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Role of Molecular Interaction in Stability of Celecoxib−PVP Amorphous Systems

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Abstract: Stabilization of an amorphous solid against devitrification can be achieved using additives that interact specifically with the parent molecule, and restrain it from rearranging into a crystal lattice. The amorphous form of celecoxib (CEL) was stabilized by poly(vinylpyrrolidone) (PVP), both in the solid state and during dissolution. A comprehensive characterization of CEL−PVP binary amorphous systems by thermal, spectroscopic, and computer simulation techniques provided greater insight into the molecular interaction between the two species. PVP antiplasticized the amorphous CEL, thus raising its glass transition temperature (T_g) and restricting the molecular mobility. The $T_{g_{mix}}$ values for CEL−PVP binary amorphous systems of varying composition showed positive deviation from those predicted through the Gordon−Taylor/Kelley−Bueche equation, thus indicating a molecular interaction between CEL and PVP. This was further substantiated by shifts observed in DSC melting endotherms of CEL, and FTIR bands for C═O stretching vibrations in PVP for CEL−PVP binary amorphous systems. Computer simulation showed stronger H-bonds between amido protons of CEL and carbonyl O of a monomeric unit of PVP, compared to those observed in pure amorphous CEL. These molecular interactions between CEL and PVP supported the stabilizing action of PVP for the amorphous form of CEL.

Keywords: Celecoxib; PVP; amorphous; molecular interaction

Introduction

The amorphous state of solids is characterized by short-range molecular order in contrast to their ordered crystalline counterparts, and their greater disorder translates thermodynamically into higher enthalpy, entropy, and free energy.[1] The metastability of these phases is associated with continual mobility of molecules, even below the glass transition temperature (T_g),[2] favoring structural relaxation to release energy, and return to a thermodynamically stable crystalline phase. These phase transformations involve altered molecular arrangements in the two solid states: crystalline and amorphous.

Stabilization of amorphous solids can be conferred through various approaches, viz., (i) storage at a temperature favoring zero molecular mobility, T_0; (ii) antiplasticization with the help of high T_g additives; and (iii) specific interactions with additives, resulting in reduced molecular flexibility.[3] Out of

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these three approaches, the first one has limited utility, due to the requirement of subambient storage conditions for most of the pharmaceuticals. Additives play a significant role, in terms of both stability and solubility of amorphous solids. An ideal mixture of drug with high T_g additive raises the T_g of the amorphous form of the drug with subsequent stabilization. Further, any specific interaction between the drug and additive would discourage the rearrangement of drug molecules, thus retaining their disordered structure in the glassy state.

The amorphous form of celecoxib (CEL), a biopharmaceutics classification system (BCS) class II drug, was found to provide an initial increase in solubility over its crystalline form, but a rapid devitrification,[4] both on storage and during dissolution, resulted in a loss of solubility advantage. On the other hand, thermodynamic principles predicted a nearly 7−21-fold solubility advantage for this moderately fragile liquid ($D = 11.5$ and $m = 67.0$).[5] The zero and critical molecular mobility regions, represented by the Kauzmann temperature (T_K) and T_g, respectively, were found to lie near −27 and 50 °C for amorphous CEL, suggesting the use of additives for stabilizing the amorphous form for meaningful time scales.

Selection of a stabilizer for the amorphous form should be guided by structural aspects wherein the functional groups of a stabilizer molecule should be able to interact with those of drug molecules, and block the interaction sites, thus retarding self-association of drug molecules into its crystalline form. Comparison of various additives for their stabilizing action showed poly(vinylpyrrolidone) (PVP) to maximally reduce the mobility of CEL molecules trapped in amorphous form.[6] A CEL−PVP (4:1 w/w) binary amorphous system also provided nearly a 6.3-fold solubility advantage over crystalline CEL.[7] This contribution to enhanced solubility was specific to the amorphous form of the drug as a physical mixture of crystalline CEL and PVP showed poor solubility, similar to crystalline drug. The present study was aimed at exploring the molecular-level interactions between CEL and PVP to understand their role in enhancing stability and solubility of amorphous CEL.

Experimental Section

Materials. CEL was purchased from Unichem Laboratories Ltd., Raigad, India. PVP (K 29/32) and *N*-methyl-2-pyrrolidone (NMP) were obtained from ISP Technologies, NJ.

