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Differential molecular interactions between the crystalline and the amorphous phases of celecoxib

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Abstract

We have investigated the differences in molecular interactions between the crystalline (ordered) and amorphous (disordered) phase of a poorly soluble drug, celecoxib. Molecular interactions in the crystalline phase were investigated with the help of Mercury software, using single crystal X-ray diffractometric data for celecoxib. A simulated annealing molecular dynamics approach was used for the assessment of altered molecular interactions in the amorphous phase. Crystalline celecoxib was found to contain an ordered network of H-bonding between all its electron donors (–S=O group, 2-*N* of pyrazole ring and –C–F) and the acceptor (–N–H). Amorphous celecoxib retained all these interactions in its disordered molecular arrangement, with a relatively stronger H-bonding between the interacting groups, as compared with crystalline celecoxib. However, these inter-molecular interactions differed in strength in the two solid-state forms. The altered configurations of the molecular arrangement in the two phases were supported by the shifts observed in the Fourier-transform infra-red vibrational spectra of respective states. These interactions could have strong implications on devitrification kinetics of amorphous celecoxib, and could further guide the choice of stabilizers for the amorphous form.

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Introduction

Generation of amorphous product involves entrapment of molecules in a 'liquid-like' disordered state that is characterized by glass transition temperature due to non-equilibrium between experimental time scales and dynamics of molecular motion (Kaushal et al 2004). The freezing of molecular motions during supercooling, during the melt-cool process, may result in random conformations of the molecules that may not have been feasible in the crystalline state, due to constraints of crystal packing. Consequently, there is a chance of diverse molecular interaction in the crystalline (ordered) and the amorphous (disordered) phases. The strength of these molecular interactions could decisively affect their stability and solubility benefits from the amorphous form of a drug.

The amorphous form of a solid is usually referred to as a 'disordered molecular arrangement'. With the available analytical tools such as Fourier-transform infra-red (FTIR) spectroscopy, it is only possible to have a comparative assessment on the extent of molecular interactions in the two phases (Tang et al 2002). The real representation of the molecular arrangement in the amorphous form is somewhat difficult because of the possibility of multiple loci of different molecular conformations. Hence, a single conformation for the molecular arrangement in the amorphous form may be ambiguous. Molecular modelling studies have been used to characterize the random arrangement of molecules in the amorphous form. Very few reports cite computer simulation of the amorphous state, and most of the studies have dealt with high molecular weight polymers (Li et al 1997; Alvarez et al 2000; Gestoso & Brisson 2001; Pavel & Shanks 2003; Roberge et al 2004) that inherently exist in the amorphous form. Very few reports exist for low molecular weight substances (Langer et al 2003; Yoshioka et al 2003). This study has explored the possibility of simulating the molecular conformations in the amorphous form of a drug molecule.

Celecoxib, chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide (Figure 1), is a diaryl-substituted pyrazole class of

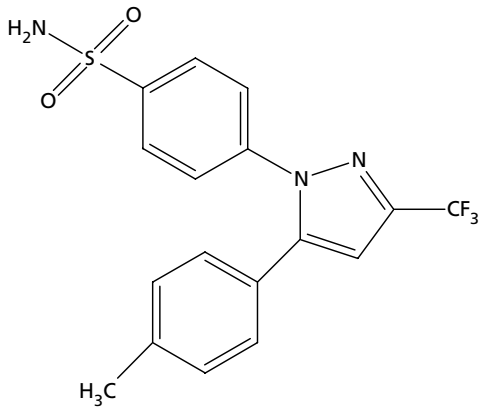

Figure 1 Chemical structure of celecoxib.

compound. Structural inspection of celecoxib reveals that its amido protons (H atoms covalently bonded to N, an atom of greater electronegativity than C) are the only potential electron-acceptors, whereas the O of the sulfonyl group, N atoms of the pyrazole ring, and the F atom of the trifluoromethyl group are the three electron-donating centres. The amido N loses the electron-donating capability due to delocalization of its electrons over neighbouring O atoms (Adsmond & Grant 2001). These electron-accepting and -donating centres are the potential sites for intra- or inter-molecular H-bonding in celecoxib molecules.

