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Molecular and Thermodynamic Aspects of Solubility Advantage from Solid Dispersions

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Abstract: The solubility behavior of solid dispersions of two drugs with similar structures was studied. Valdecoxib (VLB) and etoricoxib (ETB) were used as model drugs, and their solid dispersions were prepared with 1, 2, 5, 10, 15, and 20% w/w poly(vinylpyrrolidone) (PVP) by the quench cooling method. The interactions between the drug and polymer molecules were studied by Fourier transform infrared spectroscopy (FT-IR). The thermodynamic aspects of solubility behavior were studied by plotting van't Hoff plots. Both the drugs showed significant differences in their solubility behavior. In the case of VLB, solubility was found to increase significantly with increasing PVP concentration. ETB however did not show any significant solubility enhancement and was found to have decreased solubility at high PVP concentrations. H-bonding interactions were established between VLB and PVP molecules, while none were observed in ETB–PVP dispersions. Solution thermodynamics of amorphous and crystalline forms of both the drugs were studied by van't Hoff plots. The results obtained showed very high negative value of Gibbs free energy for VLB as compared to ETB, thus demonstrating high spontaneity of VLB solubilization. Entropy of amorphous VLB was found to be highly favorable, while being slightly unfavorable for ETB. From this study H-bonding interactions were found to play a major role in dictating the solubility behavior of these drugs from solid disperions.

Keywords: Solubility; solid dispersions; amorphous; entropy; solution thermodynamics; valdecoxib; etoricoxib; interactions

Introduction

Solubility and permeability are the two most important biopharmaceutical properties that together with potency determine the clinical efficacy of drug[1] and form the basis of the biopharmaceutics classification system (BCS). Poor biopharmaceutical properties can lead to the failure of even highly potent molecules during the preformulation stage. More than 40% of new drug molecules fail to reach clinical trials because of this shortcoming.[2] Therefore, approaches that can help to improve delivery of such molecules are highly sought after by the formulation scientists.

Widely used approaches to improve the solubility include prodrugs, complexation, salt formation, cosolvency, solid state modifications (polymorphs, particle size reduction), surfactants, and hydrotropy.[2] Solid state modifications like particle size reduction, use of different high-energy forms (polymorphs, amorphous forms) are widely employed by formulation scientists. Use of high-energy amorphous forms is often desirable because the extent of solubility enhance-

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ment by this method ranges from a few-fold to many-fold.[3] However, because of their high enthalpy and molecular mobility, amorphous systems are thermodynamically and kinetically unstable and hence often necessitate the incorporation of polymeric stabilizers to form solid dispersions.[4]

The presence of hydrophilic polymers in close contact with the drug molecules increases the solubility by maintaining the drug in a molecular state of subdivision (absence of lattice energy) and maximizing the surface area of the compound.[5] The polymeric carrier also acts as crystallization inhibitor and hence helps in maintaining the drug in its high-energy amorphous state. Engineering of amorphous alloys result in a unique delivery system because of the absence of predefined templates (regular molecular arrangements) observed in crystalline substances.[6,7] Despite the advantages offered by amorphous systems, the marketed products based on this technology are few. The main factors responsible for this situation include manufacturing limitations, stability considerations, and above all lack of predictability of their dissolution behavior, attributed mainly to the lack of understanding of their molecular behavior.[8] The mechanism of dissolution enhancement, the state of dispersal of drug within the polymeric matrix, storage stability, and in vitro and in vivo correlation still need thorough exploration.[8]

Poor understanding of dissolution and solubility behavior of solid dispersions is a major conundrum in successful implementation of this technique. The present work aims at assessing the influence of a drug's nature, thermodynamic and other molecular level factors, affecting its solubility and dissolution. Two drugs from the same therapeutic class having similarity in chemical structure were selected to study the influence of a drug's nature on the solubility profile. The study is based on the hypothesis that drug carrier interactions play a major role in determining the solubility and stability aspects of solid dispersions. Therefore, we chose valdecoxib (VLB) and etoricoxib (ETB) (Figure 1) as model drugs and poly(vinylpyrrolidone) as the polymeric carrier. VLB, because of the presence of the $-SO_2NH_2$ group, acts as an H-donor and can interact with –C═O of PVP, whereas such interactions are not feasible with ETB. Furthermore, in our previous work we observed a perfect inverse correlation between enthalpy relaxation (a measure of molecular mobility and hence kinetic instability) and the solubility behavior of celecoxib–PVP dispersions.[9] Another objective of this work was to extend our previous findings to these two molecules to unravel the molecular phenomenon leading to such a correlation.

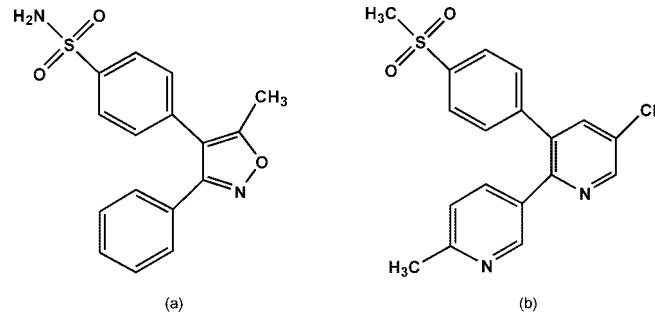

Figure 1. Structures of (a) VLB and (b) ETB.