Preparation of Amorphous Systems of CEL. Amorphous CEL and CEL−PVP binary amorphous systems of varying composition were prepared by heating the crystalline drug or its physical mixture with PVP, respectively up to 175 °C, followed by quench cooling of their melt over crushed ice. The CEL−PVP physical mixtures were prepared by dissolving the components in dichloromethane, so as to allow their mixing at a molecular level, followed by solvent evaporation under heat and vacuum. No visible sign of degradation was observed in quench-cooled samples, and the purity of the amorphous samples was established by high-performance liquid chromatography. Samples were analyzed immediately after preparation, after due protection from atmospheric moisture.

Differential Scanning Calorimetry (DSC). The calorimetric response of different samples was measured using a DSC instrument (821^e, Mettler-Toledo GmbH, Schwerzenbach, Switzerland), operating with STAR^e software version 5.1, and equipped with an intracooler. The samples (3−5 mg) were analyzed under dry nitrogen purge (80 mL/min) in sealed and pinholed aluminum pans at a heating rate of 5 °C/min, unless specified otherwise.

Adsorbed moisture can significantly affect the T_g of amorphous solids. To prevent such a possibility, determination of T_g was done by DSC analysis from 25 °C to 175 °C at 20 °C/min for samples prepared within the DSC instrument, as reported previously.[7] All determinations were made in triplicate. The instrument was calibrated for temperature and heat flow using high purity standards of 4-nitrotoluene, indium, and zinc. The T_g has been reported as the midvalue of the glass transition event, T_c as the onset crystallization temperature, and T_m as the peak melting temperature.

Fourier Transform Infrared (FTIR) Spectroscopy. The FTIR spectra were recorded on a FTIR multiscope spectrophotometer (Perkin-Elmer, Buckinghamshire, U.K.) equipped with spectrum v3.02 software, by a conventional KBr pellet method. Liquid samples were taken neat on KBr disks. All determinations were made in triplicate.

Molecular Modeling Studies. Molecular interactions between CEL and PVP were investigated by computer simulation of CEL and *N*-vinyl-2-pyrrolidone (NVP), the monomeric unit of PVP, by a molecular silverware method using the Sybyl 6.8 program (Tripos, Inc., MO) running on a Silicon Graphics onyx workstation. The CEL starting ensemble was built from available crystal data. Random arrangement of molecules to simulate the amorphous form was modeled by subjecting 18 molecules of CEL to energy optimization using the MMFF94 force field[8] until gradient convergence of 0.05 kcal/mol was reached. Out of the optimized model, 9 CEL molecules were randomly extracted and subjected to energy optimization in the presence of 18 molecules of NVP. This finally optimized model of CEL

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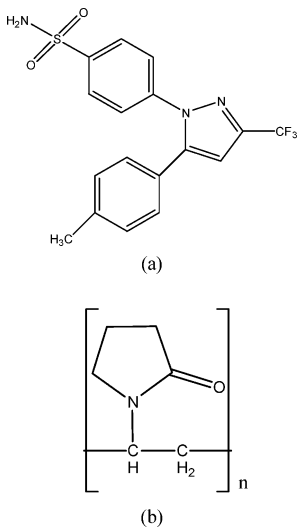

Figure 1. Chemical structures of (a) CEL and (b) PVP.

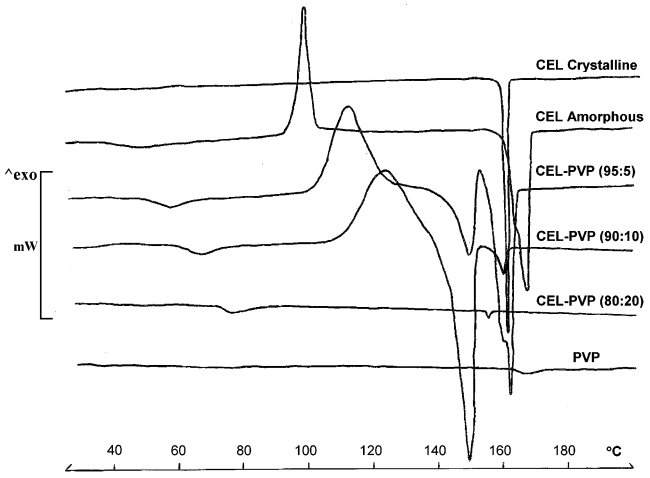

Figure 2. DSC thermograms of crystalline CEL, amorphous CEL, CEL−PVP binary amorphous systems of varying PVP content, and PVP.