This investigation has dealt with the altered molecular interactions in the crystalline and amorphous phases of celecoxib. The extent of interaction within a phase predicts the possible stability of molecular conformation on a temperature scale. A comparative understanding of molecular associations in the amorphous and crystalline form should provide an in-depth understanding of devitrification of the amorphous form, and help in devising strategies for preventing the same. The possible sites for self-association of drug molecules in crystalline form could be blocked by using specific stabilizers in the amorphous state.

Materials and Methods

Materials

The crystalline form of celecoxib was purchased from Unichem Laboratories Ltd, Raigad, India.

Preparation of amorphous celecoxib

Amorphous celecoxib was prepared by melting the crystalline drug in a stainless steel beaker over a hot plate (approximately 175°C) and quench cooling over crushed ice. No visible signs of degradation were observed, and chemical stability of the amorphous sample was assessed by high-performance liquid chromatography, wherein the peak purity was above 99.99%. Samples were analysed immediately after being made amorphous.

Fourier-transform infra-red (FTIR) spectroscopy

The FTIR spectra were recorded on a FTIR multiscope spectrophotometer (Perkin Elmer, Buckinghamshire, UK) equipped with spectrum v3.02 software, by the conventional KBr pellet method.

Investigation of molecular interactions in the crystalline and the amorphous phase

The inter-molecular interactions within crystalline celecoxib were investigated with the help of the Mercury program (version 1.2, Cambridge Crystallographic Data Centre, Cambridge, UK), using single crystal X-ray diffractometric (XRD) data of celecoxib (Dev et al 1999).

The intermolecular interactions within amorphous celecoxib were assessed using the Sybyl 6.8 program (Tripos, Inc., MO) running on a Silicon Graphics Onyx Workstation. The celecoxib starting ensemble was built from available crystal data. Random arrangement of molecules to simulate the amorphous form was modelled by the molecular silverware method using periodic boundary conditions. The ensemble of celecoxib molecules was refined using MMFF94 force field till a gradient convergence of 0.05 kcal mol^{-1} was reached. This force field has been explicitly parameterized for small molecules and pharmaceuticals (Halgren 1996). The optimized model was further subjected to molecular dynamics simulation using the simulated annealing approach. The system was heated to 500 K to transform the crystal to the liquid state and equilibrated for 1000 fs at 500 K, and finally cooled to 250 K. The technique was analogous to the experimental procedure adopted for preparing the amorphous form of celecoxib by melting the drug and suddenly cooling it. A molecular dynamics simulation was run for 10 cycles, which captured 400 snapshots. Out of these, nine conformations of the lowest energy were selected from the molecular spreadsheet, and assessed for molecular interactions.

Results and Discussion

Spectral variations in the crystalline and the amorphous phase of celecoxib

The comparative assessment of FTIR spectra (Figure 2) revealed the sharp doublet for N–H stretching vibration band at 3338 cm^{-1} and 3232 cm^{-1} in crystalline celecoxib to shift as a broader hump at a higher wave number of 3367 cm^{-1} ($\Delta\nu = -29\,cm^{-1}$) and 3264 cm^{-1} ($\Delta\nu = -32\,cm^{-1}$) in amorphous celecoxib. This was an indication of the broader distribution of H-bond lengths in the disordered phase. Another major difference was evident for the asymmetric stretching vibration band for S=O, which shifted from 1347 cm^{-1} in crystalline celecoxib to 1339 cm^{-1} ($\Delta\nu = 8\,cm^{-1}$) in amorphous celecoxib. Further, the C–F stretching vibration band observed at 1230 cm^{-1} for crystalline celecoxib shifted to the higher wave number of 1238 cm^{-1} ($\Delta\nu = -8\,cm^{-1}$) for amorphous celecoxib. This particular band shift for C–F

