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Polymer-mediated disruption of drug crystallinity

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Abstract

Ibuprofen (IB), a BCS Class II compound, is a highly crystalline substance with poor solubility properties. Here we report on the disruption of this crystalline structure upon intimate contact with the polymeric carrier cross-linked polyvinylpyrrolidone (PVP-CL) facilitated by low energy simple mixing. Whilst strong molecular interactions between APIs and carriers within delivery systems would be expected on melting or through solvent depositions, this is not the case with less energetic mixing. Simple mixing of the two compounds resulted in a significant decrease in the differential scanning calorimetry (DSC) melting enthalpy for IB, indicating that approximately 30% of the crystalline content was disordered. This structural change was confirmed by broadening and intensity diminution of characteristic IB X-ray powder diffractometry (PXRD) peaks. Unexpectedly, the crystalline content of the drug continued to decrease upon storage under ambient conditions. The molecular environment of the mixture was further investigated using Fourier transform infrared (FT-IR) and Fourier transform Raman (FT-Raman) spectroscopy. These data suggest that the primary interaction between these components of the physical mix is hydrogen bonding, with a secondary mechanism involving electrostatic/hydrophobic interactions through the IB benzene ring. Such interactions and subsequent loss of crystallinity could confer a dissolution rate advantage for IB.

Keywords: Ibuprofen; Polyvinylpyrrolidone; Amorphous; Hydrogen bonding; Physical mixing; Solid dispersion

1. Introduction

Solubilisation of poorly water soluble drugs continues to be a challenge within pharmaceutical formulation. Many compounds currently under development are Biopharmaceutical Classification System (BCS) Class II compounds, i.e. high permeability but poor solubility (Amidon et al., 1995). These physicochemical characteristics may be inherent in the chemical structure of the drug compounds but may also result from optimisation of lead compounds to enable site or receptor specificity. The dissolution rate in the aqueous environment of the gastrointestinal fluids is typically the rate limiting step for absorption of these drugs.

Since oral dosing is the desired administration route for most drugs and considering that tablets are the most widely used dosage form, drug dissolution is a prerequisite for absorption and clinical efficacy. Therefore improvements in the dissolution profile of these Class II drugs can greatly enhance the bioavailability of these compounds. Conversion of the molecule into a more soluble salt form, or identification of optimum polymorphic forms, are two common approaches for overcoming the problem of low solubility (Serajuddin, 1999). However, manipulation of the lead compound is not always possible, or if successful, will not necessarily lead to a product with sufficient stability for commercial use (Datta and Grant, 2004). Other strategies have therefore been developed to solubilise poorly soluble drugs.

Co-grinding is one such technique, i.e. the comminution of the drug and a carrier through high-energy milling. This results in size reduction of the active compound and can often facilitate conversion of the drug to an amorphous form (Mura et al., 2002). Both of these factors can positively affect the dissolution profile of the drug. Another effective technique for improving the dissolution properties and bioavailability of poorly water-soluble drugs is the inclusion of a drug within a solid dispersion (Shin et al., 1998; Leuner

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and Dressman, 2000). Solid dispersions are produced from drug-excipient mixtures either by co-crystallization from a common solvent, or by exposure to elevated temperatures that facilitate simultaneous melting and intimate mixing of the components (Craig, 2002). Both methods result in dispersion of the active compound within the carrier matrix at solid state (Chiou and Riegelman, 1971).

Co-grinding and solid dispersions may solubilise the drug through excipient facilitated wetting, dispersion due to excipient swelling, decreased drug particle size, and/or improved kinetics due to stabilisation of the amorphous form of the drug. However solid dispersions can have disadvantages, such as a lack of suitable co-solvents or lack of miscibility in the molten state, toxicity due to residual solvent, degradation of thermolabile compounds, sublimation of drug or carrier, or polymorphic transition of the drug resulting in loss of activity (Ford, 1986; Hancock and Zografi, 1997). Co-grinding can also result in thermal degradation of drug compounds as the highly energetic nature of the process can considerably increase the temperature of the product. The formation of "fines" can also have a detrimental effect on subsequent processing to produce solid dosage forms. Developing alternative methods of dry solubilisation is therefore desirable.