and NVP molecules was investigated for interactions between the two species. This procedure was analogous to that previously followed for studying molecular interactions of CEL with *N*,*N*-dimethylformamide, *N*,*N*-dimethylacetamide,[4] and meglumine.[9]

Results and Discussion

Structural Attributes of CEL and PVP. The chemical structures of CEL and PVP are shown in Figure 1. CEL is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl]benzenesulfonamide (MW 381.38) and is a diaryl-substituted pyrazole class of compound. Structural inspection of CEL reveals that its amido protons (H atoms covalently bonded to N, an atom of greater electronegativity than C) are the only potential electron-accepting centers, whereas the sulfonyl O, the N atoms of the pyrazole ring, and the F atoms of the trifluoromethyl group are the three electron-donating centers. The amido N, however, loses its electron-donating capability due to delocalization of its electrons over neighboring O atoms.[10] These electron-accepting and -donating centers are the potential sites for H-bonding in and among CEL molecules.

PVP (K 29/32) is chemically 1-ethenyl-2-pyrrolidinone homopolymer (weight average MW 58 000) composed of a hydrophobic backbone with a hydrophilic side group. It lacks acidic protons, but contains two electron-donating centers (the −C═O group and the N atom of the pyrrole ring). The −C═O group of PVP is considered to be the most favorable site for interaction due to the steric constraints on the N atom.[11] Various reports have cited the complexation led stabilizing action of PVP for amorphous forms of various drug molecules like ajmaline,[12] furosemide,[13] indomethacin,[14] and probucol.[15]

Commercially, NVP is available as a liquid (Merck, Germany), stabilized with *N*,*N*′-di-*sec*-butyl-1,4-phenylenediamine. Due to possible interference of this stabilizer in the FTIR spectrum, NMP, a structural analogue to NVP, was used since it is available in pure form. NMP (MW 99.13) was used in the present study to model the participation of the −C═O group of PVP[14] in H-bonding with the $-NH_2$ group of CEL.

Thermal Transitions in CEL−PVP Binary Amorphous Systems. The effect of PVP on the thermal response of CEL was studied by comparing the DSC thermogram of amorphous CEL with that of CEL−PVP binary amorphous systems of varying composition (Figure 2). All systems, except with 20% w/w PVP, exhibited a common trend of glass transition event, followed by exothermic transition and endothermic events. At 20% w/w PVP, no exothermic transition was observed (explained later). These thermal transitions can have a significant bearing on the molecular-level interaction of the drug with the additive.

Effect on Glass Transition. Mixing of amorphous components at the molecular level results in production of an amorphous phase, the properties of which can be related to the properties of individual components (e.g., T_g) and its

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composition. The molecular interaction between the drug and the additive can influence their T_g.[16] A stronger bonding between unlike molecules raises the T_g from a value expected from ideal mixing,[17] due to the reduced mobility of molecules in the complexed state. The T_g of amorphous CEL and PVP was found to be 58.1 and 168.4 °C, respectively. Ideal molecular-level mixtures of these two components can be expected to exhibit T_g values intermediate of their original values, with a higher T_g for amorphous CEL due to the antiplasticization by PVP.

CEL−PVP binary systems of varying composition showed a single content-dependent T_g, the value of which was between those of the individual components, thereby establishing the drug−additive miscibility. These experimentally determined T_g values were compared with theoretically predicted values using the Gordon−Taylor/Kelley−Bueche (G-T/K-B) equation.[18,19] The equation is based on the additivity of free volumes of the individual components characteristic of ideal mixing, and is given by the expression

$$T_{g_{mix}} = \frac{w_1 T_{g_1} + K w_2 T_{g_2}}{w_1 + K w_2} \quad (1)$$

where numerals in the subscript represent the two components, and w is the weight fraction of the components. The constant K, a measure of interaction between the components, can be approximated using eq 2,[20]

$$K \approx \frac{\Delta C_{p_2}}{\Delta C_{p_1}} \quad (2)$$

where ΔC_p denotes the change in heat capacity at T_g. The goodness of fit of experimental data to the G-T/K-B equation indicates the ideality of mixing of the two components, and also provides a predictive tool for assessing the effect of different levels of one component on the T_g of the other. Deviation from ideal behavior signifies differences in the strength of intermolecular interactions between individual components and those of the blend. The predicted and experimentally determined $T_{g_{mix}}$ values for CEL−PVP binary systems of varying composition are plotted against PVP content in Figure 3. These $T_{g_{mix}}$ values increased continuously with increasing PVP content, due to the antiplasticizing effect of PVP. At 10% w/w PVP content, the predicted and experimental $T_{g_{mix}}$ values were nearly similar, while positive deviation was observed at higher PVP content (20−80% w/w). This deviation of $T_{g_{mix}}$ values indicated specific interaction between CEL and PVP, noticeable at intermediate content of PVP.