Experimental Section

Materials. Valdecoxib (VLB) and etoricoxib (ETB) were generous gifts from Aarti Drugs Limited (Mumbai, India), and PVP K-29/32 was purchased from ISP Technologies Inc. (Wayne, NJ). Both drugs were crystalline in nature as indicated by sharp diffraction patterns in PXRD. All solvents used were of analytical grade and were used as obtained without further purification. In order to avoid exposure to environmental moisture, all materials were stored in desiccators containing anhydrous phosphorus pentoxide (P_2O_5) at room temperature.

Preparation of Amorphous Forms of Drugs and Their Solid Dispersions (SDs). Amorphous forms of VLB and ETB were prepared by quenching the crystalline drug melts over crushed ice. To prepare solid dispersions, an accurately weighed sample of drug and polymer in required amounts was taken in a steel beaker and dissolved in a minimum amount of a methanol–dichloromethane mixture. The solvent was evaporated on a water bath maintained at 70 °C. This step was necessary to ensure homogenous mixing of drug with polymer especially at low polymer concentrations. Dried product obtained was heated to a temperature of 190 °C and then quench-cooled over crushed ice. The glassy dispersion obtained was scrapped, lightly triturated, and sieved (BSS no. 60). These triturated SDs were analyzed by PXRD after preparation to ensure the absence of crystallization and were used immediately for solubility studies.

Solubility Studies. Aqueous solubility studies of crystalline and amorphous forms of valdecoxib and etoricoxib were carried out as described by Simonelli et al.[10] Poly(vinylpyrrolidone) (PVP) aqueous solutions of 0.1, 0.2, 0.3, 0.4, 0.5,

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and 1.0% w/v were prepared, and the equilibrium solubility value of the crystalline and amorphous forms of both drugs was determined in these solutions. These studies were carried out by placing an excess quantity of about 10 mg of crystalline and freshly prepared amorphous drug samples at 37 ± 0.5 °C in pre-equilibrated 15 mL screw-capped glass vials containing 5 mL of the respective PVP solutions (n = 3). The vials were shaken mechanically (at 200 rpm) in a shaker water bath (Julabo SW 23, Seelbach, Germany) for 2 h, after which the vials were removed, the contents were filtered through a 0.45 μm nylon filter, diluted adequately, and analyzed for drug content spectrophotometrically at 232 and 285 nm for VLB and ETB, respectively, using a double-beam UV spectrophotometer (Specord 200, Analytik Jena, Germany) using the winASPECT software, version 2.

Aqueous solubility studies of dispersions of VLB and ETB with PVP were also carried out at 37 ± 0.5 °C by following the same method except that distilled water was used instead of PVP solutions and the samples were analyzed for solubilized drug content after 5, 10, 15, 20, 30, 60, 90, 120, 180, 240, and 360 min.

Preparation of Physical Mixtures. Weighed proportions of crystalline and amorphous VLB/ETB fractions and PVP were mixed physically in geometric progression for use in solubility studies, as described in the previous section.

van't Hoff Plots. The temperature dependence of the aqueous solubility of crystalline and amorphous forms of both drugs was studied at 300, 310, 320, 330, and 340 K. The extrapolation method described by Simonelli et al.[9] was used in which equilibrium solubility values in PVP solutions were determined and were plotted against PVP concentration. The linear plot obtained was extrapolated to 0% PVP concentration to obtain the solubility with 0% PVP for each temperature studied. The values obtained were plotted against 1/T to obtain van't Hoff plots.

Fourier Transform Infrared Spectroscopy (FT-IR) Studies. FT-IR spectroscopy was performed on a Perkin-Elmer spectrometer (Synthesis Monitoring System, Shelton) that was equipped with the Spectrum 3.0 analyzing software. The spectra were collected with powder samples dispersed as a 0.5–1% mix in potassium bromide and scanned immediately after mixing. The analyses were performed with samples from two batches and in duplicate.

Results and Discussion

VLB and ETB belong to BCS class II with maximum experimental solubilities of 21.5 and 108 μg/mL, respectively, at 37 ± 0.5 °C. Amorphous forms of these drugs showed an increased peak solubility of 24.3 and 130 μg/mL in water, respectively. However, amorphous forms of these drugs are unstable and tend to revert to the crystalline form in the presence of water.[11] Solid dispersions with hydrophilic polymers like PVP, inulin, hydroxypropylmethyl cellulose, polyethylene glycol, and dextran have been demonstrated to stabilize the amorphous form, thus providing enhanced solubility.[5,12] Therefore, the SDs of both drugs with varying concentrations of PVP were prepared and compared for the advantages in "peak solubility" and "plateau solubility" (Figures 2 and 3).