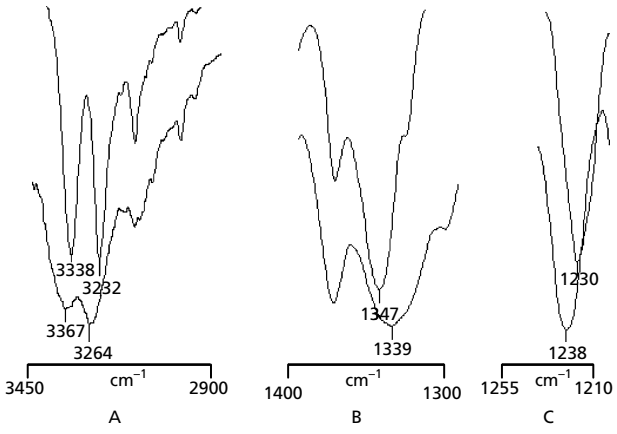

Figure 2 Shifts in FTIR spectra for crystalline (upper recording) and amorphous (lower recording) celecoxib. A. N–H stretching. B. S=O asymmetric stretching. C. C–F stretching.

stretching was left unexplained in previous publications (Chawla et al 2003; Paradkar et al 2003) citing spectroscopic characterization of crystalline and amorphous celecoxib, which has now been facilitated by molecular modelling studies (explained below). These broadness and shifts in vibration frequencies (Lin-Vien et al 1991) indicated greater strength of average H-bonding for −N–H as well as −C–F in the crystalline form, and for −S=O in the amorphous form of celecoxib.

Molecular interactions in the crystalline form of celecoxib

Dev et al (1999) reported in the single crystal XRD data that the celecoxib crystal structure was triclinic, space group P-1, with a = 10.136 Å, b = 16.778 Å and c = 5.066 Å, and $\alpha = 97.62°$, $\beta = 100.65°$ and $\gamma = 95.95°$. Investigation using the Mercury program facilitated the visualization of the molecular arrangement within the crystalline lattice. As per the Kitagorodski's rule of close packing (Brock & Dunitz 1994), in the crystalline form molecules favour packing in such a fashion that the free volume is minimized, and hence, density is maximized. Each unit cell was found to consist of two molecules (i.e. Z = 2) arranged diagonally in a head-to-head fashion, with $-CH_3$ groups positioned at centre and $-SO_2NH_2$ groups apart at the corners. The intra- or inter-molecular H-bonding was absent within the unit cell, but present between the molecules of adjacent unit cells to form an ordered network.

The one −N–H of the celecoxib molecule of a unit cell was H-bonded with the −S=O of the celecoxib molecule of an adjacent unit cell, forming a chain of −N–H . . . O=S- bonds (N–H . . . O 2.952 Å, H . . . O 2.085 Å) with an eight atom repeat unit (Figure 3A′). This seemed to be the preferential and most dominant H-bond pattern among sulfonamides (Adsmond & Grant 2001), thus substantiating the general rule "all good donors and acceptors are used in H-bonding" (Donohue 1952). As per the graph set notation (Etter et al 1990), this chain arrangement of −N–H . . . O=S-bond represented a $C(4)$ molecular arrangement (Figure 3A″). The other −S=O of celecoxib molecule was free and devoid of any H-bonding. Another −N–H of a celecoxib molecule of the same unit cell was H-bonded with the 2-*N* of pyrazole ring of a celecoxib molecule of another neighbouring unit cell, forming a bimolecular ring with −N–H . . . N-bonds (N–H . . . N 3.087 Å, H . . . N 2.235 Å) (Figure 3B′) with $R_2^2(18)$ graph set (Figure 3B″). The preferential affinity of −N–H for H-bonding with 2-*N* instead of 1-*N* of pyrazole ring could be due to steric constraints for electron sharing and overlapping of molecular orbitals. Further, both the −N–H groups were found to H-bond with the same −C–F group of the trifluoromethyl moiety, forming a bimolecular ring with two −N–H . . . F–C-bonds (N–H . . . F 3.781 and 3.851 Å, H . . . F 2.909 and 2.983 Å) (Figure 3C′) with $R_2^1(24)$ graph set (Figure 3C″). Thus, −N–H groups of celecoxib were found to exhibit bifurcated H-bonds (Nakamoto et al 1955; Steiner 2002), with −N–H . . . O=S− and −N–H . . . N− as the major components, while −N–H . . . F–C- was the minor one (Figure 4).

