22–40%). Since the pK_a of CEL is 11.1, its solubility is likely to be low at physiological pH values. Though it is highly permeable (apparent octanol/water partition coefficient $> 10^3$ at pH 7) and absorbable throughout the gastrointestinal tract, poor aqueous solubility precludes sufficient absorption of this highly effective non-steroidal anti-inflammatory drug.

The amorphous form of CEL provided only minimal (≅ 1.2-fold) enhancement in solubility over the crystalline form (Chawla et al. 2003). This enhancement was very short-lived due to rapid water-mediated devitrification of amorphous CEL. Stabilization of the amorphous form by poly(vinyl pyrrolidone) (PVP) resulted in enhanced solubility for CEL (Gupta et al. 2004a). Increasing the PVP content to 20% w/w in the CEL-PVP amorphous system provided ≅ 6.3-fold enhancement of CEL solubility. A further increase in PVP content was ineffective in providing solubility advantage. Thus, a possible molecular level interaction between CEL and PVP, responsible for arresting the self-association of CEL molecules, became saturated at 20% w/w PVP content in the amorphous system. Mere stabilization of the amorphous system in the solid-state by addition of polymers does not allow the exploitation of their full solubility advantage. The latter fact can be easily understood by comparing the theoretical (≅ 7–21-fold) and practical (≅ 1.2-fold) solubility advantages of the amorphous form of CEL (Gupta et al. 2004b).

The success rate of amorphous solid dispersions in the market place has been abysmally low. Despite extensive research, very few of them are available commercially (Kaushal et al. 2004). One of the important reasons for this failure is the requirement for a high quantity of the stabilizing/solubilizing additive, which makes formulations, especially for high dose drugs, too bulky. Previous reports (Leuner and Dressman 2000) have indicated the use of very high polymer : drug ratios such as 1 : 1 or 2 : 1 w/w. These high quantities pose numerous formulation related problems (Serajuddin 1999) like difficulty in pulverizing and sieving, poor flow and mixing properties, poor compressibility, etc. Thus, to release the greatest solubility advantage from amorphous systems, another additive, besides the stabilizing additive, can be incorporated to further increase the solubility of amorphous drug.

The present study attempted to further exploit the possibility of enhancing CEL solubility by the addition of a third component to CEL-PVP systems, while maintaining the drug in an amorphous state. Further, the mechanistic as-

pects of the role of additives in enhancing the solubility and stability of amorphous drug forms were major avenues of research in this study.

2. Investigations, results and discussion

All samples prepared by quench-cooling the melt showed absence of crystallinity, as evidenced by microscopy and differential scanning calorimetry (DSC). Under crossed-polarizers, the samples showed an absence of birefringence for irregularly shaped particles, in contrast to the needle-like shapes observed for crystalline CEL (Chawla et al. 2003). DSC analysis also showed thermal behavior characteristic of amorphous samples.

During optimization of the composition of ternary system, due concern was given to limiting the content of additives, to provide greater flexibility in designing the formulation of this high dose drug.

2.1. Aqueous solubility

Binary systems of CEL and meglumine (MEG) of varying MEG content (5–20% w/w) showed no enhancement in CEL solubility over that observed for amorphous CEL. This could have been due to the negligible effect of MEG on stabilization of the amorphous form of CEL in an aqueous medium, in contrast to PVP (Gupta et al. 2004a), which stabilized amorphous CEL in the solid-state as well as during dissolution.

Inclusion of MEG in amorphous systems of CEL containing PVP had a positive effect on solubility enhancement. All amorphous systems exhibited a common trend of a peak in solubility in the initial time period (15–30 min), followed by a decrease to plateau levels (90 min). Peak solubility values varied with the composition of the ternary amorphous system, while plateau solubility values were similar ($\cong 21$ μg/ml). A comparative analysis of peak solubility values of amorphous systems of CEL with varying PVP and MEG contents is presented in Table 1.

CEL-PVP-MEG ternary amorphous systems of varying MEG content were tested for the effect of variation in PVP content on CEL solubility enhancement. The observations made were as follows:

- With only PVP (i.e. 0% w/w MEG), CEL solubility increased up to 20% w/w PVP content. No further advantage in solubility was provided by higher PVP content.
- With 5% w/w MEG, CEL solubility increased only up to 10% w/w PVP content. The solubility changed only marginally ($P < 0.05$) compared with 0% w/w MEG. These results indicated the solubilizing potential of MEG for CEL in the presence of PVP.
- With 10% w/w MEG, CEL solubility increased only up to 20% w/w PVP content. This observation was analogous to that for CEL-PVP binary systems (Gupta et al. 2004a), thus emphasizing the saturation of the stabilizing activity of PVP above 20% w/w content. Compared with 5% w/w MEG, the solubility was significantly higher ($P < 0.05$) at all PVP contents.
- With 20% w/w MEG, solubility increased only up to 20% w/w PVP content. As compared with 10% w/w MEG, a significant ($P < 0.05$) improvement in CEL solubility was obtained in compositions with 10, 20, 30 and 40% w/w PVP.