Cross-linked polyvinylpyrrolidone (PVP-CL) is a polymeric carrier commonly used within oral formulations, including solid dispersions (Leuner and Dressman, 2000). It is widely used as a disintegrant due to its highly hydrophilic character, rapid water uptake and excellent swelling properties upon contact with solvents (Moneghini et al., 2000). Cross-linked polyvinylpyrrolidone has also been successfully used as an excipient for co-grinding, creating an amorphous form of the drug shown to be stable after 1 year (Shin et al., 1998). Also, in excipient compatibility studies (Botha and Lotter, 1989a,b, 1990a,b) it was reported that decreased drug melting endotherms were seen upon co-grinding with both linear, and/or cross-linked forms of the polymer, as measured by differential scanning calorimetry.

Decreased crystallinity has also been noted for drug compounds combined with cross-linked polyvinylpyrrolidone in physical mixes (Fujii et al., 2005; Williams et al., 2005); similar results were not observed for other excipients, e.g. microcrystalline cellulose. Whilst strong molecular interactions between active pharmaceutical ingredients (APIs) and carriers within delivery systems would be expected on melting, through solvent depositions or through co-grinding, this is not the case with less energetic mixing. These systems therefore confer some of the previously described solubility advantages of solid dispersions without exposing the drug molecules to the same manufacturing stresses associated with heat or solvents.

In depth examination of this phenomenon has not yet been reported and no mechanisms have been elucidated. Within the context of this paper, we have explored the novel interaction between cross-linked polyvinylpyrrolidone and crystalline poorly water-soluble drug compounds. Here ibuprofen (IB), a non-steroidal anti-inflammatory BCS Class II drug was used as a model compound. This is one of the compounds noted to interact with cross-linked polyvinylpyrrolidone (Williams et al., 2005); interactions were also noted within solid dispersions with the linear form of the polymer (Sekizaki et al., 1995; Martinez-Oharriz et al., 2002).

Thermal and X-ray diffraction methods have been used to assess drug crystallinity within samples. In addition to melting transitions, glass transition temperature (T_g) of a polymer and subsequent drug mixtures can usually be measured by differential scanning calorimetry (DSC). When an interaction occurs between the two compounds a single T_g will be observed at a temperature between the two T_gs of the individual compounds as the drug acts as a plasticizer for the polymer (Cilurzo et al., 2002). This data can therefore provide an indication of the degree of interaction of two compounds and the stability of the combined systems (Nair et al., 2001; Corrigan et al., 2004). In contrast to linear polyvinylpyrrolidone that shows a defined T_g using DSC (temperature dependant on chain length), the cross-linked polyvinylpyrrolidone displays only broad changes in thermal character over a wide temperature range. It was not possible to investigate the T_g of this polymer by either thermomechanical analysis or dynamic thermomechanical analysis as the polymer is insoluble in all solvents preventing the casting of a thin film required for both techniques. No T_g has been reported for cross-linked polyvinylpyrrolidone by the two main manufacturers (BASF and ISP) and none has been found in a review of current literature. This prevented the use of T_g in characterising this system. Accordingly, ibuprofen crystallinity has been used to assess the stability of the physical mix systems and spectroscopic methods have been pursued to probe the mechanisms for the interaction explored here.

2. Materials and methods

2.1. Materials

Ibuprofen (IB) (Wessex Fine Chemicals), Fig. 1a, an anti-inflammatory, analgesic and antipyretic agent, was chosen as a model BCS Class II compound. It exists as a colourless crystalline solid with no reported polymorphs, and pK_a of 5.3, implying low aqueous solubility in acidic pH media (Herzfeldt and Kummel, 1983). IB was sieved to obtain a particle size range of 90–150 μm, thereby enhancing flowability and reducing potential variations in results due to particle size. The melting

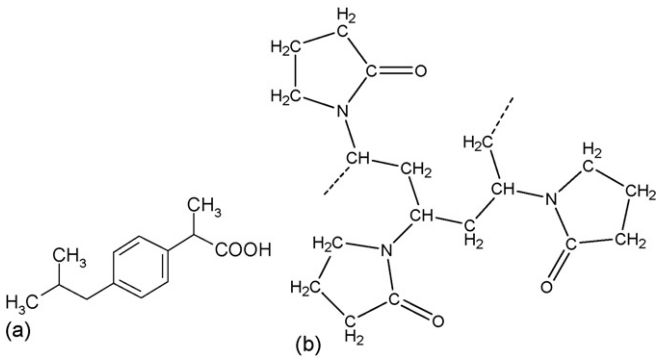

Fig. 1. Molecular structure of (a) model BCS Class II drug ibuprofen (IB) and (b) cross-lined polyvinylpyrrolidone (PVP-CL).