Before the solubility studies were carried out, the dispersions were analyzed by PXRD in which a halo pattern in all the cases confirmed the absence of any crystalline component

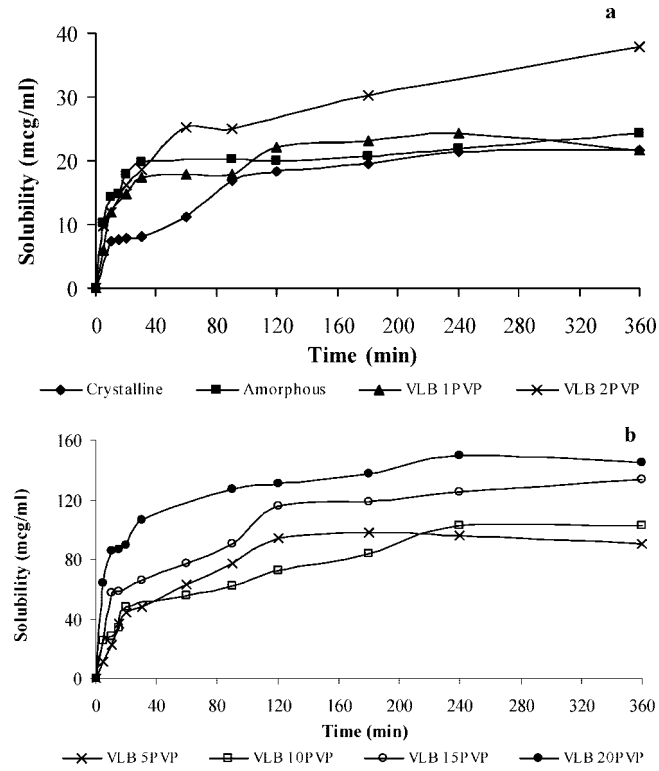

Figure 2. Solubility profile of (a) crystalline VLB, amorphous VLB, and VLB–PVP dispersions at 1 (VLB 1PVP) and 2 (VLB 2PVP) % w/w PVP concentrations and (b) VLB–PVP dispersions at 5 (VLB 5PVP), 10 (VLB 10PVP), 15 (VLB 15PVP), and 20 (VLB 20PVP) % w/w PVP concentrations (n = 3, standard deviation of <5%).

Table 1. Peak Solubility Values (in μg/mL) of Crystalline and Amorphous Forms, Solid Dispersions (at 1, 2, 5, 10, 15, and 20% w/w PVP Concentrations), and Physical Mixtures and Phase Solubility Values of VLB and ETB[a]

	peak solubility values (μg/mL)									
			PVP concentration (% w/w)							
			SDs						PM	Ph Sol (μg/mL)
	crys	amor	1	2	5	10	15	20	20	20
VLB	21.5	24.3	25	38	98	103	134	150	24	48
ETB	108	130	135	146	156	140	136	126	97	86

[a] SDs, solid dispersions; PM, physical mixtures; crys, crystalline; amor, amorphous; Ph Sol: phase solubility.

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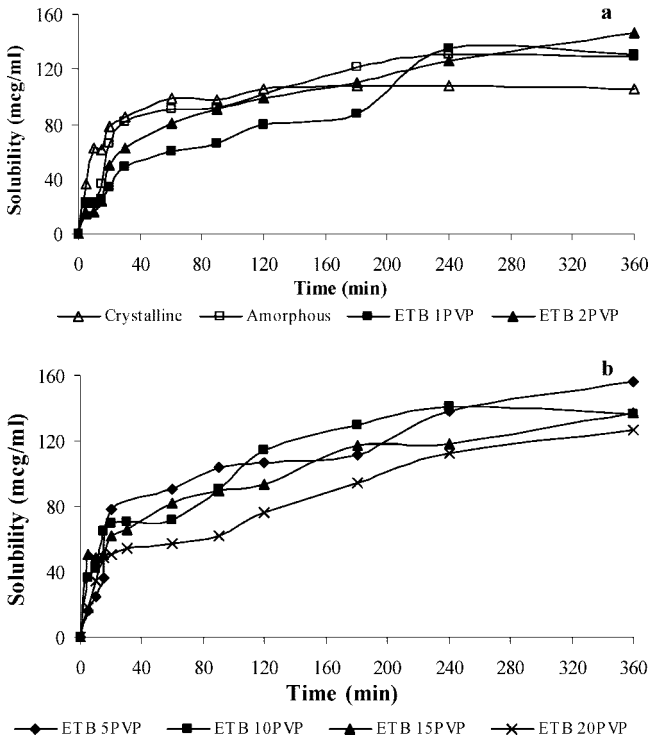

Figure 3. Solubility profile of (a) crystalline ETB, amorphous ETB, ETB–PVP dispersions at 1 (ETB 1PVP) and 2 (ETB 2PVP) % w/w PVP concentrations and (b) ETB–PVP dispersions at 5 (ETB 5PVP), 10 (ETB 10PVP), 15 (ETB 15PVP), and 20 (ETB 20PVP) % w/w PVP concentrations (n = 3, standard deviation of <5%).

in the samples. As is evident from Figure 2, in the case of VLB, increasing polymer concentration alters both the rate and extent of "peak" solubility that can be achieved with the SDs. Although both crystalline and amorphous forms of VLB and its PVP dispersions attained maximum peak solubility after 180–360 min, their initial rates of solubilization increased continuously with increasing polymer concentrations. VLB's dispersions with 1, 2, 5, 10, 15, and 20% w/w PVP showed increasing "peak" solubility values of 25, 38, 98, 103, 134, and 150 μg/mL, respectively, which are much higher than the value of the crystalline drug (21.5 μg/mL) (Table 1), and these peak solubility values were maintained for 4–6 h. It suggests their stabilization toward devitrification even in the presence of an aqueous dissolution medium.