Table 1: CEL peak solubility values (in μg/ml) from CEL-PVP-MEG ternary systems of varying composition

PVP content (% w/w)	MEG content (% w/w)			
	0	5	10	20
0	4.57 ± 0.06	5.82 ± 0.65	6.92 ± 0.62	6.74 ± 0.26
10	14.79 ± 0.52	21.61 ± 1.72	28.59 ± 1.31	48.99 ± 3.54
20	23.45 ± 0.87	21.22 ± 0.31	38.04 ± 2.69	54.67 ± 4.31
30	23.26 ± 0.43	21.97 ± 2.38	37.35 ± 2.88	55.49 ± 1.53
40	24.29 ± 0.22	21.91 ± 1.03	38.67 ± 2.15	54.12 ± 0.87

Values are reported as mean ±S.D. (n = 3)

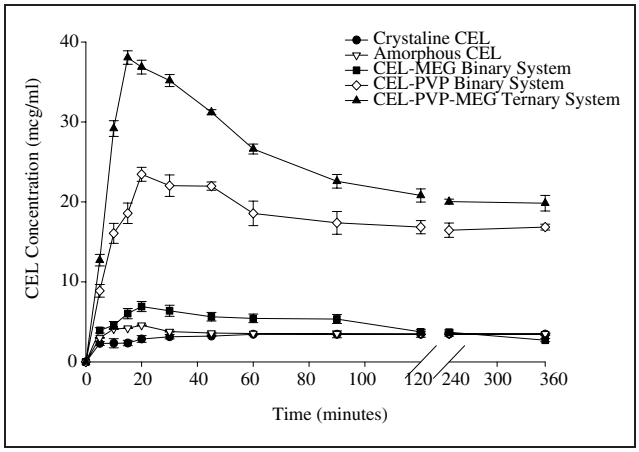


Fig. 1: Comparative dynamic aqueous solubility of crystalline CEL, amorphous CEL, CEL-MEG (9 : 1 w/w) binary, CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary amorphous systems. Error bars represent S.D. values. The X-axis has been broken from 120–240 min time interval so as to allow better comparative analysis of data in the initial time period

Thus, MEG (above 10% w/w) made a significant contribution to enhancing the solubility of CEL, when it was present together with PVP. Based on these results, the composition of the CEL-PVP-MEG ternary amorphous system was finalized at 7 : 2 : 1 w/w, which provided 10.2-fold enhancement in CEL solubility over its crystalline form. The MEG content was limited to 10% w/w as this appeared to be the lowest content with a positive effect on the solubility and stability of the amorphous form of CEL. Higher contents of MEG in ternary amorphous systems increased the hygroscopicity of the product. Moreover, lower additive contents in the amorphous system are also conducive to flexibility in formulation.

Fig. 1 depicts the comparative solubility profiles of various crystalline and amorphous CEL systems. Compared with binary systems of CEL with PVP or MEG alone,

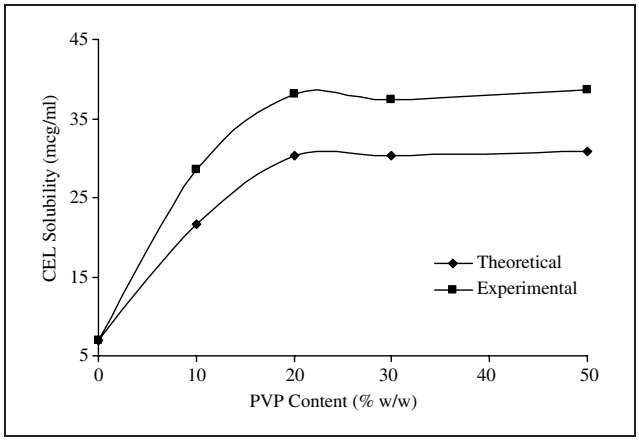


Fig. 2: Comparison of theoretical vs experimental CEL solubility values from CEL-PVP-MEG ternary amorphous systems of varying PVP content and 10% w/w MEG content

MEG was found to synergistically (Loftsson et al. 1994; Nandi et al. 2003) enhance the solubility of CEL when used at a content of 10% w/w in the ternary system. Fig. 2 presents the theoretical and experimental values of CEL solubility for ternary systems with 10% w/w MEG and varying PVP contents. The theoretical values were obtained by additing the solubility values of the CEL-PVP and CEL-MEG binary systems corresponding to the MEG and PVP contents in the ternary system. At all compositions, the experimental values were higher than the predicted values. This behavior was unique for MEG, having no effect when used alone, but tremendously enhancing the solubility of CEL in the presence of PVP. This is a result of molecular interaction between MEG and randomly configured CEL in the amorphous state, made possible by PVP (detailed later).

2.2. Thermodynamic stability

The relative thermodynamic stability of amorphous CEL, and the CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary amorphous systems was assessed in terms of structural relaxation during annealing at 25 °C/0% RH for various periods of time. A decrease in enthalpy due to structural relaxation was seen as enthalpy recovered from the surroundings during heating in the DSC scan.

A single glass transition event in the binary/ternary systems established drug-additive(s) miscibility. The heating rescan of unaged amorphous CEL showed a small enthalpy recovery event, signifying relaxation during the cooling and equilibrating steps of CEL glass formation. The area under the enthalpy recovery endotherm increased considerably during 24 h of aging for amorphous CEL, signifying high mobility of CEL molecules in the glassy state. On the other hand, the heating rescans of unaged binary/ternary systems were devoid of enthalpy recovery endotherms, which increased minimally after 24 h of aging. Thus, the presence of additives restrained the molecular motions observed with amorphous CEL, and conferred higher stability.