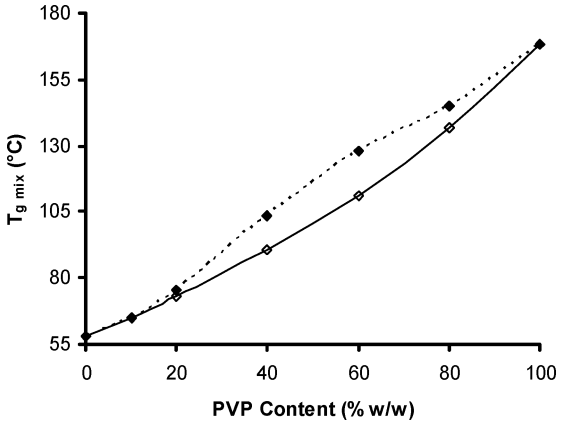

Figure 3. Influence of PVP content on $T_{g_{mix}}$ values of CEL−PVP binary amorphous systems. The solid line represents the prediction of the Gordon−Taylor/Kelley−Bueche equation; the dotted line represents the measured values.

Mixing of a small amount of a macromolecule like PVP with an amorphous small molecule like CEL will introduce a considerable excess free volume in the system. Despite intermolecular interaction and subsequent influence on lowering the free volume, this might not result in considerable decrease in free volume of the mixture, which has been observed as minimal difference in predicted and measured $T_{g_{mix}}$ values at 10% w/w PVP content. Similarly, addition of low levels of CEL to PVP (as with 80% w/w PVP content in the CEL−PVP binary system) is probably much less disruptive in terms of influencing the net free volume of the mixture. Thus, considerable deviations can be expected at intermediate content of PVP, which provides excessive differences in free volumes of each component. This nonideality of mixing at intermediate PVP content is a result of a lower free volume of binary system from that possible on ideal mixing, due to the higher strength of interaction between CEL and PVP than the arithmetic mean of bond strengths of individual components. Similar behavior has been reported for mixtures of PVP and MK-0591, an investigational drug.[21]

For mixing to occur, the Gibb's free energy of mixing (ΔG_{mix}) must be negative,[22]

$$\Delta G_{mix} = \Delta H_{mix} - T\Delta S_{mix} \quad (3)$$

where ΔH_{mix} and ΔS_{mix} are the enthalpy and entropy of mixing, respectively, at temperature T. The three main

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Table 1. Effect of PVP Content on Crystallization Exotherm and Melting Endotherms in CEL−PVP Binary Amorphous Systems[a]

			melting					
	crystallization		peak 1			peak 2		
PVP content (% w/w)	T_c (°C)	ΔH_c (J/g)	T_m (°C)	ΔH_m (J/g)	A_s	T_m (°C)	ΔH_m (J/g)	A_s
0	96.3 ± 0.3	53.5 ± 1.0				165.9 ± 0.1	86.8 ± 0.3	2.9 ± 0.3
5	101.9 ± 0.1	47.9 ± 0.5	149.0 ± 0.5	21.2 ± 0.9	4.2 ± 0.4	161.6 ± 0.2	45.4 ± 0.6	3.8 ± 0.4
10	111.0 ± 0.4	26.7 ± 0.4	149.1 ± 0.1	31.4 ± 0.6	3.8 ± 0.3	160.1 ± 0.5	1.9 ± 0.1	3.5 ± 0.2
20						155.3 ± 0.1	0.5 ± 0.1	2.5 ± 0.4

[a] Values are reported as mean ± SD, $n = 3$.

thermodynamic effects that contribute to ΔG_{mix} through influencing ΔH_{mix} and ΔS_{mix} are (i) the combinatorial entropy of mixing, (ii) the free volume effect, and (iii) the intermolecular interactions. For high molecular weight polymers, the combinatorial entropy gain is insufficient to achieve miscibility, and it is considered that miscibility can only be achieved through specific interactions.[22] Specific interactions such as H-bonding can lead to a significant negative contribution to ΔG_{mix}. Thus, for high molecular weight polymers, such a specific interaction is deemed to be necessary to obtain a stable mixture.