As per the classification of Jeffrey (1997) for strengths of H-bonds, a moderate H-bond had a H . . . Y (where Y was the acceptor atom) distance of ∼ 1.5–2.2 Å and a X-H . . . Y distance of ∼ 2.5–3.2 Å, and weak H-bond had corresponding values of ∼ 2.2–3.2 Å and ∼ 3.2–4.0 Å, respectively. These three inter-molecular associations of −N–H of celecoxib seemed to be weak enough for rearrangement, with the first two being moderate and the last one a weak H-bond.

Molecular interactions in the amorphous form of celecoxib

Molecular modelling is an excellent computational tool, which helps in rationalizing the experimental observations, provides information not amenable to explanation, and even makes predictions concerning the outcome of future experiments (Anonymous 1997). One of the major advantages of computer modelling over experimental is that the interaction energy and its variation with structure may be investigated at the atomic and molecular levels. In flexible molecular conformations, such as those of the amorphous solid-state, it is impossible to describe accurately their structure as a single conformation. The structure can be thought of as an ensemble of individual conformations, which give rise to characteristic average molecular properties. Molecular dynamics simulations calculate the time dependent behaviour of a molecular system, thus providing detailed information on fluctuating and conformational changes of the molecules.

Simulated annealing (Kirkpatrick et al 1983) is a type of molecular dynamics experiment in which the temperature of the system is cycled over time with the goal of widely sampling conformational space. It is a computational analogue of experimental annealing techniques, involving first 'melting' the system being optimized at a high effective temperature, so as to allow the system to rearrange from its present state, and then lowering the