The maximum enthalpy recovered at a given temperature (ΔH_∞) was calculated as

$$\Delta H_\infty = (T_g - T_a) \cdot \Delta C_p \quad (1)$$

where ΔC_p corresponds to the heat capacity difference at T_g. The extent to which a material relaxes (φ_t) under any given time and temperature was calculated using Eq. (2) (Cowie and Ferguson 1989)

$$\varphi_t = 1 - (\Delta H_t / \Delta H_\infty) \quad (2)$$

This information was then used to calculate the mean molecular relaxation time (τ) using the empirical Kohlrausch-Williams-Watts (KWW) equation (Hancock and Shamblin 2001).

$$\varphi(t) = \exp\left[-(t/\tau)^\beta\right] \quad (3)$$

Typically, it is assumed that there are multiple relaxation processes with a distribution of relaxation times, and the data are fitted to a stretched exponential function using non-linear regression. An iterative non-linear regression algorithm based on the Levenberg-Marquardt method (Press et al. 1987) was used to obtain the best fit for the relaxation time distribution parameter (β) and τ. The initial parameters provided were, $\tau = 100$ sec and $\beta = 0.5$. The half-life ($t_{1/2}$), defined as the time at which $\Delta H_{recovery}$ reaches half its theoretical maximum, was determined

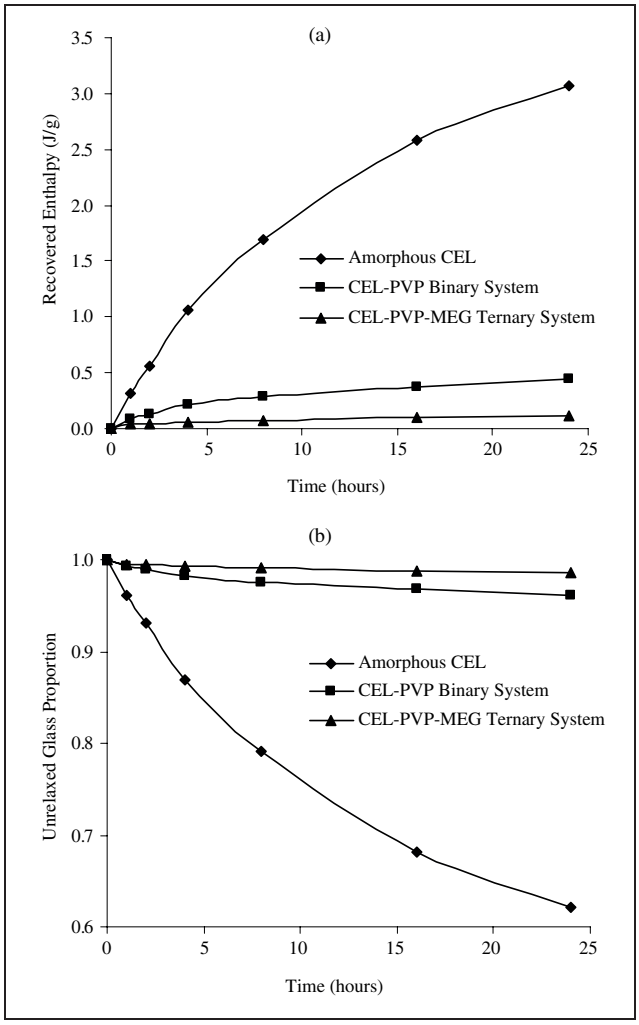


Fig. 3: Variation with aging time of (a) enthalpy recovery, and (b) proportion of unrelaxed glass for amorphous CEL, CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary amorphous systems annealed at 25 °C/0% RH

using Eq. (4) (Sertosu et al. 2003)

$$t_{1/2} = [\ln(2)]^{1/\beta} \cdot \tau \quad (4)$$

$\Delta H_{recovery}$ increased in a non-linear fashion with increase in aging time for all samples (Fig. 3a). Comparison of enthalpy changes for amorphous CEL and binary/ternary systems indicated that the latter two exhibited smaller enthalpy changes than did CEL alone. φ_t was 0.64 after 24 h for amorphous CEL, while the presence of additives produced significantly less relaxation, with φ_t values of 0.96 and 0.99 for binary and ternary systems, respectively (Fig. 3b). Thus, additives raised the T_g of amorphous CEL, and reduced the degree of structural relaxation to a considerable extent.

While the relaxation of amorphous CEL could be described by the KWW expression with reasonable values for τ (= 71.26 h), β (= 0.71) and $t_{1/2}$ (= 42.65 h), this was not the case for binary/ternary systems. There was a significant error associated with the estimation of τ and β using a non-linear regression algorithm to describe the experimental data for binary/ternary systems, preventing any meaningful comparisons. The inability of the KWW expression to describe relaxation indicated differences in the distribution of relaxation times for mixtures in comparison to single component amorphous materials. It is likely that

in multi-component systems, there is a more complex distribution of relaxation times, or a different distribution of relaxation processes. The values of τ and β calculated for amorphous CEL were different from those reported previously (Kakumanu and Bansal 2002) due to an alteration in the experimental methodology of using a correction factor for recovered enthalpy observed in the 0 h sample.

