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Molecular interactions in celecoxib–PVP–meglumine amorphous system

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Abstract

Stabilization of the amorphous form of a drug is conferred by additives that interact with it at the molecular level. Ternary systems of celecoxib, poly(vinyl pyrrolidone) (PVP) and meglumine were studied for molecular interactions responsible for enhanced drug stability and solubility in amorphous form. Meglumine was found to lower the glass transition temperature (T_g) of the drug due to its plasticization effect. However, the presence of PVP masked its destabilizing effect and provided net anti-plasticization to the celecoxib–PVP–meglumine (7:2:1 w/w) ternary amorphous system. Positive deviation of the experimentally determined $T_{g\,mix}$ value for this composition, from those predicted by the Gordon–Taylor/Kelley–Bueche equation, inferred molecular interaction between the three species, which was also supported by band shifts from their Fourier-transform infra-red (FTIR) spectra. Further, shift of differential scanning calorimetry (DSC) melting endotherms of celecoxib in its amorphous systems from those observed for crystalline celecoxib confirmed the complexation between these components, which was also substantiated by molecular modelling studies that showed H-bonding of -S=O, 2-*N* of the pyrazole ring and -C-F groups of celecoxib with -O-H group of meglumine. These molecular interactions of amorphous celecoxib with meglumine were found to be the potential cause for enhanced stability and solubility of the celecoxib–PVP–meglumine ternary system.

Introduction

The biopharmaceutical properties of a molecule contribute critically towards its 'drug-ability' (Lipinski 2000). Over the years, drug discovery tools, including rational drug design and high-throughput screening, have led to the identification of numerous drug-like compounds with optimum biological receptor affinity but poor biopharmaceutical properties. The efficacy of an orally administered drug depends on the triad of potency (dose), solubility and permeability (Lipinski et al 1997). According to the biopharmaceutics classification system (BCS) (Amidon et al 1995), class II and IV drugs exhibit solubility-limited bioavailability and pose serious delivery challenges. Alterations within the physical state of the drug, by retaining the rigidity of solids and supplementing with the fluidity of liquids via conversion of crystalline to amorphous form, can be a viable approach to enhance drug dissolution, and in turn, bioavailability (Kaushal et al 2004).

The amorphous form of celecoxib, a BCS class II drug, provides an initial increase in solubility over its crystalline form, but a rapid devitrification (Chawla et al 2003), both on storage and during dissolution, results in loss of solubility advantage. The stabilization of the amorphous form of celecoxib has been achieved using poly(vinyl pyrrolidone) (PVP) (Kakumanu & Bansal 2002), which led to $\cong$ 6.3-fold enhancement in solubility (Gupta et al 2004). A further enhancement in celecoxib solubility was observed by including meglumine in celecoxib–PVP amorphous system (Bansal et al 2002). A ternary system of celecoxib–PVP–meglumine (7:2:1 w/w) was found to synergistically enhance celecoxib solubility over that achieved with celecoxib–PVP (4:1 w/w) or celecoxib–meglumine (9:1 w/w) binary systems, with peak solubility values of 38.04 ± 2.69, 23.45 ± 0.87 and $6.92 \pm 0.62\ \mu g\,mL^{-1}$, respectively.

Solubility enhancement by additives may be related to molecular-interaction-based stabilization of the amorphous form of the drug and interactions in the solution state

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between the components of amorphous molecular dispersions. This study was designed to explore the molecular-level interactions between celecoxib and meglumine, alone or in combination with PVP, and the contribution of these interactions towards the enhancement of stability and solubility of amorphous celecoxib. Techniques of differential scanning calorimetry (DSC), Fourier-transform infra-red (FTIR) spectroscopy, and molecular modelling were used to investigate these interactions.

Materials and Methods

Materials

Celecoxib was purchased from Unichem Laboratories Ltd (Raigad, India), PVP (K 29/32) was obtained from ISP Technologies (NJ) and meglumine was purchased from Sigma-Aldrich Chemie GmbH (Steinheim, Germany).