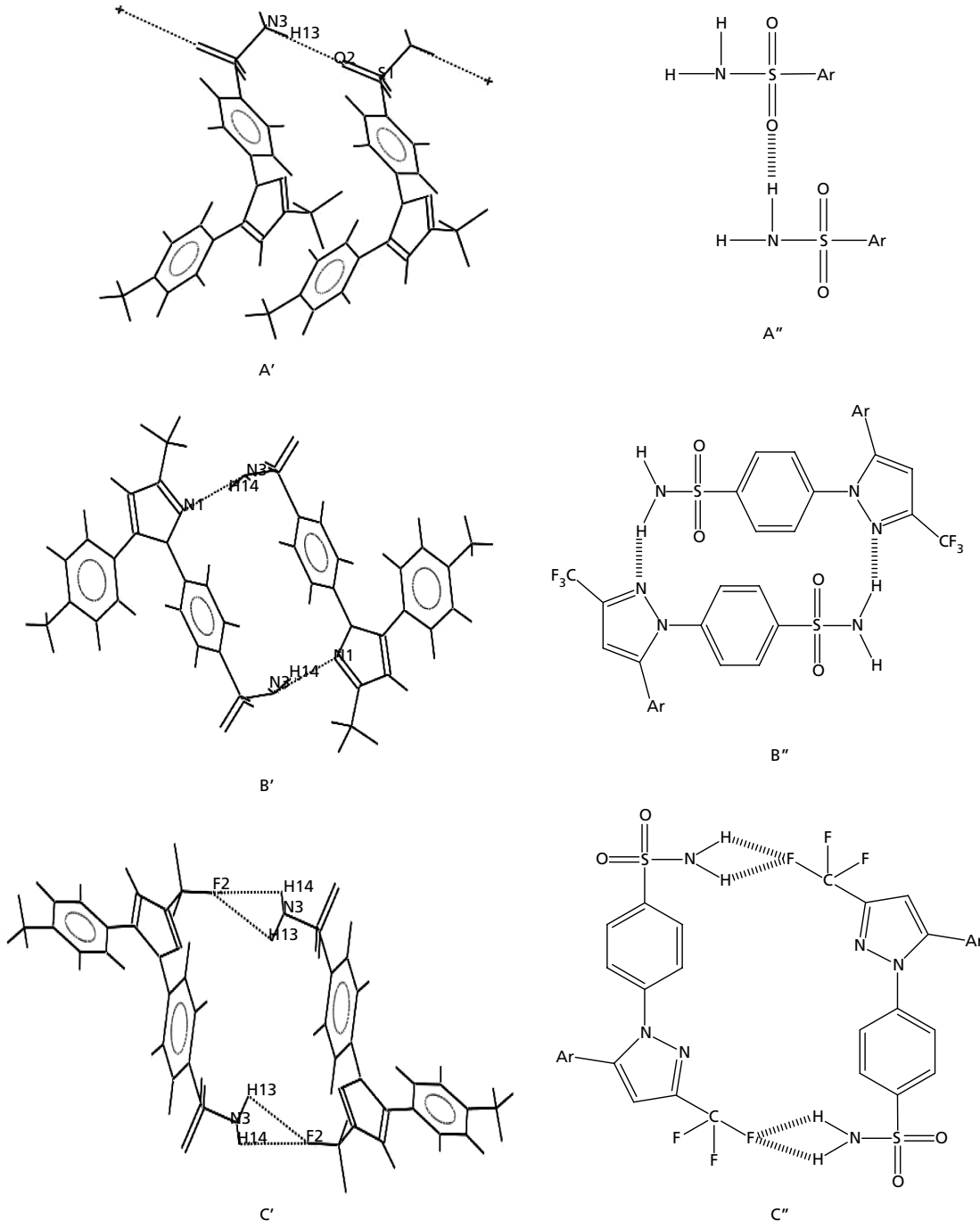

Figure 3 Inter-molecular associations between (A) −N–H and −S=O, (B) −N–H and 2-*N* of the pyrazole ring, and (C) −N–H and −C–F, in the crystalline form of celecoxib. Figures with single prime notation are stereoviews, while those with double prime are schematic representations of the interaction. The dotted lines represent H-bonding.

temperature until the system 'freezes' to bring the system into a stable state. The kinetics of molecular motions can be altered by employing high cooling rates to model the molecular arrangement in the amorphous form.

In this study, use of the periodic boundary condition for simulating molecular association in amorphous celecoxib resulted in accumulation of 74 molecules of celecoxib within the simulation box. These molecular ensembles were then subjected to repeated cycles of molecular dynamics simulation, and the optimized model was investigated for inter-molecular interactions.

Computer simulation of the amorphous form of celecoxib resulted in a disordered molecular arrangement.

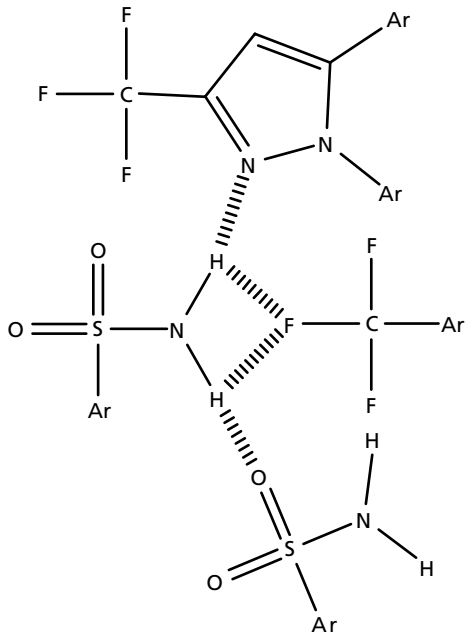

Figure 4 Bifurcated H-bonding of the $-NH_2$ group with 2-*N* of the pyrazole ring, the $-CF_3$ group, and $-SO_2$ group in celecoxib crystal lattice. The broken lines represent H-bonding.