Effect on Crystallization and Melting. The exothermic transitions for a drug−additive amorphous system could correspond to the amorphous solidification of the drug in additive and/or to the beginning of the formation of a complex.[23] The T_c, as such, corresponds to a temperature favoring spontaneous crystallization of the amorphous phase (i.e., molecular mobility permits nucleus growth, resulting in evolution of heat).[24]

DSC analysis of amorphous CEL showed the T_c at 96.3 °C and the T_m at 165.9 °C. Inclusion of PVP in the amorphous system of CEL raised the T_c and lowered the T_m value. As detailed in Table 1, the increase in PVP content up to 10% w/w in CEL−PVP binary systems resulted in an increase of T_c and a corresponding decrease in enthalpy of crystallization (ΔH_c) of amorphous CEL, signifying the crystallization inhibitory activity of PVP. At and above 20% w/w PVP, no exothermic peak was observed, implying the lower limit of PVP suitable for preventing devitrification of amorphous CEL. After the crystallization event, two endothermic peaks were observed at temperatures lower than that for melting of pure CEL. The enthalpy of melting (ΔH_m) of lower melting peak (T_m = 149 °C) increased from 21.2 to 31.4 J/g on increase in PVP content from 5% to 10% w/w. Thus, this endothermic peak could be attributed to melting of the CEL−PVP complex formed during DSC heating scan, which was abolished at 20% w/w and above PVP content. Similar features have been reported for spray-dried phenobarbitone−PVP systems,[25] signifying the tendency toward generation of amorphous drug−PVP complex. On the contrary, the high-melting peak showed a decrease in both T_m (165.9−155.3 °C) and ΔH_m (86.8−0.5 J/g) with an increase in PVP content from 0% to 20% w/w. This peak could be from the initially remaining crystalline fraction of CEL in the binary system, which got reduced with an increase in PVP content. These shifts in the melting endotherm[26,27] of CEL in the presence of PVP strongly suggest molecular-level interaction between the two species. Similar thermal behaviors were exhibited by a spray-dried hydroflumethiazide−PVP system,[25] substantiating the drug−PVP complex formation.

Further, the asymmetry index (A_s)[28] of these melting endotherms was measured as an indicator of molecular interactions.

$$A_s = \frac{[(T_{ons} - T_i)/(T_{end} - T_i)]_{CEL-additive\ amorphous\ system}}{[(T_{ons} - T_i)/(T_{end} - T_i)]_{crystalline\ CEL}} \quad (4)$$

Referring to the DSC plot, T_{ons} (onset temperature) is the temperature of the intercept between the base line and the tangent to the descending part of the graph at its inflection point, and T_{end} (endset temperature) is the same, but refers to the rising part of the calorimetric peak. The temperature T_i is of the interception point of the two previous tangents, and its value is the same as or very close to T_m. Melting endotherms for all CEL−PVP binary systems were significantly asymmetric, with A_s values higher than 1 (Table 1), signifying their skewness toward lower temperatures, com-

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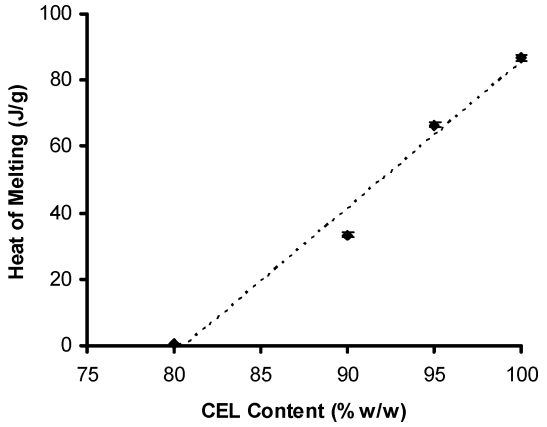

Figure 4. Heat of melting of CEL−PVP binary amorphous systems of varying composition.

pared with that for crystalline CEL. This indicated a greater strength of interaction[29] between CEL and PVP than within the individual components.