Preparation of amorphous systems of celecoxib

Amorphous celecoxib and its amorphous systems with PVP or meglumine, or both PVP and meglumine, were prepared by heating the crystalline drug or its physical mixture with additives up to 175°C, holding isothermally for 1 min and then quench cooling over crushed ice. The celecoxib–additive(s) physical mixtures were prepared by dissolving the components in mixtures of water and methanol, so as to allow their mixing at the molecular level, followed by solvent evaporation under heat and vacuum. No visible sign of degradation was observed in quench-cooled samples, and the purity of the amorphous samples was established by high-performance liquid chromatography. In each case, samples were analysed immediately after preparation.

Differential scanning calorimetry (DSC)

The calorimetric response of different samples was measured using DSC instrument (821^e; Mettler-Toledo GmbH, Schwerzenbach, Switzerland), operating with STAR^e software version 5.1, and equipped with an intracooler. The samples (3–5 mg) were analysed under dry nitrogen purge (80 mL min^{-1}) in sealed and pin-holed aluminium pans at a heating rate of 5°C min^{-1}, unless specified otherwise. Determination of glass transition temperature (T_g) was performed by DSC analysis from −15°C to 175°C at 20°C min^{-1} for samples prepared within the DSC instrument, as reported previously (Gupta et al 2004). All determinations were made in triplicate. The instrument was calibrated for temperature and heat flow using high purity standards of 4-nitro toluene, indium and zinc. The T_g has been reported as the mid-value of the glass transition event, T_c as the onset crystallization temperature and T_m as the peak melting temperature.

Fourier-transform infra-red (FTIR) spectroscopy

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

Molecular modelling studies

All studies were performed using Sybyl 6.8 program (Tripos Inc., MO) running on a Silicon Graphics onyx workstation. The inter-molecular interactions between celecoxib and meglumine were studied using the molecular silverware method. The celecoxib starting ensemble was built from available crystal data. Random arrangement of molecules to simulate the amorphous form was modelled by subjecting 18 molecules of celecoxib to energy optimization using MMFF94 force field till gradient convergence of 0.05 kcal mol^{-1} was reached. Out of the optimized model, 9 celecoxib molecules were randomly extracted and subjected to energy optimization in the presence of 18 molecules of meglumine. This finally optimized model of celecoxib and meglumine molecules was investigated for interactions between the two species. This procedure was analogous to that previously followed for studying the interaction between celecoxib and solvent molecules (*N*, *N*-dimethyl formamide and *N*, *N*-dimethyl acetamide) (Chawla et al 2003) for the formation of pseudo-polymorphs.

Statistical analysis

Statistical analysis of the effects of increasing PVP concentration (0–20% at 5% meglumine and 0–20% at 10% meglumine) on various parameters for crystallization and melting, as recorded on DSC, was performed using Kruskal–Wallis analysis of variance on ranks (SigmaStat version 2.03; Systat Software Inc., CA). Individual differences for these parameters (present in unequal sample size) between various PVP concentrations were determined by Repeated Measures analysis of variance on ranks using Dunn's test, post-hoc for multiple comparisons. The effect of 0 and 10% PVP in the presence of 20% meglumine on different parameters was statistically examined using the Mann–Whitney rank sum test. A significance level of $P < 0.05$ denoted significance in all cases.

Results and Discussion

Structural attributes of celecoxib and meglumine

Celecoxib is chemically designated as 4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1*H*-pyrazol-1-yl] benzenesulfonamide (MW 381.38) and is a diaryl-substituted pyrazole class of compound. Structural inspection of celecoxib reveals that its amido protons (H atom covalently bonded to an atom of greater electronegativity than C) are the only potential electron-accepting centres, whereas the sulfonyl O, the N atoms of the pyrazole ring and the F atom of the trifluoromethyl group are the three electron-donating centres. The amido N however, loses its electron-donating capability due to delocalization of its electrons over neighbouring O atoms (Adsmond & Grant 2001).

These electron-accepting and -donating centres are potential sites for H-bonding in and among celecoxib molecules.

Meglumine is chemically designated as 1-deoxy-1-(methylamino)-D-glucitol (MW 195.22), and is an amino sugar used as an organic base. Meglumine consists of several electron-accepting centres in the form of -OH and -NH groups, which provide varied possibilities for H-bonding.