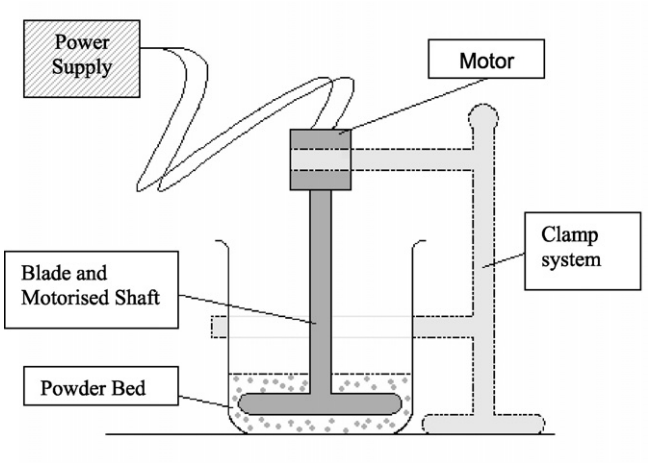

Fig. 2. Schematic diagram of the low energy mixer system used to prepare physical mixes of IB and PVP-CL.

range was determined to be 75–77 °C by differential scanning calorimetry (DSC), in agreement with literature values. The material it was identified as racemic by comparison of its powder X-ray diffraction pattern with the Cambridge Chemical Database.

Cross-linked polyvinylpyrrolidone (PVP-CL) (ISP technologies Inc.), Fig. 1b, is an insoluble, swellable polymer with excellent disintegration properties. It does not display an obvious melting range due to the complex nature of the cross-linking between the polymer chains and is PXRD amorphous.

2.2. Mixing

A purpose built mixer was used, shown schematically in Fig. 2. It is a low shear, highly versatile system that allows mixing of small batches. Physical mixing (PM) of IB and PVP-CL 30% w/w, batch size 10 g, was carried out in triplicate. Samples were removed at 5, 10, 15, 30 and 60 min. Crystallinity of these samples was then assessed relative to crystallinity of starting material (assumed 100%). All sampling was performed in triplicate and mixing efficiency was confirmed using UV analysis.

2.3. Differential scanning calorimetry

Starting materials, all PM samples and stability samples were analysed by differential scanning calorimetry (DSC Perkin-Elmer Series 7, power compensated); instrument calibration used indium (melting point 156.6 °C, ΔH_f 28.45 J g^{-1}) and zinc (melting point 419.6 °C, ΔH_f 108.2 J g^{-1}). Triplicate samples from mixes (4–5 mg) were heated under dry nitrogen purge, at 10 °C/min, from 5 to 85 °C. Percentage crystallinity of samples was calculated using the following equation:

$$\text{percentage crystallinity} = \left(\frac{\Delta H_{\text{mPM}}}{\Delta H_{\text{mIB}} \times W}\right) \times 100$$

where ΔH_{mPM} is the melting enthalpy of the physical mix (J g^{-1}), ΔH_{mIB} the melting enthalpy of IB (J g^{-1}) and W is the weight fraction of IB in PVP (here $W = 3/10 = 0.3$).

This equation accounts for the 3:7 ratio of the IB in the physical mix. Melting enthalpy of ibuprofen was calculated from triplicate measurements of IB standards, assumed to be 100% crystalline. All crystallinity levels reported in this paper are relative to the original IB sample.

2.4. Powder X-ray diffraction

Starting materials, 60 min PM samples and stability samples were analysed in a powder X-ray diffractometer (Siemens D5000) using Cu Kα radiation (λ = 1.5406 Å) over 2–73°, with a step size of 0.05°(2Θ) and count time of 3 s at 40 mV, 30 mA, sample rotation 30 rpm.

2.5. Stability testing

Samples were stored under ambient laboratory conditions. DSC analysis was performed at 12, 24, 48 and 72 weeks. Samples were also analysed by PXRD after 60 weeks storage. No further mixing was performed on these samples during this period. While the stability assessment methodology employed here is not as robust as testing multiple samples stored at varying temperature and relative humidity's, it gives an approximation of the stability of this system when full scale stability testing was not feasible.