The ΔH_m of CEL, as determined for various CEL−PVP binary systems, was plotted (Figure 4) against CEL content in the binary system. Extrapolation of the plot[30] resulted in determination of the theoretical CEL solubility in PVP to be about 80.82% at its melting point, which represented a 1.2:1.0 molar ratio of drug to each PVP subunit for formation of glass solution.[31] Thus, a CEL−PVP (4:1 w/w) binary system that showed maximal solubility enhancement[7] can be interpreted as a glass solution, wherein the drug is dissolved in solid carrier, thus favoring rapid dissolution in aqueous milieu.

Spectral Variations in CEL−PVP Binary Amorphous Systems. Vibrational spectroscopy has been extensively used to investigate interactions between the components of solid dispersions.[13−15,21,32] The mixing of two components at the molecular level is expected to cause changes in their oscillating dipoles, which will manifest itself as changes in the frequency and bandwidth of interacting groups in the spectrum.[33]

The FTIR spectrum of PVP showed a strong band at 1663 cm^{-1} characteristic of C═O stretching vibration. In the case of the CEL−PVP (4:1 w/w) binary system, the composition with maximal solubility gain for amorphous CEL,[7] there was a negligible shift in the position of this band, indicating the absence of H-bonding between CEL and PVP. However, structurally, CEL and PVP present a possibility of intermolecular H-bonding. The possible reason for failure of FTIR spectroscopy in detecting the H-bonding could be a marked difference in the number of molecules of CEL and PVP available for interaction. PVP is a polymeric compound with a large number of monomers, each possessing a −C═O group. Thus, a greater number of −C═O groups of PVP molecules in comparison to $-NH_2$ groups of CEL can raise the possibility of a large number of nonbonded −C═O groups than the H-bonded ones, which was seen as a negligible shift in the C═O stretching vibration band.

In order to prove this hypothesis, the overlapping bands of "bonded" and "nonbonded" −C═O groups were resolved by FTIR analysis of CEL−PVP binary systems with low PVP content. The perfect mixing of a low amount of PVP with CEL in the binary systems was assured by the observance of a single glass transition event during the DSC analysis of these samples. The FTIR spectra of CEL−PVP binary systems with low PVP content (Figure 5a) showed the shift of the C═O stretching vibration band from 1663 cm^{-1} at 1% w/w PVP content to 1655 cm^{-1} at 0.25% w/w PVP content, possibly due to an increase in the number of bonded C═O groups, hinting toward hydrogen bonding between the −C═O group of PVP and $-NH_2$ group of CEL. A further confirmation of this interaction and ruling out of these spectral changes, being only a "dilution effect", was done by performing a study on a CEL and NMP system (reported later in the text). NMP was chosen as a model monomer of PVP. Below 0.25% w/w PVP content in the CEL−PVP binary system, the C═O stretching vibration band was lost due to the lower content of PVP.

The bandwidth at half-height of the −C═O stretching vibration of PVP was further measured as an indicator of heterogeneous species contributing to the band.[34] The bandwidth for pure PVP was found to be 198.7 cm^{-1}, while it varied from 33.4 to 19.5 cm^{-1} (Figure 6) for CEL−PVP binary systems of PVP content from 1.00% to 0.25% w/w. This substantiated that higher PVP content led to a greater probability of nonbonded −C═O groups, which reduced to only bonded ones at lower PVP content. This further indicates toward inequivalence in the number of "bonded" and "nonbonded" −C═O groups present at different PVP content in the CEL−PVP binary systems. Due to strong absorbing tendencies of −C═O group, these shifts of H-bonded states were not resolvable at higher PVP content.

Amorphous CEL shows a shift to higher wavenumber for the N−H stretching vibration band, and to lower wavenumber for the S═O stretching vibration band,[4] compared with crystalline CEL. These spectral shifts indicate alteration of intermolecular H-bonding between −N−H and −S═O