A higher distribution of relaxation times for binary/ternary systems was quantified in terms of ΔT_{gw} (Crowley and Zografi 2001). Higher ΔT_{gw} values of 19.8 °C for the binary system and 34.3 °C for the ternary system, as compared to 10.0 °C for amorphous CEL, again suggested probable heterogeneity in the molecular dynamics of multi-component systems, in excess of those in single components (Assman and Schneider 1989; Fried et al. 1978; Pomposo et al. 1993). These high ΔT_{gw} values also indicated a higher thermal resistance to devitrification of amorphous CEL in binary/ternary systems (Aida et al. 2000; Pikal et al. 2004). A possible molecular level interaction between the components of binary/ternary systems reduced the flexibility for molecular motion, which was extensive in amorphous CEL.

2.3. Elucidation of mechanism of solubility enhancement

The mechanism of the enhanced solubilization of CEL conferred by MEG in the ternary amorphous system was investigated by the following techniques.

2.3.1. Hot stage microscopy

HSM facilitated visual observation of thermal transitions encountered in various amorphous systems of CEL. In the case of crystalline CEL, the solid sample was found to melt and appear as droplets in the temperature range 160–165 °C. On the other hand, amorphous CEL showed crystallization as the formation of rosettes of needles arranged in a circle with a common center at 102 °C, followed by transformation to melt droplets at around 165–170 °C. The CEL-MEG (9 : 1 w/w) binary system also showed thermal events analogous to those of amorphous CEL (Fig. 4). On the other hand, CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary systems showed no crystallization or melting events due to stabilization of the amorphous form by the additives. This indicated that unlike the PVP or PVP-MEG combinations, use of 10% w/w MEG alone was unable to prevent thermally-induced crystallization of amorphous CEL.

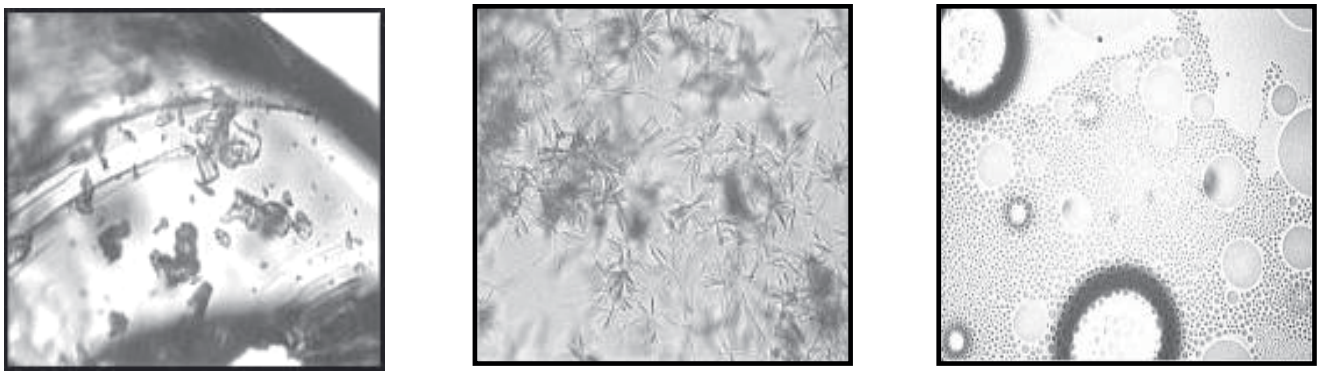
2.3.2. Phase-solubility studies

The relative contribution of additives, present either in solid-phase (in drug-additive mixtures) or in solution (in pre-dissolved state in water), was ascertained by studying the solubilities of physical mixtures and co-melt-cooled products of crystalline/amorphous CEL, PVP and MEG in water and aqueous solutions of PVP and/or MEG. The compositions of the CEL-PVP, CEL-MEG and CEL-PVP-MEG systems were 4 : 1, 9 : 1 and 7 : 2 : 1 w/w, respectively. The PVP and/or MEG aqueous solutions were prepared so as to provide similar concentrations to those produced after the addition of 10 mg of the respective binary/ternary systems to 5 ml water.

The results of these phase-solubility studies are summarized in Table 2. To aid in comparison of results, the columns in the table have been labelled from a–d, while the rows are numbered from 1–13. The salient observations made were as follows [Numeral and alphabet in parentheses indicate the row (numeral) and column (letter), respectively, corresponding to CEL solubility in Table 2]:

- MEG – Molecular dispersion (8a), and physical mixtures (6a and 7a) as well as aqueous solutions (1c and 2c) of MEG alone did not provide enhanced solubility for crystalline or amorphous CEL. This indicated that MEG was unable to stabilize the amorphous form of CEL, and prevent devitrification of CEL molecules from a supersaturated solution.
- PVP – Molecular dispersion (5a), and physical mixture (4a) as well as aqueous solution (2b) of PVP provided enhanced solubility for amorphous CEL. A very similar value for 4a and 2b indicated that PVP was able to rapidly disperse in water, thus giving values similar to pre-dispersed PVP (2b). No influence of PVP was observable for crystalline CEL, either as physical mixture (3a) or aqueous solution (1b). Thus, PVP was able to stabilize the amorphous form of CEL against water-mediated devitrification when present in a molecularly dispersed, physically mixed or pre-dissolved form in water.
- MEG and PVP combination – Molecular dispersion (13a) of CEL with a combination of MEG and PVP provided the highest solubility advantage.