2.6. Thermogravimetric analysis (T_GA)

T_gA used a Perkin-Elmer Series 7 T_GA. The platinum sample pan was heated in a Bunsen flame remove any residues. Once cooled, 5–10 mg of sample was placed in the sample pan and weighed using the T_GA microbalance. The sample was then heated at 20 °C/min.

2.7. Dissolution testing

Dissolution testing was performed on IB and IB/PVP-CL PM (partially amorphous) according to Apparatus II (British Pharmacopoeial Commission, 2004) under sink conditions ($C < 10\%$ Cs) using an OPT-DISS in situ UV fibre optic dissolution system (Leap Technologies, USA). Dissolution media was phosphate buffer pH 6.8 (United States Pharmacopoeial Commission, 2003), volume 1000 ml, sampling every 20 s for 10 min, then every 5 min for 50 min, 37 ± 1 °C with paddles at 50 rpm UV path length 0.1 cm, exposure time 8 ms, 4 scans. UV measurement occurred via a fibre optic relay system with probes placed within the dissolution vessel. This system allows drug concentrations to be measured at very early time points and at small time intervals; there is no delay due to removing the sample from the dissolution vessel as measurement occurs in situ.

2.8. Spectroscopic studies

Starting materials and 60 min PM samples were analysed using FT-Raman spectroscopy (Bruker IFS 66, Nd:YAG Laser 1064 nm) over a range of 50–3500 cm^{-1}, 1000 scans, with a

resolution of 4 cm^{-1} and FT-IR spectroscopy (Matteson Galaxy 6020 series), 1000 scans, with a resolution of 4 cm^{-1}.

In the Raman analysis, a theoretical spectrum was produced for an ideal "non-interacting" physical mix. Peaks were chosen on both the IB and PVP-CL spectra that showed an unchanged profile in the PM, i.e. no band broadening. The overall intensities of the two spectra were normalised using these two peaks and then combined to produce a theoretical physical mix spectrum (TPM). The real Raman data for the PM was then compared to this TPM; differences between these two spectra are caused by changes in the molecular environment of IB and PVP-CL caused by interactions between these two compounds.

Standard peaks, i.e. non-broadened, could not be identified for IB and PVP-CL in the PM spectrum. Therefore, normalisation of spectra intensity was not possible. Accordingly the FT-IR spectra for IB, PVP-CL and PM were compared directly without producing a theoretical physical mix spectrum.

3. Results and discussion

3.1. Mixing studies

UV assays showed an average IB value of 30.12 ± 0.79 % (±S.D., $n = 3$) of the total weight in good agreement with the theoretical IB weight fraction of 30%. Assay variation minimised after 60 min (S.D. 0.19), indicating reproducible mixing at this time-point and that variance after short mixing times probably arises from incomplete mixing.

Percentage crystallinity of IB, as measured by DSC, decreased upon simple mixing with PVP-CL, reaching a plateau at approximately 77% (Fig. 3). Significant mixing time and therefore energy was not required before drug crystallinity begins to decrease. This suggests that the conversion to an amorphous form is facilitated simply by intimate contact of the particles and that the process is not induced or driven by shearing or grinding forces. An initial minimum in percentage crystallinity was observed after 5 min of mixing; seen in multiple batches. We attempted to probe early fluctuations by repeating these experiments taking samples every 30 s over the first 20 min of mixing. The crystallinity profile observed in Fig. 3 was not

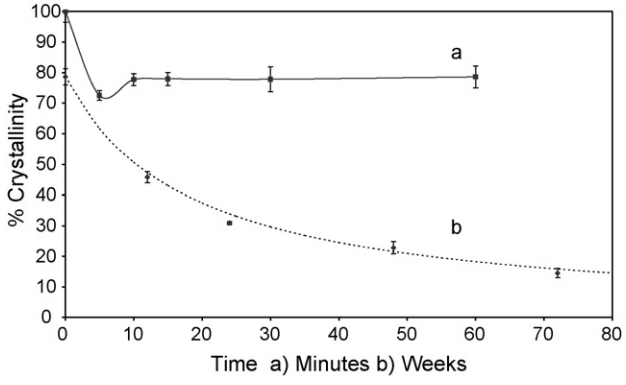

Fig. 3. Relative percentage crystallinity of IB during (a) mixing period (min) and (b) stability testing (weeks).