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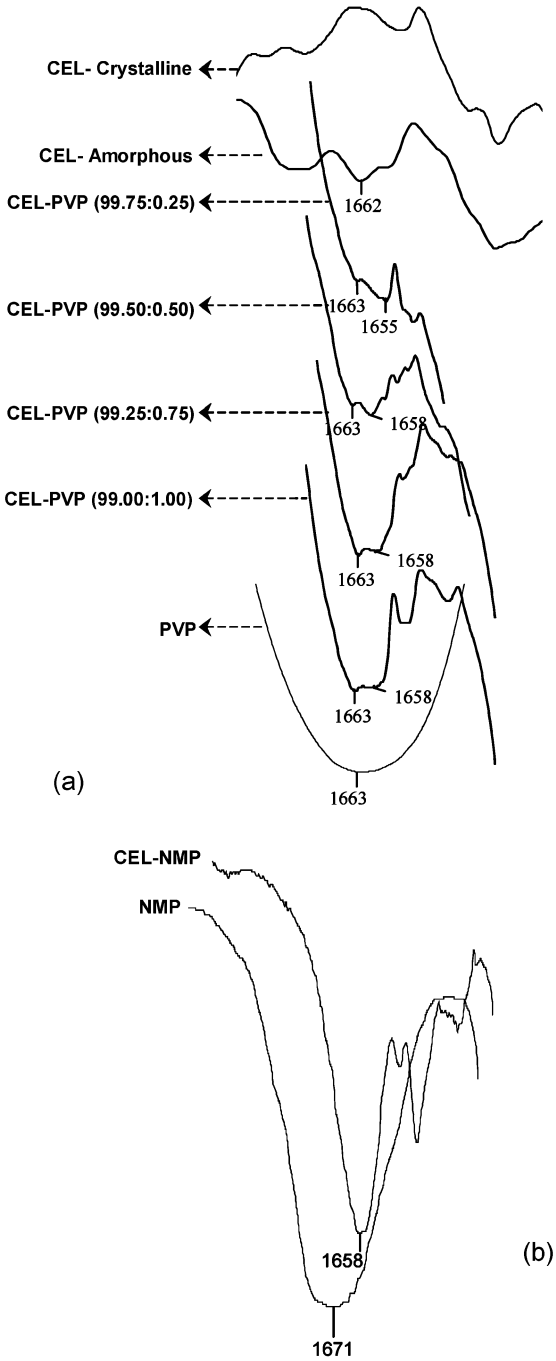

Figure 5. FTIR spectra in C═O stretching vibration region for (a) crystalline CEL, amorphous CEL, CEL−PVP binary amorphous systems of varying PVP content, and PVP and (b) NMP and a CEL−NMP (1:1 molar ratio) binary system.

groups of CEL in crystalline and amorphous phases. Even at the lowest content (0.25% w/w) of PVP in the CEL−PVP binary system, the bands of N−H and S═O stretching vibrations for CEL were observed at positions characteristic for amorphous CEL. These results implied that CEL−PVP binary amorphous systems consisted of CEL-CEL as well as CEL−PVP in H-bonded states. The existence of H-bonding between CEL and PVP can thus have strong

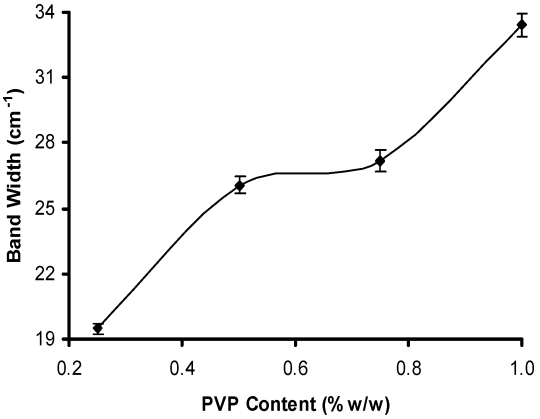

Figure 6. FTIR bandwidth at half-height for C═O stretching vibration of PVP in CEL−PVP binary amorphous systems of varying composition.

implications on limiting the molecular motions of the drug in the amorphous state, and maintaining its physical stability.

Further, the possibility of interaction between $-NH_2$ and −C═O groups was concluded using NMP as the model of the −C═O group. The neat sample of NMP showed a strong C═O stretching vibration band at 1671 cm^{-1} (Figure 5b). This band shifted to 1658 cm^{-1} in the case of a CEL-NMP (1:1 molar ratio) binary system. This result clearly indicated the H-bonding affinity between the $-NH_2$ and −C═O groups. On the other hand, the S═O stretching vibration band of CEL was observed at 1346 cm^{-1}, implying its nonparticipation in H-bonding. This may be a result of the plasticizing effect of NMP, a liquid substance that disfavored the molecular arrangement of CEL in amorphous form.

Computer Simulation of a CEL−NVP Mixture. Computer simulation has been an efficient tool for gaining a deeper understanding of molecular interactions between drug and additives.[35,36] It helps in rationalizing the experimental observations, provides information not amenable to explanation, and even makes predictions concerning the outcome of future experiments. In this study, computer simulation was used as an adjunct to the results of FTIR studies, to confirm the molecular interactions between CEL and PVP. Instead of building the polymeric structure of PVP, its monomeric unit, NVP, was investigated for interaction with CEL to assist the interpretation of data, which could have been difficult in the polymer due to the presence of multiple −C═O groups.