ETB, in comparison with VLB, showed a contrasting behavior with less significant differences in the drug release behavior in the presence of different polymer concentrations (Figure 3). The solubility was found to be relatively unaffected with increasing polymer concentration, and they achieved solubility values beyond those observed for crystalline drug, after a lag period of 2–3 h. Crystalline and amorphous ETB showed peak solubility (108 and 130 μg/mL, respectively) after 3 and 4 h, respectively. The peak solubilities observed with 1, 2, 5, 10, 15, and 20% w/w PVP were 135, 146, 156, 140, 136, and 126 μg/mL, respectively (Table 1), achieved after 4–6 h. The extent of solubility increase in the case of VLB was 6 times that of the crystalline drug with 20% w/w PVP and was only 1.2 times in the case of ETB.

Solubility is an interplay of three phenomena that occur simultaneously during solubilization:

$$\text{solubility} = f[(\text{hydration/solvation energy}) + (\text{crystal lattice energy}) + (\text{cavitation energy})]$$

Solubilization involves the disruption of strong intermolecular forces between the solute molecules (crystal lattice energy) and the solvent molecules (cavitation energy). These processes are endothermic in nature, and this energy is provided by hydration of the solute molecules by solvent molecules (hydration/solvation energy). Since in amorphous state molecules are disordered and no long-range order exists, the crystal lattice energy in such systems decreases, leading to increased rate as well as extent of solubilization.[1] But it appears that this is not the only contributing factor, as in such a case both drugs should have shown similar kinds of solubility enhancement from PVP dispersions, without any significant contribution of the drug's inherent nature as suggested by Craig et al.[12]

This increase in solubility from solid dispersions has been attributed to three factors: (1) particle size reduction, (2) hydrophilicity and wetting effect of the polymer, and (3) development of specific molecular interactions between the drug and the polymer.[2] All of the above factors contribute critically toward increased solubility, but the extent of contribution from individual factors may differ widely. Particle size reduction is known to give an enhanced dissolution rate, without affecting the solubility which is a constant thermodynamic quantity.[13] Hydrophilic polymers like PVP have wetting properties that can also contribute positively toward the solubilization process. To assess this, the solubility of a physical mixture (PM) of 20% PVP was also determined for both drugs. The presence of 20% PVP gave increased solubility with crystalline VLB (24 μg/mL), which was less than that achieved by 20% PVP SDs (150 μg/mL). Phase solubility studies done with amorphous VLB in 20% w/w PVP solution also showed an increased solubility (48 μg/mL) compared to amorphous drug alone, but it was also significantly less than the solubility achieved with 20% w/w PVP SD (150 μg/mL). In the case of ETB, the solubility in the presence of PVP decreased in the case of both crystalline (97 μg/mL) and amorphous forms (86 μg/mL) of the drug.

Water is a strong plasticizer (T_g = 136 K)[14] and tends to increase the molecular mobility of amorphous drugs and drives them toward devitrification, with consequent loss of solubility.[9] The presence of high T_g polymeric carriers is

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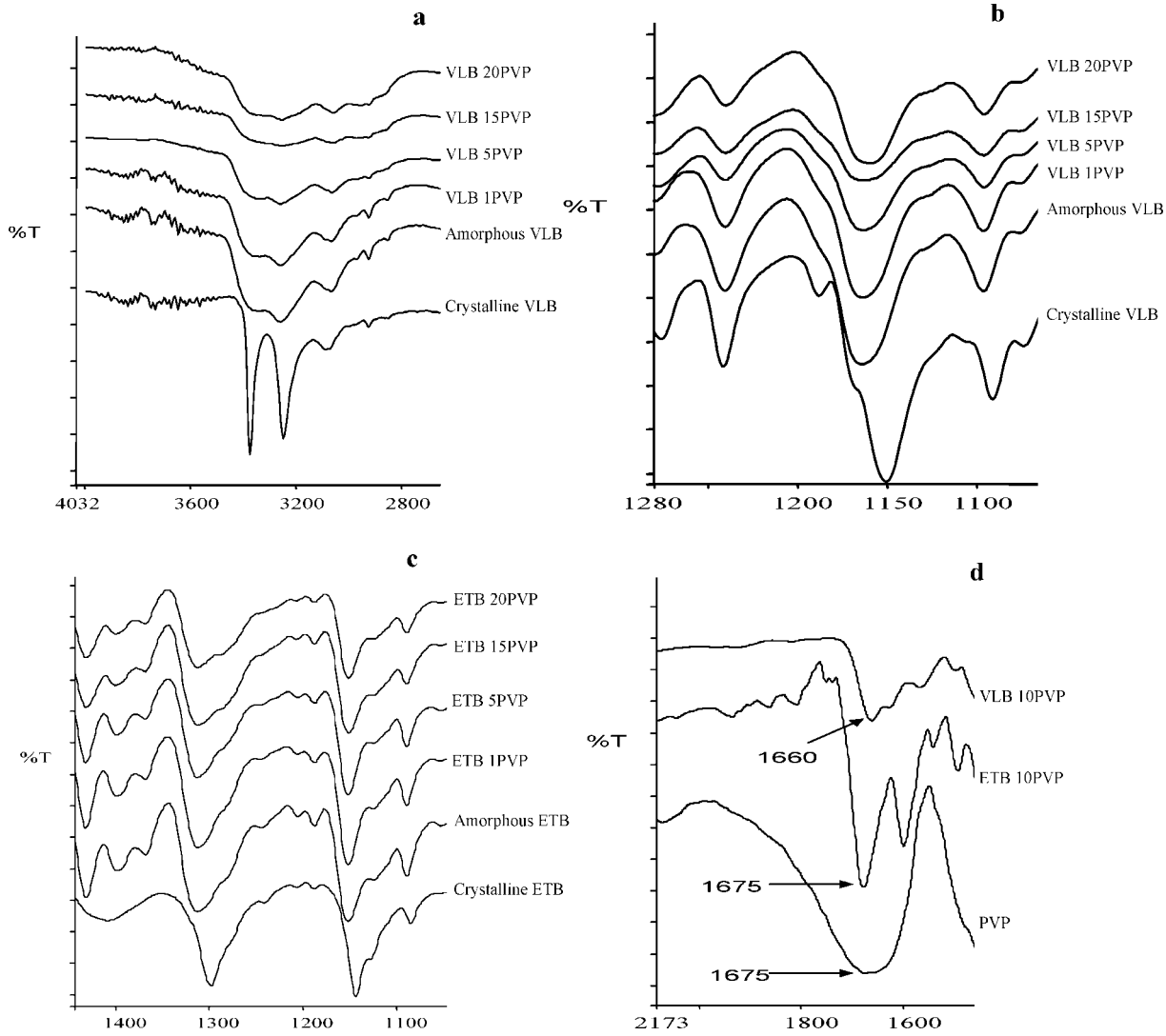