Thermal transitions in celecoxib–meglumine and celecoxib–PVP–meglumine amorphous systems

The effect of meglumine or PVP–meglumine combination on the thermal response of celecoxib was studied by comparing the DSC thermogram of amorphous celecoxib with that of celecoxib–meglumine and celecoxib–PVP–meglumine amorphous systems of varying composition (Figure 1). All systems exhibited a common trend of glass transition event, followed by exothermic transition and endothermic events. These thermal transitions can have a significant bearing on the molecular-level interaction of the drug with the additives.

Effect on glass transition

Mixing of amorphous components at the molecular level results in production of an amorphous phase, the properties of which can be related to the properties of individual components (e.g., T_g) and its composition. The molecular interaction between the drug and additives can influence their T_g (Okhamafe & York 1989). A stronger bonding between unlike molecules raises the T_g from a value expected from ideal mixing (Shamblin et al 1998), due to the reduced mobility of molecules in the complexed state. The T_g of amorphous celecoxib and meglumine was found to be 58.1 and 18.9°C, respectively. Ideal molecular-level mixtures of these two components can be expected to exhibit T_g values intermediate to their original values, with a lower T_g for amorphous celecoxib due to the plasticizing effect of meglumine.

Celecoxib–meglumine binary systems of varying composition showed a single content-dependent T_g, the value of which was between those of the individual components, thereby establishing the drug–additive miscibility. These experimentally determined T_g values were compared with theoretically predicted values using the Gordon–Taylor/Kelley–Bueche (G-T/K-B) equation (Gordon & Taylor 1952; Kelley & Bueche 1961). The equation is based on the additivity of free volumes of the individual components characteristic of ideal mixing, and is given by the expression:

$$T_{g\,mix} = \left[(w_1.T_{g1}) + (K.w_2.T_{g2})\right]/[w_1 + (K.w_2)] \qquad (1)$$

where numerals in the subscript represent the two components, and w is the weight fraction of the components. The constant K, a measure of interaction between the components, can be approximated using equation 2 (Couchman & Karasz 1978).

$$K \approx (\Delta C_{p2})/(\Delta C_{p1}) \qquad (2)$$

where ΔC_p denotes the change in heat capacity at T_g. Ideal mixing of two or more amorphous substances results in mere addition of their free volumes. Self-association among any of the components would result in a higher free volume than that expected from ideal mixing, thus leading to higher molecular mobility, and lower T_g values. On the other hand, interaction between unlike components results in a lower free volume, lesser flexibility for molecular rearrangement and higher T_g values. The goodness of fit of experimental data to the G-T/K-B equation indicates the ideality of mixing of the two components and also provides a predictive tool for assessing the effect of different levels of one component on the T_g of the other. Deviation from ideal behaviour signifies differences in the strength of intermolecular interactions between individual components and those of the blend.

The predicted and experimentally determined $T_{g\,mix}$ values for celecoxib–meglumine binary systems of varying composition are plotted against meglumine content in Figure 2A. These $T_{g\,mix}$ values decreased continuously with increasing meglumine content, due to the plasticizing effect of the meglumine. The predicted and experimentally determined $T_{g\,mix}$ values showed large deviations. At 10% w/w meglumine content, the predicted and experimental