  MEG-PVP combination as a physical mixture was effective in enhancing the solubility only of amorphous CEL (10a), with no effect on crystalline CEL (9a). Thus, PVP continued to provide a protective effect on stabilization of the amorphous form of CEL in the presence of water, and allowed MEG to interact with CEL



30 °C 100 °C 167 °C

Fig. 4: Hot-stage photomicrographs (50 × 10 X) for CEL-MEG (9 : 1 w/w) binary amorphous system

Table 2: CEL solubility (μg/ml) from physical mixtures and molecular dispersions of crystalline/amorphous CEL, PVP and/or MEG, as determined in water and aqueous solutions of PVP and/or MEG

Composition		Water a	PVP Solution b	MEG Solution c	PVP-MEG Solution d
1	Crystalline CEL	3.74 ± 0.20	4.37 ± 0.11	5.50 ± 0.14	5.28 ± 0.23
2	Amorphous CEL	4.57 ± 0.06	20.43 ± 0.03	6.75 ± 0.21	24.72 ± 0.13
3	Crystalline CEL − PVP (PM)	3.26 ± 0.67	–	5.50 ± 0.20	–
4	Amorphous CEL − PVP (PM)	20.72 ± 0.41	–	25.66 ± 0.20	–
5	Crystalline CEL − PVP (MC)	23.45 ± 0.87	–	37.75 ± 0.39	–
6	Crystalline CEL − MEG (PM)	4.43 ± 1.43	4.45 ± 0.89	–	–
7	Amorphous CEL − MEG (PM)	4.14 ± 0.81	35.13 ± 0.14	–	–
8	Crystalline CEL − MEG (MC)	6.92 ± 0.62	35.41 ± 0.54	–	–
9	Crystalline CEL − PVP − MEG (PM)	5.32 ± 0.45	–	–	–
10	Amorphous CEL − PVP − MEG (PM)	29.71 ± 0.95	–	–	–
11	Crystalline CEL − PVP (MC) − MEG (PM)	36.14 ± 1.97	–	–	–
12	Crystalline CEL − MEG (MC) − PVP (PM)	14.84 ± 0.56	–	–	–
13	Crystalline CEL − PVP − MEG (MC)	38.04 ± 2.69	–	–	–

PM − Physically mixed; MC − Melt cooled
Values are reported as mean ±S.D. (n = 3)

present in stable and random configurations. A physical mixture of PVP with a molecular dispersion of CEL and MEG (12a) was able to raise the CEL solubility marginally. This was due to the relatively lesser degree of configurational stability of amorphous CEL in the molecular dispersion of MEG. On the other hand, the physical mixture of MEG with a molecular dispersion of CEL and PVP (11a) provided CEL solubility similar to that observed for the molecular dispersion of CEL with the MEG-PVP combination (13a). Thus, the stabilization of amorphous CEL by PVP supports a molecular interaction between MEG and CEL.

An aqueous solution of MEG was ineffective in enhancing the solubility of a physical mixture of crystalline CEL with PVP (3c), but provided higher values for a physical mixture of PVP with amorphous CEL (4c), as well as their molecular dispersion (5c). This was again due to the configurational stability of amorphous CEL provided by PVP, allowing interaction between MEG and CEL. An aqueous solution of PVP was again ineffective in enhancing the solubility of a physical mixture of crystalline CEL with MEG (6b), but provided similar and enhanced values for the physical mixture of MEG with amorphous CEL (7b), as well as for their molecular dispersion (8b). Also, the aqueous solution of MEG-PVP combined did not provide enhanced solubility for crystalline CEL (1d), but was able to raise it for amorphous CEL (2d). A relatively lower value for 2d than that for 8b indicated that in the PVP-MEG aqueous solution, an early interaction between the two additives in solution form blocked some of the sites for interaction between CEL and MEG.

These results indicated that CEL molecules were unavailable for interaction with additives when present in an ordered crystalline lattice arrangement. PVP was able to interact at a molecular level with CEL, given the disorder of the amorphous form. MEG also had the potential of interacting with CEL molecules that had been stabilized in the amorphous form by PVP. When MEG was used alone, its homo-interaction was stronger than the hetero-interaction between CEL and MEG molecules, thus restricting the solubility advantage from the amorphous form of CEL.

These results further confirmed that the drug release mechanism from CEL-PVP binary and CEL-PVP-MEG ternary amorphous systems was drug-controlled (Corrigan 1985; Craig 2002), since both the additives could interact only with the amorphous form of CEL, and not with its crystalline form. Instead of additives, it was the solid-state property of the drug that had a profound effect on CEL solubility.

2.3.3. Temperature-dependence of solubility

The energetics of solubilization for crystalline CEL, amorphous CEL, and CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary amorphous systems were studied by determining the temperature dependence of their solubility. Solubility studies were conducted at 35, 45, 55, 65, 75, 85 and 95 °C, and as reported earlier for amorphous systems (Elamin et al. 1994) and metastable polymorphs (Vachon and Grant 1987), peak solubility values were taken as estimates of their solubility. The natural logarithm of solubility (σ) was plotted against the inverse of temperature (T)

$$\ln \sigma = -\Delta H_{sol}(R.T)^{-1} \quad (5)$$

where R is the gas constant, and heat of solution (ΔH_{sol}) was derived from the slope of the resultant van't Hoff plots (Fig. 5).