Apart from the intermolecular interaction between two randomly oriented CEL molecules, H-bonding was also observed between CEL and NVP molecules (Figure 7). The

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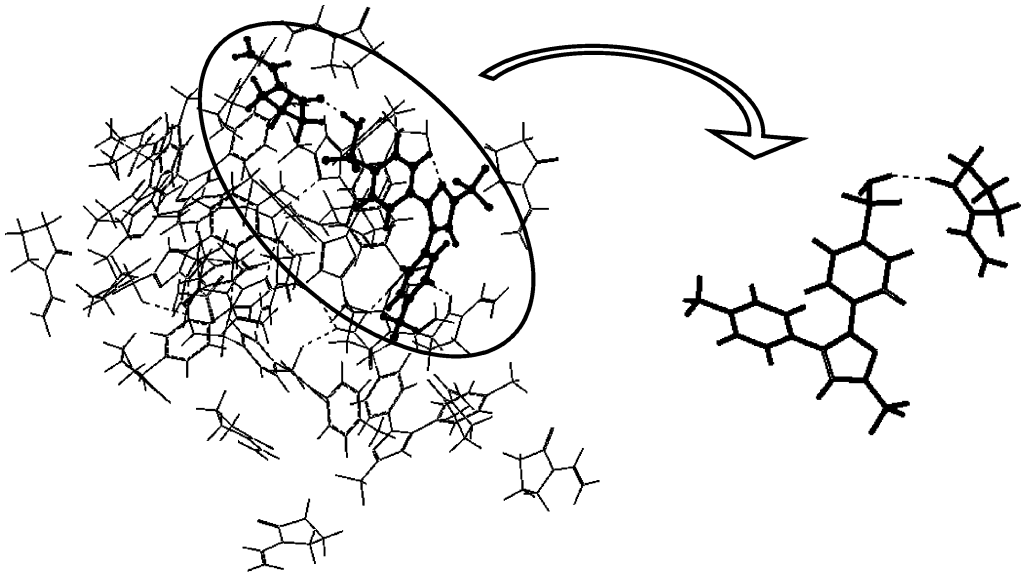

Figure 7. Stereoview of intermolecular association between CEL and NVP, the monomeric unit of PVP. The H-bonding is represented by dotted lines between the interacting groups of CEL and NVP.

−C═O group of NVP H-bonded with the $-NH_2$ group of CEL, forming −N−H···O═C− bonds (N−H···O 2.742 Å, H···O 1.738 Å). Amide carbonyl O is a stronger proton acceptor than sulfonyl O,[10] thus leading to a stronger H-bond between the $-NH_2$ group of CEL and the −C═O group of NVP. Thus, apart from antiplasticization, this specific molecular interaction might be an important reason for stabilization of the amorphous form of CEL in CEL−PVP binary systems, wherein the amorphous form of CEL remains in complexed form with PVP, restraining it from self-association to generate CEL crystal nuclei.

Conclusions

The higher molecular mobility in the amorphous state increases the tendency of devitrification, thus negating the biopharmaceutical advantage of this otherwise beneficial technology. PVP was found to stabilize the amorphous form of CEL in the solid state as well as during dissolution. A specific molecular interaction between the $-NH_2$ group of CEL and the −C═O group of PVP, as postulated by thermal, spectroscopic, and computer simulation studies, was found to be the major reason behind the formation and performance of a stable CEL−PVP amorphous system.

PVP antiplasticized the amorphous CEL, and increased the T_g of the amorphous system to reduce the molecular motions. Besides this, a specific molecular interaction between CEL and PVP was indicated by shifts in DSC melting endotherms of CEL, and FTIR bands for the C═O stretching vibration of PVP in CEL−PVP binary systems. Computer simulation of the CEL−NVP mixture exhibited H-bonding between $-NH_2$ and −C═O groups of CEL and NVP, respectively. By specifically interacting with CEL, PVP arrested the molecular motions, and prevented the rearrangement of CEL molecules from disordered molecular conformation into a thermodynamically stable, ordered crystalline form. Thus, the interaction with PVP renders an enhanced physical stability to the amorphous form of CEL, resulting in an obvious solubility advantage.

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