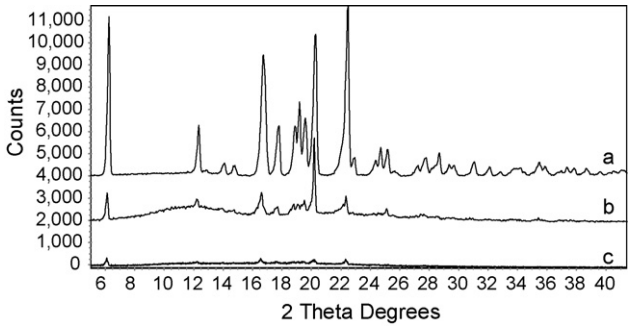

Fig. 4. Powder X-ray diffraction pattern for (a) IB, (b) physical mix of IB with PVP-CL and (c) physical mix of IB with PVP-CL after 52 weeks storage. Same scale, offset for clarity.

seen with this increased sampling frequency and was probably due to heterogeneity caused by the mixer geometry. Significant melting peak broadening, as indicated by a drop in T_m or peak maxima, as seen in previous work (Williams et al., 2005) was not observed upon loss of crystallinity (as measured by decreasing peak enthalpy).

Diminution of intensity and broadening of characteristic IB peaks was observed in the PM PXRD data (Fig. 4). This confirms that the partial loss of crystalline IB structure is not merely a thermal artefact caused during the DSC heating cycle, and so conversion to an amorphous form is strongly suggested. A PVP-CL diffraction pattern is not shown as this material is X-ray amorphous and therefore PXRD will not elucidate any changes in its structure or bonding. No evidence of IB degradation was found in the DSC or PXRD profiles.

From solid dispersion literature, it may be expected that polymers used in solid dispersions reduce recrystallisation by restricting mobility of an amorphous API either through anti-plasticizing effects (Van den Mooter et al., 2001) or through interactions between the drug and the polymer (Weuts et al., 2005). However, some degree of recrystallisation is still expected over time due to the inherently unstable nature of the amorphous form (Aso et al., 2004). Interestingly with this system, IB became more amorphous over time, as measured by DSC, when stored under ambient laboratory conditions (Fig. 3b), falling to only 15% crystalline IB remaining after 72 weeks. This reduction in crystallinity is confirmed by dramatic broadening and diminution of characteristic IB peaks in the PXRD diffraction pattern (see Fig. 4c). This decrease in crystallinity with storage time follows near second order kinetics as indicated by a linear relationship between $1/[R_t]$ and t where R is the percentage crystallinity ($R^2 = 0.98$).

Considering these kinetics, it appears that the PVP-CL polymer may have a saturation limit where all the energetically favourable binding sites on the carrier have interacted with ibuprofen molecules or may not be accessible due to steric hindrances. Accordingly, the rate of conversion of IB to an amorphous form slows over time as the saturation limit is approached. We suggest that by creating an amorphous system by traditional formulation method, e.g. solvent solid dispersion, could result in "supersaturation" or overloading of the system, resulting in subsequent recrystallisation. We can speculate that the slowly

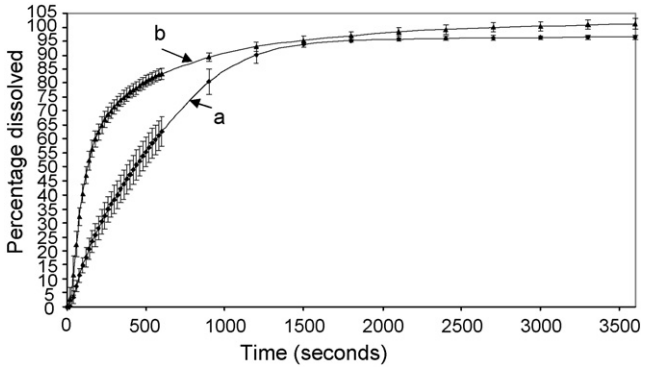

Fig. 5. Mean dissolution profiles for (a) IB (100% crystalline) and (b) physical mix of IB with PVP-CL (approximately 15% crystalline IB). $n = 6$.

induced disorder observed here might result in a more stable system compared to rapidly formed highly amorphous delivery systems.