Various inter-molecular interactions in amorphous celecoxib were bimolecular in nature (Figure 5), in place of multi-molecular order in crystalline celecoxib. The amorphous form of celecoxib showed interaction of all the three electron donors with the electron acceptor. Interestingly, the amorphous state has been suggested as an intermediate stage en route to the formation of a thermodynamically stable crystalline state (Desiraju 2003). The two states differ only in the degree of order and all basic inter-molecular interactions are likely to be retained in the amorphous state as well. However, these associations can differ in the two solid-states in their relative strengths.

In contrast to orderly chain arrangement in the crystalline form, these results showed inter-molecular H-bonding between −N–H and −S=O groups of two celecoxib molecules to form an 8-membered ring (Figure 5A′) with graph set R^2_2 (8) (Figure 5A″). The bimolecular ring association between −N–H and 2-*N* of pyrazole ring in crystalline celecoxib transformed into a diad in the amorphous form (Figure 5B′) with graph set *D* (Figure 5B″). Also, the bimolecular ring association through H-bonding between −N–H and −C–F groups of two celecoxib molecules in the crystalline form was transformed into a diad in the amorphous form (Figure 5C′) with graph set *D* (Figure 5C″). Table 1 summarizes the comparative H-bond lengths for these inter-molecular associations between crystalline and amorphous celecoxib. In amorphous celecoxib, the −N–H . . . O=S− interaction was the strongest, followed by −N–H . . . F–C, and −N–H . . . N–. All these inter-molecular interactions in amorphous celecoxib were of moderate strength, as per the classification given by Jeffrey (1997).

Comparative assessment of molecular interactions in crystalline and amorphous celecoxib

Comparison of H-bond lengths for different inter-molecular associations in crystalline and amorphous celecoxib (Table 1) indicated a relatively stronger interaction in the amorphous phase. The H-bond lengths for −N–H . . . O=S–, −N–H . . . F–C− as well as −N–H . . . N− interactions were consistently lower in the case of the amorphous form than the crystalline form. Thus, weaker H-bonds in crystalline celecoxib seemed amenable to rearrangement, resulting in relatively stronger inter-molecular association in amorphous celecoxib. These altered molecular interactions in the two phases might be contributing towards successful generation of glassy celecoxib during supercooling of its melt.

However, FTIR revealed two counter-intuitive findings by showing a shift to higher wave numbers for N–H as well as C–F stretching vibration bands while transiting from crystalline to amorphous form. These could be explained based on the differences in participating atoms in the H-bond formation. In the crystalline form, the −N–H groups of the same molecule were found to form bifurcated H-bonds with the −S=O group, the 2-*N* of the pyrazole ring and the −C–F group of different celecoxib molecules, whereas, in the amorphous form, they H-bonded separately with these electron donating groups of other celecoxib molecules. Thus, in the amorphous form only one −N–H group per celecoxib molecule H-bonds and the other is free, whereas in the crystalline form both the -N-H groups are involved in bifurcated H-bonding. This greater extent of H-bonding of the −N–H group results in lower N–H vibration wave number in crystalline celecoxib despite a weaker H-bond than that in the amorphous form. With regard to the −S=O group, it was involved in chain formation in crystalline celecoxib, while in amorphous celecoxib it was associated with ring formation. The delocalization of electrons over the ring helped in stabilizing this particular molecular conformation, strengthening the interaction in the amorphous form, reflected as shift of the S=O stretching vibration band to a lower wave number as compared with that in the crystalline form. Another striking feature observed was for −C–F, which showed greater interaction in the crystalline form, with a single F atom participating in bifurcated H-bonding with two different H atoms, while in the amorphous form it interacted with a single H atom. Hence, the involvement of a higher number of H atoms in H-bonding resulted in the shift of C–F stretching vibration band to a lower wave number in crystalline celecoxib despite a weaker H-bond than that in amorphous celecoxib. On a broader perspective, the steric constraints posed by the crystal lattice dictated the type of inter-molecular interaction in the