Figure 4. FT-IR spectra of (a) –N–H region of VLB, (b) –S═O region of VLB, (c) –S═O region of ETB, and their dispersions prepared with 1 (VLB 1PVP), 5 (VLB 5PVP), 15 (VLB 15PVP), and 20 (VLB 20PVP) % w/w PVP and (d) FT-IR spectra of –C═O region of PVP and its dispersions with VLB and ETB containing 10% w/w PVP.

known to stabilize these forms toward devitrification.[15] However, at low polymer concentrations, the polymer is not sufficient enough to stabilize the entire drug content against water-induced devitrification. Higher concentrations of polymer can arrest this phenomenon more efficiently, and thus, there is always an increased solubility shown by amorphous drug dispersions compared to crystalline drug.[13] But ETB was devoid of such an effect, and even in SDs with 20% w/w PVP concentration, the extent of solubility increase that occurred after a lag period was very less. This lag period can be explained from the observation that the particles of all SDs of ETB–PVP tend to aggregate immediately after addition into water. This phenomenon was not observed in case of VLB–PVP dispersions, and it appears that in this case, PVP is behaving differently for both drugs. PVP's tendency to act as a binder in some cases[16] seems to be the contributing factor for increased aggregation potential and decreased solubility at high polymer concentrations in the case of ETB.

Assuming that the effect of particle size reduction, polymer hydrophilicity, and wettability is same for both drugs, the major contribution appears to be various intermolecular interactions between the drug and the polymer molecules that are somehow increasing the solubility of the drug. However, the benefits derived from the above factors are continuously opposed by solvent-mediated devitrification and the overall solubility benefit is a balance between these contrasting forces.

FT-IR Studies. The FT-IR spectrum obtained for VLB, ETB, and their dispersions are shown in Figure 4. Valdecoxib contains a sulfonamide group (Figure 4a); therefore, bands at 3377 and 3249 cm^{-1} in crystalline form can be attributed

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to asymmetric and symmetric N–H stretching.[17] The sulfonyl group also showed two bands of –S═O: one asymmetric stretching band at 1334 cm^{-1} and one symmetric stretching band at 1150 cm^{-1} in the crystalline form[17] (Figure 4b). In amorphous VLB, the N–H stretching band broadened and the 3249 cm^{-1} crystalline band shifted to 3256 cm^{-1} (Figure 4a). The stretching frequency of the sulfonyl group was also found to be increased upon amorphization, and asymmetric and symmtetric bands of –S═O shifted to 1338 and 1164 cm^{-1}, respectively (Figure 4b). This is in accord with the single-crystal data of VLB,[18] which showed that the unit cell of the VLB crystal lattice consists of two VLB molecules interacting through H bonds between –N–H and –S═O groups, which might have been disrupted/diminished in the amorphous form of VLB.

In the case of amorphous SDs of VLB with 1, 5, 15, 20% w/w PVP, the –N–H stretching bands broadened and the intensity of the bands decreased in direct proportion to the polymer. At around 15 and 20% PVP, only one broad band can be observed and no shift in bands in –S═O was observed compared to the amorphous form of the drug (parts a and b of Figure 4). It therefore appeared that with an increase in polymer concentration, the extent and strength of H bonding between –N–H of VLB and –C═O of PVP strengthened, resulting in the observed changes.

Crystalline ETB due to the presence of –S═O of the methylsulfonyl group showed the presence of characteristic bands at 1298 and 1144 cm^{-1} [19] (Figure 4c). In the amorphous form of the drug, stretching frequencies of the –S═O group were observed to shift at 1310 and 1152 cm^{-1}. It seems that in each unit cell of ETB, molecules might be interacting by weak H bonding and van der Waals interactions between –S═O of one molecule and the –C–H group of the other molecule. However, significant differences could not be seen in the FT-IR spectra of the amorphous form of ETB and its dispersions with PVP, which indicates the absence of any strong H-bonding interactions between their molecules.