CEL solubility from all samples increased linearly with an increase in temperature, signifying the endothermic nature

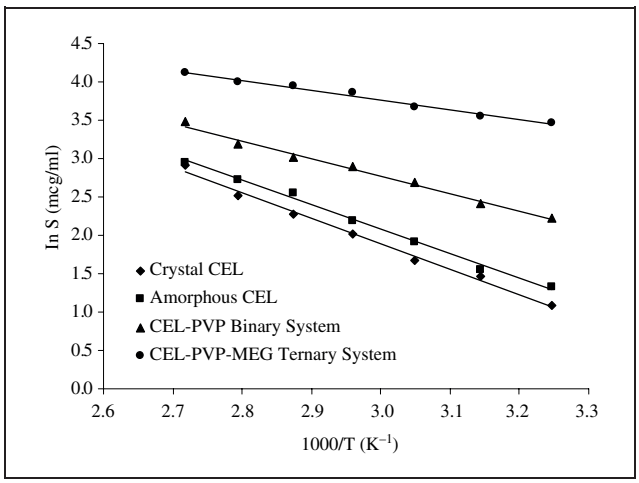


Fig. 5: van't Hoff plots for crystalline CEL, amorphous CEL, CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary amorphous systems

of the solubilization process. This increase in solubility was higher at all temperatures for amorphous systems in the increasing order of amorphous CEL, binary and ternary systems, as compared to crystalline CEL. The heat of transition (ΔH_{trans}) for solvent-mediated devitrification was calculated as the difference between ΔH_{sol} of the amorphous and crystalline forms. The changes in Gibb's free energy (ΔG) and entropy (ΔS) for amorphous systems, relative to the crystalline form, were calculated using the following equations:

$$\Delta G = R.T\,(\ln \sigma_{amorphous} - \ln \sigma_{crystalline}) \quad (6)$$

$$\Delta G = \Delta H_{sol} - T \cdot \Delta S \quad (7)$$

The various thermodynamic parameters calculated for crystalline and amorphous CEL systems are detailed in Table 3. The ΔH_{sol} was lower for amorphous systems in the decreasing order of amorphous CEL, binary and ternary amorphous systems. The difference between the ΔH_{sol} values for amorphous and crystalline CEL were statistically insignificant ($P > 0.05$), possibly due to rapid water-mediated devitrification of amorphous CEL. These differences were significantly enhanced ($P < 0.05$) by the presence of PVP and/or MEG due to their role as stabilizer and solubilizer of amorphous CEL, respectively. The lower ΔH_{sol} for binary and ternary amorphous systems indicated the ease and spontaneity of the solubilization process, favored by the greater degree of disorder in the molecular conformation of CEL in these systems, and their possible role in enhancing drug solubility, thus reducing the amount of energy required for drug solubilization.

The ΔH_{trans}, ΔG and ΔS increased in the order of amorphous CEL, binary and ternary amorphous systems. A remarkably lower ΔH_{trans} for amorphous CEL indicated its propensity to devitrify in the presence of water. On the other hand, the higher ΔH_{trans} for binary/ternary amorphous systems signified the greater degree of stabilization conferred by the presence of additives. Both ΔG and ΔS, the determinants of degree of disorder, were substantially higher for binary/ternary amorphous systems, implying a strong positive effect of PVP and MEG on the drug solubilization process.

2.4. Implications of solubility advantage from amorphous composites

The solubility differences between crystalline and amorphous composites indicate a possibility of improving absorption of CEL by using of its stabilized amorphous form. These possibilities were quantified in terms of absorbable dose (D_{abs}), which is the amount of drug that can be absorbed during the period of transit time when the solution contacting the effective intestinal surface area for absorption is saturated with the drug (Yu 1999).

$$D_{abs} = P_{eff} \cdot C_s \cdot A \cdot T_{si} \quad (8)$$

where P_{eff} is the effective human intestinal permeability; C_s is the solubility; A is the effective intestinal surface area for absorption [$\cong 800\ cm^2$ (Yu 1999)]; and T_{si} is the mean small intestinal transit time [$\cong 199$ min (Yu and Amidon 1998)]. The $P_{eff\ Caco\text{-}2}$ value for CEL was taken as $13.8 \pm 1.3 \times 10^{-6}$ cm/sec (Yazdanian et al. 2004). Using a linear relationship between Caco-2 cell and human intestinal drug permeability (Sun et al. 2002),

$$\log P_{eff\ human} = 0.6532 \times \log P_{eff\ Caco\text{-}2} - 0.3036 \quad (9)$$

the $P_{eff\ human}$ was calculated to be 3.32×10^{-4} cm/sec for CEL. For C_s, peak solubility values of amorphous systems were taken, as studies in our laboratory have shown that for CEL-PVP binary (4 : 1 w/w) and CEL-PVP-MEG ternary (7 : 2 : 1 w/w) amorphous systems, the ratio of improvement of peak solubility, apparent equilibrium solubility and oral BA (data communicated elsewhere) were found to be 1.62, 1.18 and 1.51, respectively. A better correlation between peak solubility and benefit for oral BA reiterated the importance of improved peak solubility for better overall oral BA. Use of such apparent solubility values has also been advocated (Yazdanian et al. 2004) for drug classification under BCS, which refers to the equilibrium solubility as a static parameter, underestimating the dynamic nature of absorption. As is evident from eq. (8), there is a direct correlation between D_{abs} and C_s. The D_{abs} values for crystalline CEL, amorphous CEL, CEL-PVP (4 : 1 w/w) binary and CEL-PVP-MEG (7 : 2 : 1 w/w) ternary amorphous systems were calculated to be 11.88, 14.51, 74.47 and 120.81 mg, respectively. Thus, amorphous CEL systems could provide significant biopharmaceutic advantages, in terms of faster and higher absorption of the administered dose.