Water has previously been suggested to facilitate interactions between linear PVP and drug molecules by solubilising the drug (Zerlia et al., 1989). PVP-CL contains 5% water content at the time of manufacture (International specialty products, 2004; BASF, 2004). Although humidity was not controlled during the period of stability data collection, the PMs contained $5.73 \pm 0.11\%$ water ($n = 3$) at the time of preparation and $5.34 \pm 0.04\%$ ($n = 3$) at 72 weeks (measured by T_GA). This suggests no increase in water content over this period. Consequently it can be assumed that the PM contained approximately 6% (0.6 ml) of water and 3 g (3000 mg) of IB through this assessed period. The reported solubility of IB in water (assuming pH 7) is 2.24 mg/ml (Herzfeldt and Kummel, 1983). The 0.6 ml of water present in the PM sample would thus maximally (if saturated) dissolve approximately 1.34 mg of IB, i.e. 0.05% of the total quantity of IB present. From this, it seems unlikely that dissolution of IB by the water is the sole mechanism for disruption of IB crystallinity initially or over time.

IB interacted with linear PVP, which had been exposed to CO_2, though hydrogen bonding (Kazarian and Martirosyan, 2002); competitive H-bonding with the PVP chain was observed for the CO_2 and IB. From this it may be expected that other compounds with H-bonding potential, such as water, might also compete with IB for such sites on the PVP. Thus, water may have some role in mediating the IB/PVP-CL interaction although a mechanism for this remains unclear.

Mean dissolution profiles ($n = 6$) of IB/PVP-CL PM with approximately 15% crystalline (85% amorphous) IB content is in shown in Fig. 5, compared to an IB standard (assumed 100% crystalline). IB itself showed 30% dissolved at 260 s (4 min 40 s) and 85% dissolved at 1020 s (17 min) whereas the IB/PVP-CL PM (85% amorphous) showed 30% dissolved at 88 s (1 min 25 s) and 85% dissolved at 680 s (11 min 20 s). The presence of the PVP-CL is likely to have a positive effect on the wetting characteristics of the PM. However the clear improvement in dissolution characteristics of the IB/PVP-CL compared to the IB standard suggests the amorphous IB fraction in the PM also has a positive effect on dissolution rate. From these data it can be concluded that the dissolution characteristics of the IB/PVP-CL PM stability samples will have changed upon storage time as the amorphous IB fraction increased.

Interactions between active pharmaceutical ingredients (APIs) and carriers are anticipated in solid dispersions or co-grinding, as observed in literature. However, our work shows that we do not need highly energetic or solvent mediated process to facilitate an interaction between IB and PVP-CL. Various workers have documented interactions between this polymer and other drug compounds in solid dispersions and co-ground environments. Based upon this, it is suggested that the interaction examined in this work could potentially transfer to physical mixes of PVP-CL and other drug compounds. The formation of this amorphous fraction has positively affected the dissolution rate of ibuprofen, therefore such formulations would not necessarily show predictable release characteristics, and their dissolution profiles could change upon storage. In the light of these current results, existing formulations involving PVP-CL should be examined to ensure that interactions of this type are not adversely affecting the dissolution behaviour of the system.

3.2. Spectroscopic studies

The PM (Fig. 6b) showed significant differences in the characteristic FT-IR molecular modes for both IB and PVP-CL to those observed for the individual compounds (Fig. 6a and c). The alcohol O–H stretch vibration, which usually would appear around 3640–3610 cm^{-1}, was masked by a broad O–H peak of water molecules adsorbed on the PVP-CL polymer. The multiplet observed around 3100–3000 cm^{-1} in Fig. 6a can be attributed to C–H stretching vibrations; the intensity of these peaks is greatly reduced in Fig. 6b, the PM. The carbonyl stretch mode from the carboxylic acid appears at 1710 cm^{-1} for IB (Fig. 6c) and 1650 cm^{-1} for PVP-CL (Fig. 6a). Both of these move to lower wavenumbers in the PM and the PVP-CL mode broadens dramatically (Fig. 6b). This indicates a modified carbonyl environment consistent with hydrogen bonding.