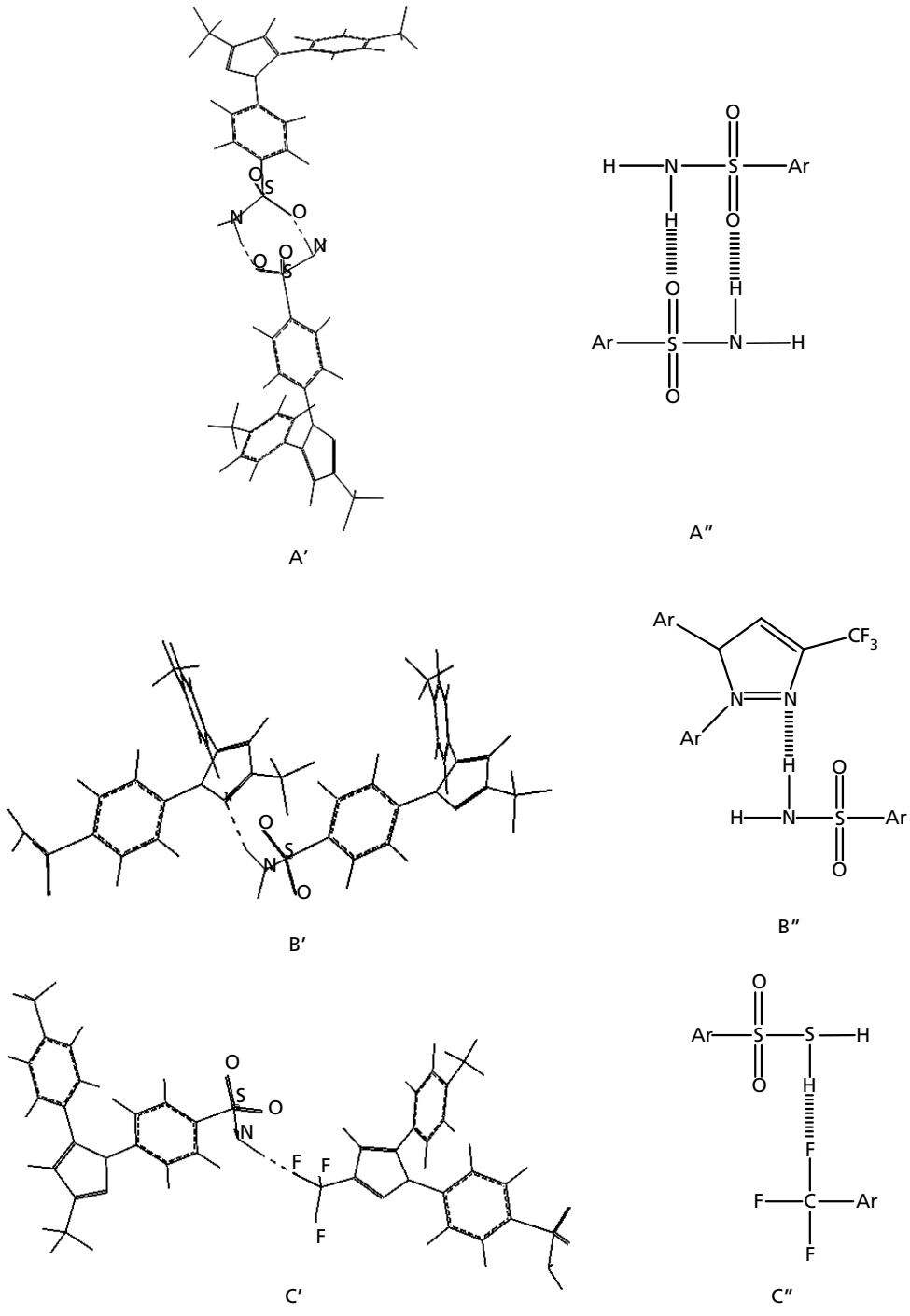

Figure 5 Inter-molecular associations between (A) −N–H and −S=O, (B) −N–H and 2-*N* of the pyrazole ring, and (C) −N–H and −C–F, in the amorphous form of celecoxib. Figures with single prime notation are stereoviews, while those with double prime are schematic representations of the interaction. The dotted lines represent H-bonding.

crystalline state. On the other hand, the lack of molecular order in the amorphous state introduced conformational flexibility, thus contributing to greater strengths in inter-molecular interactions.