Dissolution and absorption of an orally administered drug are dynamic processes affected by numerous parameters. It is well reported in the literature that drugs can have solubility-limited ($D_{abs} <$ Dose) as well as dissolution-limited ($D_{abs} \gg$ Dose) oral absorption (Yu 1999). However, the situation is more complex in the case of amorphous dispersions where drug dissolution and devitrification to a crystalline state (leading to a fall in solubility value) occur simultaneously. Overall, the solubility benefit and in turn, the oral BA advantage will be dictated by the kinetics of these two processes. The role of *in vitro* dissolution medium ingredients on the rate of dissolution and devitrification of amorphous systems also needs to be given due consideration.

3. Experimental

3.1. Materials

CEL was purchased from Unichem Laboratories Ltd., Raigad, India. PVP (K 29/32) was received as a gift sample from ISP Technologies, Inc., NJ, USA. MEG was purchased from Sigma-Aldrich Chemie GmbH, Steinheim, Germany.

Table 3: Thermodynamic parameters for solubilization process of different systems of CEL

	Crystalline CEL	Amorphous CEL	CEL-PVP Binary System	CEL-PVP-MEG Ternary System
ΔH_{sol} (kJ/mol)	27.56 ± 2.35	26.55 ± 1.93	19.06 ± 2.18	10.63 ± 2.67
ΔH_{trans} (kJ/mol)	–	1.01 ± 0.21	8.50 ± 0.67	16.93 ± 1.32
ΔG^* (J/mol)	–	569.86 ± 35.24	3097.08 ± 124.32	6441.92 ± 149.65
ΔS^* (J/K/mol)	–	1.48 ± 0.46	18.13 ± 1.28	35.19 ± 3.54

* At 25 °C
Values are reported as mean ±S.D. (n = 3)

3.2. Preparation of CEL-additive(s) amorphous systems

CEL-MEG binary systems and CEL-PVP-MEG ternary systems of varying PVP (10–40% w/w) and MEG content (5–20% w/w) were prepared by heating the CEL-additive(s) physical mixture of appropriate composition, to melting (up to 175 °C), followed by quench cooling over crushed ice. The CEL-additive(s) physical mixtures were previously prepared by dissolving the components in methanol-water mixtures, followed by solvent evaporation under heat and vacuum. This step was necessary to allow uniform mixing of the components at a molecular level, especially at lower contents of any one of the components. The purity of the quench-cooled samples was above 99.99%, as assessed by HPLC. Samples were analyzed immediately after preparation.

3.3. Microscopy

Optical microscopy was performed using a polarized light microscope (DM LP, Leica Microsystems Wetzlar GmbH, Wetzlar, Germany). Hot-stage microscopy (HSM) was carried out using a Leica LMV hot stage. Photomicrographs were taken using a Leica DC 300 camera, and analyzed using Leica IM 50, version 1.20 release 19 software.

3.4. Differential Scanning Calorimetry

The calorimetric response of different samples was measured using DSC (821^e, Mettler-Toledo GmbH, Schwerzenbach, Switzerland), operating with STAR^e software version 5.1, and equipped with an intra-cooler. The samples (3–5 mg) were analyzed under dry nitrogen purge (80 ml/min) in sealed and pin-holed aluminum (Al) pans at a heating rate of 5 °C/min, unless specified otherwise.

For enthalpy recovery studies, amorphous samples were prepared within the DSC instrument. A weighed amount of crystalline CEL or CEL-additive(s) physical mixture, sealed in a pin-holed Al pan, was heated to 175 °C at a rate of 20 °C/min, held isothermally for 2 min, and then immediately cooled to 25 °C (the annealing temperature, T_a) at −20 °C/min. After cooling, the pans were immediately removed from the instrument, transferred to desiccators containing phosphorus pentoxide (for maintaining 0% RH), which were vacuum-sealed, and then stored in incubators at 25 °C. Aged samples were analyzed at different time intervals by DSC at 20 °C/min for enthalpy recovery ($\Delta H_{recovery}$). The $\Delta H_{recovery}$ was obtained by subtracting the unaged heat flow curve from the aged heat flow curve, and integrating the difference in area between the two curves. $\Delta H_{recovery}$ for binary/ternary systems was corrected for dilution with additive(s) to allow comparison with that of the pure amorphous CEL.

T_g has been reported as the mid-value of the glass transition event, and the width of the glass transition (ΔT_{gw}) was determined as the difference in the extrapolated offset (following enthalpy recovery) and extrapolated onset T_g values. The instrument was calibrated for temperature and heat flow using high purity standards of 4-nitro toluene, indium and zinc.

3.5. Solubility determination

The dynamic aqueous solubility of crystalline CEL, and freshly prepared, ground and sieved (BSS No. 60, mesh size 250 μm) amorphous samples was determined by placing an excess quantity of sample in 15 ml screw-capped glass vials containing 5 ml of distilled water, pre-equilibrated to 37 ± 0.5 °C. The vials were mechanically shaken in a shaking water bath (SW 23, Julabo Labortechnik GmbH, Seelbach, Germany) at 200 rpm. At pre-determined time intervals up to 6 h, samples were withdrawn, filtered, appropriately diluted, and analyzed for drug by UV spectrometry (Lambda 20, Perkin-Elmer Corp., CT, USA).