Raman spectra from the PM (Fig. 7b) show clear differences to the "non-interacting" theoretical spectrum (TPM), as

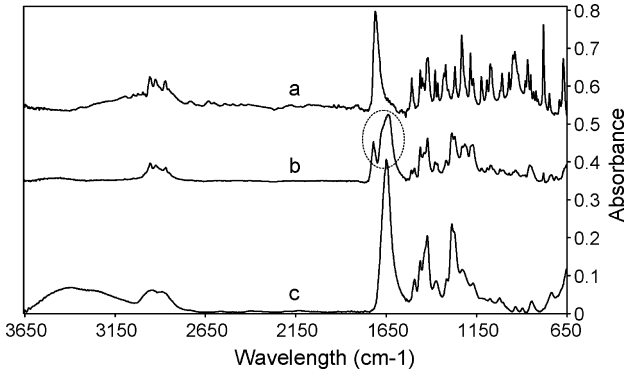

Fig. 6. FT-IR spectra for (a) IB, (b) physical mix of IB with PVP-CL and (c) PVP-CL. Same scale, offset for clarity.

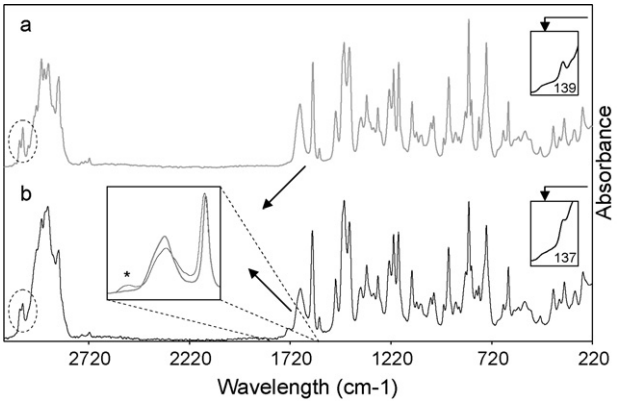

Fig. 7. FT-Raman spectra for (a) theoretical spectrum (combination of isolated IB and PVP 30:70) and (b) physical mix IB with PVP-CL. Same scale, offset for clarity.

shown in Fig. 7a. There is a general broadening of many bands which shows then an increased variety of molecular environments exist. The affected peaks include the lattice modes at 120, 139, and 195 cm^{-1} which overlay a broad band assigned to the macro molecular movement of the polymer. The changes in these groups indicate partial disruption of the IB crystal lattice. The mixed carbonyl stretching band is observed at 1670 cm^{-1} in the TPM; this band is broader and has a maximum at a lower wavenumber in the PM spectra. These differences are consistent with hydrogen bond-type interaction between the components. A new peak was also present at 1726 cm^{-1} in the PM spectra (Fig. 7b, highlighted with '*'); this finding is consistent with the emergence of a new carbonyl environment in the PM. The IB quadrant ring stretching mode observed at 1606 cm^{-1} in the TPM (Fig. 7a) shifts in the PM and an IB doublet centred around 3055 cm^{-1} in the TPM and assigned to the aromatic C–H stretching vibration, merged towards a single feature in the PM (Fig. 7b). A new peak was observed at 796 cm^{-1} in the PM in a region where aromatic deformation bands are observed for di-substituted aromatic compounds such as ibuprofen. These features are consistent with engagement of the aromatic function of IB in an interaction with PVP-CL.

There is thus clear evidence from the spectroscopic analysis of modifications to the bonding environment in the PM compared to the individual compounds. It might be expected that the main mechanism of interaction between the two compounds would be via hydrogen bonding, as was cited for interactions between polyvinylpyrrolidone and drug compounds in heat and solvent generated solid dispersions (Taylor and Zografi, 1997; Forster et al., 2001). However, the spectroscopic evidence for strong hydrogen bonding is not as clear as might be anticipated from the degree of disorder introduced into the IB crystal lattice. There is clear spectral evidence for a secondary mechanism of hydrophobic or electrostatic interactions involving the aromatic region of the IB molecule. Broadening of some other bands assigned to alky regions of both IB and PVP-CL may also indicate restricted molecular movement for both compounds in the PM. It is thus apparent that the drug/polymer interaction leading to reduced drug crystallinity is complex and that no single molecular basis for the association exists.

4. Conclusions

A reduction in the crystallinity of ibuprofen (IB) can be facilitated by simple physical mixing with polyvinylpyrrolidone (PVP-CL) allowing intimate contact of drug and carrier particles. From spectroscopic data, the primary mechanism of interaction between ibuprofen and cross-linked polyvinylpyrrolidone appears to be via hydrogen bonding, with secondary mechanisms of electrostatic/hydrophobic interactions involving the IB benzene ring also apparent. The amorphous fraction of ibuprofen in the physical mix (PM), resulting from the breakdown of the crystal lattice, increases upon storage at ambient conditions with no further mixing.

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