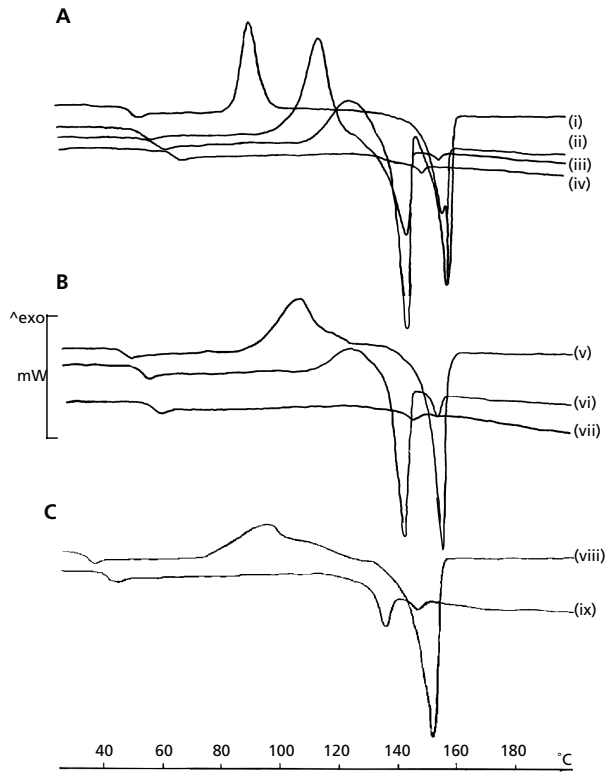

Figure 1 DSC thermograms for celecoxib–PVP–meglumine ternary systems of varying composition. A. 5% w/w meglumine and varying PVP content (i, 0% w/w; ii, 5% w/w; iii, 10% w/w; and iv, 20% w/w). B. 10% w/w meglumine and varying PVP content (v, 0% w/w; vi, 10% w/w; and vii, 20% w/w). C. 20% w/w meglumine and varying PVP content (viii, 0% w/w; and ix, 10% w/w).

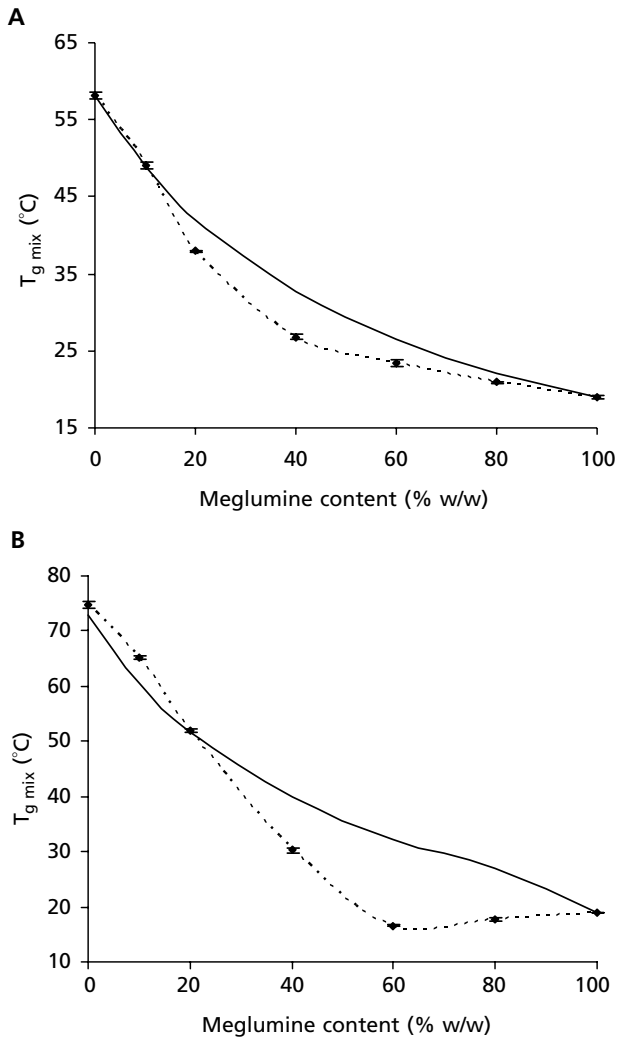

Figure 2 Influence of meglumine content on $T_{g\,mix}$ values of celecoxib–meglumine binary systems (A) and celecoxib–PVP–meglumine ternary systems (B). The solid line represents the prediction of the Gordon–Taylor/Kelley–Bueche equation; the dotted line represents the measured values.

$T_{g\,mix}$ values were nearly similar, while a large negative deviation was observed at a higher content. Low meglumine content could be expected to interact specifically with celecoxib, with ideal mixing of the two low-molecular-weight components, while self-association of meglumine molecules could be the most notable feature at higher meglumine content. Similar behaviour was observed for binary amorphous mixtures of indometacin and citric acid (Lu & Zografi 1998), a low T_g additive. The presence of numerous -OH groups and an -NH group shows the propensity of self-association between meglumine molecules, which could be precluded by the addition of a large amount of celecoxib in the binary system. The enhanced plasticizing effect of meglumine at high content results from a net increase in free volume relative to an ideal mixture, with miscibility being maintained by an increase in entropy due to a net loss of H-bonding upon mixing (Painter et al 1991; Shamblin et al 1998). Due to the plasticizing and self-associating ability of meglumine at high content, it is therefore advantageous to restrict its usage to low content in amorphous systems of celecoxib to provide an enhancement in solubility.