In order to confirm the presence of interactions between PVP and VLB molecules, the –C═O group was examined for any shifts. For this purpose, SDs with 10% w/w PVP were prepared for both drugs because below this concentration, –C═O peaks were not significant enough to detect changes, and at higher PVP concentrations –C═O peaks become broadened. Figure 4d shows the –C═O stretching bands observed in pure PVP and its SDs with VLB and ETB. The –C═O group in pure PVP and in ETB dispersion with 10% w/w PVP absorbed at 1675 cm^{-1}, whereas the same peak in the VLB–PVP dispersion with similar PVP concentration was observed at 1660. These results showed that in VLB–PVP dispersions, the drug polymer molecules might be interacting with each other significantly, which might be absent or are weaker in the case of ETB–PVP dispersions. Similar interactions were also established between celecoxib and PVP in earlier studies from our laboratory.[20] Since interactions are stronger in VLB–PVP, solvent-mediated devitrification slows down. However, in the case of ETB–PVP dispersions, interactions are weak and solvent-mediated devitrification proceeds at the usual pace, as decided by the drug's behavior in the amorphous state resulting in PVP's inability to increase the solubility of ETB.

Furthermore, it also appears that there are two different mechanisms involved in the drug release from SDs of both drugs. VLB appears to show carrier controlled release with the rate of release being controlled by carrier concentration. The release behavior of ETB seems to be dependent on the drug's concentration and nature, and hence, ETB exhibits a drug controlled behavior.

According to carrier controlled dissolution mechanism, when SDs are exposed to the solvent, both components dissolve at rates proportional to their solubilities (C_s) and diffusion coefficients (D) in the medium.[8] As a result, the interfacial layer between the dissolving front and the solvent becomes depleted in the more rapidly dissolving hydrophilic carrier (like PVP), forming a highly concentrated layer. Drug particles dissolve rapidly into this polymer-rich diffusion layer at a sufficiently rapid rate so that the release of intact particles into the medium does not take place and the drug gets molecularly dispersed within this concentrated layer.[8] Once the drug dissolves in the diffusion layer, the high viscosity of the solution renders the drug diffusion rates slower and the release becomes dependent on diffusion of the carrier.[21]

However, in drug controlled solubility behavior, dissolution of drug into the polymer diffusion layer is comparatively slow and the drug is majorly released as solid particles,[8] forming a controlling drug layer at the outer solid–liquid interface. The presence of this layer requires that there should be adequate drug concentration with necessary cohesive properties that can form and support a porous surface layer.[8] In such a scenario, carrier release will no longer act as a rate-determining step but will be a resultant of drug properties (size, physical form) itself[8] and the drug will be dispersed either as fine particles or as a solid solution in carrier.[22] Since ETB is observed to exhibit significant cohesive properties (agglomeration tendency), it therefore is probable that a drug-

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dependent release might be occurring in the case of ETB. This model also predicts that the release rate of either component in the dispersion is never greater than that of the pure components alone,[23,24] which is also found to be true in the case of ETB.

These differences in solubility behavior are reported to be due to the tendency of the drug to dissolve into the concentrated polymer diffusion layer.[25] Where the drug solubility in carrier solution is higher, carrier controlled release is observed. In cases where drug solubility is low, drug controlled release dominates. As a result, in low concentrations of carrier solutions, the solubility of drugs does not enhance significantly compared to that in water alone.[21] However, it has also been found that in some cases, the drug solubility increases disproportionately in highly concentrated carrier solutions and a log linear relationship is often observed[26] that is in direct contradiction to what is expected by considering the Noyes–Whitney equation:

$$\frac{D_m}{dt} = \frac{DA(C_s)}{h}$$

where D_m/dt is the rate of diffusion, D is the diffusion coefficient, A is the area available, C_s is the saturation solubility, and h is the thickness of the diffusion boundary. Further,

$$D = \frac{kT}{6\pi\eta R}$$

and

$$h = \left[\frac{\eta}{\rho(\text{rps})}\right]^{1/2}$$

where k is the Boltzmann constant, T is the temperature, η is the viscosity of the medium, R is the universal gas constant, ρ is the density, and rps is the speed of rotation.

An increase in PVP concentration in solution will increase the viscosity (η) of the medium, which will lead to a decrease in D and an increase in h. This will result in a thicker layer with a decreased rate of diffusion from the carrier layer. However, the opposite has been observed in case of VLB-PVP SDs where initial rates increased with PVP concentration in SDs. It implies that it is the A or C_s that increases in the solution that can account for the increased D_m/dt in the case of VLB–PVP dispersions.

Similarly, in the case of ETB also, increasing PVP concentrations will result in a decrease in D and an increase in h. Since the surface area (A) available for solubilization is also known to increase in the case of amorphous drugs, probably an increase in C_s does not occur in the case of ETB dispersions because of inefficient stabilization of its amorphous form by PVP against solvent-mediated devitrification.

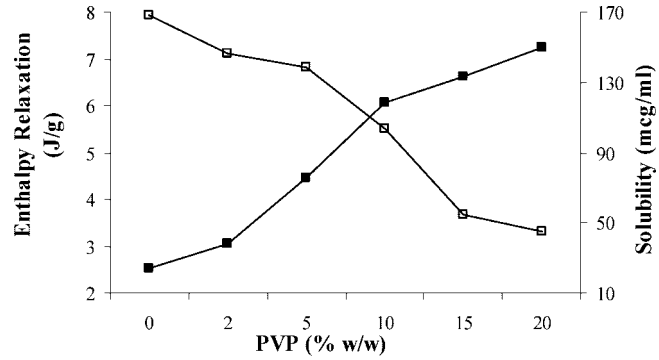

Figure 5. Correlation between enthalpy of relaxation (■) and solubility (□) advantage for VLB observed with different concentrations of PVP.