In the past molecular modelling studies on chemical interactions in the amorphous state would always be open to debate, as these were based on computer simulation of random orientation of molecules. However, complementation of these studies with spectral techniques like FTIR provides very useful information on the nature of inter-molecular interaction, and strengthens the gravity of these speculations. Such patterns of self-association

Table 1 Relative H-bond lengths for different inter-molecular interactions in crystalline and amorphous celecoxib

Inter-molecular interaction	Crystalline celecoxib bond length Å	Amorphous celecoxib average bond length Å [± s.d.]; n = 9
–N–H . . . O=S–	N–H . . . O 2.952 Å H . . . O 2.085 Å	N–H . . . O 2.575 [0.015] and 2.586 [0.012] H . . . O 1.555 [0.022] and 1.547 [0.012]
–N–H . . . N–	N–H . . . N 3.087 Å H . . . N 2.235 Å	N–H . . . N 2.777 [0.024] H . . . N 1.746 [0.020]
–N–H . . . F–C–	N–H . . . F 3.781 & 3.851 Å, H . . . F 2.909 & 2.983 Å	N–H . . . F 2.623 [0.013] H . . . F 1.595 [0.011]

within amorphous materials are considered to be important in influencing the properties of the pure phase and the interaction with other components, like stabilizers and solubilizers.

Implications of altered molecular interactions on engineering of amorphous alloys

Amorphous solids are inherently unstable due to greater free volume allowing enough molecular mobility for molecular rearrangement into the crystalline phase. An explicit understanding of the differences in molecular interactions between metastable and thermodynamically stable solid-state can be utilized in engineering of custom-made amorphous alloys using additives that can specifically interact with electron donors or acceptors of drug molecules to prevent their re-association.

Differences in molecular interactions between the crystalline and the amorphous phase of celecoxib have been exploited in the selection of stabilizers that could strongly interact with drug molecules in the amorphous state. Poly(vinyl pyrrolidone) (PVP) was found to specifically interact with celecoxib, forming –C=O . . . H–N– (N-H . . . O 2.742 Å, H . . . O 1.738 Å) bonds (Gupta et al unpublished results). The carbonyl group, being a stronger electron donor than the sulfonyl group (Adsmond & Grant 2001), was favoured in H-bonding with celecoxib molecules, resulting in stability and a solubility advantage from celecoxib–PVP amorphous systems (Kakumanu & Bansal 2002; Gupta et al 2004).

Conclusions

Celecoxib exhibited altered molecular interactions in the crystalline and amorphous forms. Crystalline celecoxib showed an ordered network of H-bonding for all of its electron donors (O of the sulfonyl group, 2-*N* of the pyrazole ring, and F atom of the trifluoromethyl group) with the electron acceptor (H of the sulfonamide group). However, amorphous celecoxib exhibited a disordered molecular arrangement with relatively stronger H-bonding between all the interacting groups, as compared with the crystalline form. These altered configurations of the molecular arrangement in the two forms were supported by the FTIR spectral shifts among crystalline and amorphous celecoxib.

This study highlighted the observation that molecules with wide avenues for interaction, due to presence of various electron donor and acceptor groups, could pose varied possibilities of altered molecular conformations in different solid-states. These differences in the 'micro-state' of the amorphous form could get translated into a characteristically different 'macro-state' as compared with their crystalline counterparts. Knowledge of the differences in these molecular associations could help in rational selection of additives that could specifically interact and limit the mobility of otherwise dynamic molecules in the glassy state.

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