The statistically significant differences between various parameters were tested using one-way ANOVA (SigmaStat, version 2.03) followed by the Student-Newman-Keuls method. The significance level was set at $P < 0.05$.

References

Aida K, Benino Y, Dimitrov V, Komatsu T (2000) Kinetics of enthalpy relaxation at the glass transition in ternary tellurite glasses. J Am Ceram Soc 83: 1192–1198.

Assman K, Schneider HA (1989) The thermal analysis of polymer blends of poly(ethylene oxide)/poly(methyl methacrylate). J Therm Anal 35: 459–468.

Chawla G, Gupta P, Thilagavathi R, Chakraborti AK, Bansal AK (2003) Characterization of solid-state forms of celecoxib. Eur J Pharm Sci 20: 305–317.

Cowie J, Ferguson R (1989) Physical aging studies in poly(vinylmethyl ether). 1. Enthalpy relaxation as a function of aging temperature. Macromol 22: 2307–2312.

Craig DQM (2002) The mechanisms of drug release from solid dispersions in water-soluble polymers. Int J Pharm 231: 131–144.

Crowley KJ, Zografi G (2001) The use of thermal methods for predicting glass-former fragility. Thermochim Acta 380: 79–93.

Elamin AA, Ahlneck C, Alderborn G, Nystrom C (1994) Increased metastable solubility of milled griesofulvin, depending on the formation of a disordered surface structure. Int J Pharm 111: 159–170.

Fried JR, Karasz FE, MacKnight WJ (1978) Compatibility of poly(2,6-dimethyl-1,4-phenylene oxide) (ppo)/poly(styrene-co-4-chlorostyrene) blends. I. Differential scanning calorimetry and density studies. Macromol 11: 150–158.

Gupta P, Kakumanu VK, Bansal AK (2004a) Stability and solubility of celecoxib-PVP amorphous dispersions: A molecular perspective. Pharm Res 21: 1762–1769.

Gupta P, Chawla G, Bansal AK (2004b) Physical stability and solubility advantage from amorphous celecoxib: The role of thermodynamic quantities and molecular mobility. Mol Pharm 1: 406–413.

Hancock BC, Shamblin SL (2001) Molecular mobility of amorphous pharmaceuticals determined using differential scanning calorimetry. Thermochim Acta 380: 95–107.

Kakumanu VK, Bansal AK (2002) Enthalpy relaxation studies of celecoxib amorphous mixtures. Pharm Res 19: 1873–1878.

Leuner C, Dressman J (2000) Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm 50: 47–60.

Loftsson T, Frioriksdottir H, Siguroardottir AM, Ueda H (1994) The effect of water-soluble polymers on drug-cyclodextrin complexation. Int J Pharm 110: 169–177.

Nandi I, Bateson M, Bari M, Joshi HN (2003) Synergistic effect of PEG-400 and cyclodextrin to enhance solubility of progesterone. AAPS PharmSciTech 4: 1–5.

Paulson SK, Vaughn MB, Jessen SM, Lawal Y, Gresk CJ, Yan B, Maziasz TJ, Cook CS, Karim A (2001) Pharmacokinetics of celecoxib after oral administration in dogs and humans: Effect of food and site of absorption. J Pharmacol Expt Therap 297: 638–645.

Pikal MJ, Chang LL, Tang XC (2004) Evaluation of glassy-state dynamics from the width of the glass transition: Results from theoretical simulation of differential scanning calorimetry and comparisons with experiment. J Pharm Sci 93: 981–994.

Pomposo JA, Eguiazabal I, Calahorra E, Cortazar M (1993) Glass transition behaviour and interactions in poly(p-vinyl phenol)/polymethacrylate blends. Polymer 34: 95–102.

Press WH, Flannery BP, Teukolsky SA, Vetterling WT (1987) In: Numerical recipes, New York, p. 521–528.

Serajuddin ATM (1999) Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs. J Pharm Sci 88: 1058–1066.

Sertosu G, Butler J, Hempenstall J, Rades T (2003) Physical stability and enthalpy relaxation of drug-hydroxypropyl methylcellulose phthalate solvent change co-precipitates. J Pharm Pharmacol 55: 35–41.

Sun D, Lennernas H, Welage LS, Barnett JL, Landowski CP, Foster D, Fleisher D, Lee K-D, Amidon GL (2002) Comparison of human duodenum and Caco-2 gene expression profiles for 12,000 gene sequences tags and correlation with permeability of 26 drugs. Pharm Res 19: 1400–1416.

Vachon MG, Grant DJW (1987) Enthalpy-entropy compensation in pharmaceutical solids. Int J Pharm 40: 1–14.

Yazdanian M, Briggs K, Jankovsky C, Hawi A (2004) The "high solubility" definition of the current FDA guidance on biopharmaceutical classification system may be too strict for acidic drugs. Pharm Res 21: 293–299.

Yu LX (1999) An integrated model for determining causes of poor oral drug absorption. Pharm Res 16: 1883–1887.

Yu LX, Amidon GL (1998) Characterization of small intestinal transit time distribution in humans. Int J Pharm 171: 157–163.