Correlation between Enthalpy Relaxation and Solubility. A previous study from our laboratory had reported an inverse correlation between enthalpy relaxation and solubility enhancement, with increasing PVP concentrations in celecoxib (CLB) PVP dispersions.[9] Therefore, we tried to correlate the decrease in enthalpy relaxation and solubility enhancement in the cases of both VLB and ETB also. We carried out the enthalpy relaxation studies of SDs of both drugs with the same concentrations of PVP (reported elsewhere) and correlated them with the observed solubility values. For this purpose, we compared the values of enthalpy relaxed at 24 h with "peak" solubility values (Figure 5). The results obtained clearly showed that in the case of VLB initially the decrease in enthalpy relaxation between two subsequent points was low. However, as the polymer concentration increased beyond 5% w/w, this rate increased tremendously. In the range of 5–15% polymer, the curve almost attains a linear shape, and at very high concentrations, it again achieves almost a constant value. Similar types of results were also found with "peak solubility" wherein an increase was observed with polymer concentration. The increase is again found to be linear in the middle portion of the curve (2–15% PVP concentration).

The enthalpy of relaxation was further correlated with enhancement in solubility with respect to PVP concentration. Both parametric (Karl Pearson's correlation) and nonparametric (Spearman correlation) tests were employed to analyze with the assumptions of presence and absence of normal distribution, respectively. All calculations were carried out by using Sigma Stat (version 2.0.3.0, SPSS Inc., Chicago, IL), which showed a significant correlation between the two phenomena. Pearson's correlation coefficient and Spearman correlation coefficient were found to be -0.9582 and -1.0000, respectively, with P values less than 0.002 in both cases. The results showed a good inverse correlation between the two in the case of VLB–PVP dispersions.

However, no such correlation was evident in the case of ETB–PVP dispersions where a decrease in solubility was

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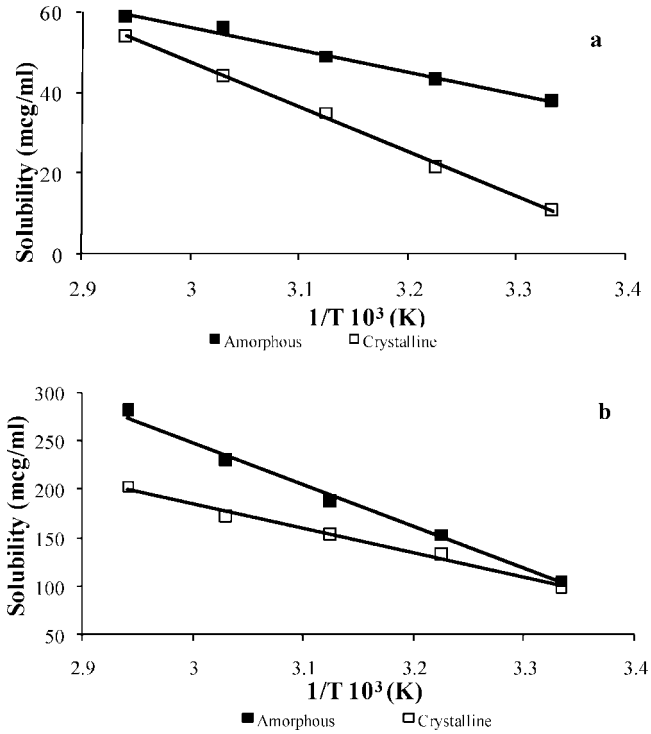

Figure 6. van't Hoff plots for (a) VLB and (b) ETB.

observed in SDs with PVP concentrations greater than 10% w/w. A decrease in enthalpy relaxation is indicative of an increase in overall solubility in the case of SDs of VLB–PVP but not in ETB–PVP dispersions. We have also observed previously that the SDs of both drugs differ only in the extent of H-bonding interactions between the drug and the polymer molecules. Since H-bonding interactions play a pivotal role in reducing enthalpy relaxation by decreasing the size of cooperatively rearranging regions (CRRs)[27] and in increasing the solubility through molecular interactions, it seems that both phenomena are manifestations of the same molecular phenomenon, i.e., H-bonding interactions occurring between the drug and polymer molecules.

van't Hoff Plots. To examine the thermodynamic behavior for observed differences in the solubility profile of both drugs, their solubilization energetics were studied. Solubility values of crystalline and amorphous forms of both drugs were determined as a function of temperature and compared for differences in enthalpy, entropy, and Gibbs free energy.[28] The van't Hoff plots for both drugs were generated by using the solubilities obtained by extrapolation to 0% polymer concentration as described by Simonelli et al.[10] and are shown in Figure 6. This approach is beneficial because the presence of PVP stabilizes the metastable forms toward crystallization and the solubility values obtained by extrapolation represent the thermodynamic values of solubility in water for actual forms.[10]

Table 2. Thermodynamic Values for Enthalpy of Solution (H_{sol}), Free Energy (ΔG_{sol}), and Entropy (ΔS_{sol}) for Solubilization of VLB and ETB

	heat of solution (J mol^{-1})	ΔG_{sol} (J mol^{-1})[a]	ΔS_{sol} (J K^{-1} mol^{-1})[a]
		VLB	
amorphous	−55.8	−1800.7	5.63
crystalline	−110.9	−1800.7	5.63
		ETB	
amorphous	−434.7	−397.6	−0.12
crystalline	−253.8	−397.6	−0.12

[a] Relative to their respective crystalline forms in solution.

The solubility of both forms for VLB and for ETB was found to increase linearly with temperature, which shows the endothermic nature of the solubilization process. The heats of solution (H_{sol}) obtained from the slope of the van't Hoff plots for both forms of these drugs are given in Table 2. As can be seen, H_{sol} is negative for both forms of VLB and ETB but is lower for the amorphous in the case of VLB and higher for ETB compared to their crystalline counterparts. It shows that the enthalpy of solubilization is more favorable for the crystalline drug in the case of VLB and for the amorphous in the case of ETB.

However, the solubility values obtained for the amorphous forms of both drugs were higher than those of their crystalline forms, which shows that these differences in behavior of both drugs are due to other thermodynamic parameters involving free energy and/or entropy.

The free energy associated with the solubilization process is a measure of the spontaneity of the process, and for different forms of both drugs, it can be given by

$$\Delta G = -RT \ln \frac{\sigma_a}{\sigma_c}$$

where σ_a/σ_b represents the ratio of activities of amorphous and crystalline forms.[10] Assuming the activity coefficient in solution to be constant for both forms, the ratio of activities is equal to the ratio of their respective solubilities [10,29] and can be given by

$$\Delta G = -RT \ln \frac{S_a}{S_c}$$

The ΔG values obtained for both drugs by using above expression are given in Table 1. The free energy of solubilization for VLB is found to be 4.5 times higher than that for ETB, which shows that the solubilization process for VLB is highly spontaneous and is less spontaneous for ETB. However, the ΔH_{sol} values for amorphous ETB were 8 times higher than those for amorphous VLB, which shows that entropy plays a major role in determining the differences in the solubilization behavior of both drugs. It is known that the disorderliness of the amorphous forms leads to their thermodynamic and kinetic instability with high solubility

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advantages.[28] Since entropy is a measure of molecular disorderliness/randomness, the entropy differences between the two forms of both drugs were calculated using previously obtained enthalpy and free energy values:

$$\Delta S = \frac{H_{sol} - \Delta G_{sol}}{T}$$

The observed entropy values for both drugs are given in Table 2. As can be seen, the entropy of solubilization is highly favorable for VLB but is slightly unfavorable for ETB. This unfavorable entropy offset the effect of the high enthalpy of the solubilization process and results in lower values of the solubilization free energy. This positive value for entropy further lends support to the observation that amorphous ETB molecules tend to aggregate together in solution. Further, such differences in thermodynamic behavior has been postulated to be due to differences in H-bonding interactions, van der Waals interaction, and their vibrational frequencies,[30] which further confirms the role of drug–polymer interactions in the solubility enhancement of SDs of VLB–PVP. Furthermore, the presence of PVP with ETB could not offset the inherent limitations of amorphous ETB. Additionally, a decrease in the diffusion coefficient (D) and an increase in the diffusion layer thickness (h), contributed negatively toward solubilization.

Conclusions

VLB and ETB were found to exhibit different solubility behavior from their solid dispersions with PVP. VLB showed a significant increase in solubility with increasing polymer concentrations, whereas no such effect was observed in the case of ETB. ETB showed an insignificant increase in solubility that decreased at high polymer concentrations. This contrasting behavior appears to be due to PVP's binding properties in ETB–PVP dispersions that were not prominent in VLB–PVP dispersions. Significant H-bonding interactions were found between the molecules of VLB and PVP. Such interactions were either weak or absent in the case of ETB–PVP dispersions. It appears that H-bonding interactions play an important role in stabilizing and increasing the solubility of the amorphous form of VLB. The inverse correlation between solubility and enthalpy relaxation, as was observed in CLB–PVP dispersions, was also found to correlate well in the case of VLB–PVP dispersions. However, deviations were found in the case of ETB. Since H-bonding interactions play an important role in decreasing the enthalpy of relaxation and increasing the solubility, these interactions appear to be the underlying mechanism for such a correlation. However, this aspect needs to be further investigated by examining different types of polymers having hydrophobic and ionic characteristics.

Solution thermodynamics showed highly favorable Gibbs free energy in the case of VLB solubilization even when its enthalpy of solubilization was low compared to that of ETB. This high Gibbs free energy was found to be due to highly favorable solution entropy in the case of VLB, which was found to be slightly unfavorable for ETB.

Abbreviations Used

VLB, valdecoxib; ETB, etoricoxib; CLB, celecoxib; PVP, poly(vinylpyrrolidone); FT-IR, Fourier transform infrared spectroscopy; SD, solid dispersions; D_m/dt, rate of diffusion; D, diffusion coefficient; h, diffusion layer thickness; A, surface area; C_s, saturation concentration; k, Boltzmann constant; T, temperature; R, universal gas constant; ΔG_{sol}, free energy of solubilization; ΔH_{sol}, enthalpy of solubilization; ΔS_{sol}, entropy of solubilization.

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