A similar response was observed for celecoxib–PVP–meglumine ternary systems with constant PVP content (20% w/w) and varying celecoxib and meglumine content. A single $T_{g\,mix}$ value was observed for different systems, confirming complete miscibility of the three components at all studied proportions. To assess the extent of ideality and non-ideality of mixing, the G-T/K-B equation was extended to three components as:

$$T_{g\,mix} = \left[(w_1.T_{g1}) + (K_1.w_2.T_{g2}) + (K_2.w_3.T_{g3})\right] / \left[w_1 + (K_1.w_2) + K_2.w_3)\right] \quad (3)$$

And

$$K_1 \approx (\Delta C_{p2})/(\Delta C_{p1}) \text{ and } K_2 \approx (\Delta C_{p3})/(\Delta C_{p1}) \quad (4)$$

At 10% w/w meglumine content, positive deviation from the predicted $T_{g\,mix}$ value was observed, whereas at higher meglumine content, the determined $T_{g\,mix}$ values were markedly lower than predicted ones (Figure 2B). These results implied that the presence of 20% w/w PVP had a positive effect on decreasing the free volume of the mixture and restricting the self-association of meglumine at 10% w/w content in the ternary system. However, at higher content, meglumine was still able to self-associate, even in the presence of 20% w/w PVP. Thus, a low content of meglumine in the celecoxib–PVP–meglumine ternary amorphous system was able to interact with celecoxib.

Effect on devitrification and melting

The exothermic transitions for a drug–additive(s) amorphous system could correspond to the amorphous solidification of the drug in additive or to the beginning of the formation of a complex (Bogdanova et al 1998), or to both of these. The T_c, as such, corresponds to a temperature favouring the spontaneous crystallization of the amorphous phase (i.e. molecular mobility permits nucleus growth, resulting in evolution of heat) (Nordwall & Staveley 1956).

DSC analysis of amorphous celecoxib showed the T_c at 96.3°C and T_m at 165.9°C. Inclusion of meglumine in the amorphous system of celecoxib lowered both these values. An increase in meglumine content from 5 to 20% w/w in celecoxib–meglumine binary systems lowered the T_c value from 86.8 to 75.6°C, indicating the inability of meglumine to stabilize the amorphous form of celecoxib – rather, it hastened the crystallization process. The T_m value decreased from 159.6 to 150.8°C, indicating the tendency of meglumine to complex with celecoxib. The variation in values of T_c and T_m with variation in meglumine content was statistically significant ($P < 0.05$). The complexing property and, in turn, the solubilizing potential, of meglumine has been reported on similar terms with various non-steroidal anti-inflammatory drugs, including indometacin,

sulindac, naproxen, ibuprofen and ketoprofen (Villiers et al 1999, 2000). Thus, meglumine in high content acted as a destabilizer for the amorphous form of celecoxib, but the molecule as such had a strong tendency to invoke complexation-led solubility enhancement.

DSC analysis of celecoxib–PVP–meglumine ternary systems with varying PVP and meglumine content also substantiated the complexation between celecoxib, PVP and meglumine (Table 1). For ternary systems tested at 5, 10 and 20% w/w meglumine content, an increase in the PVP content raised the T_c and decreased the enthalpy of crystallization (ΔH_c) of amorphous celecoxib, indicating masking of the crystallization-inducing effect of meglumine by PVP and stabilization of amorphous celecoxib. After the crystallization event, two endothermic peaks were observed at temperatures lower than that required for melting of pure celecoxib. The T_m, as well as the enthalpy, of melting (ΔH_m) for both these peaks decreased with an increase in PVP and meglumine content in the ternary system. These endothermic peaks could be attributed to melting of the celecoxib–PVP–meglumine complex formed during the DSC heating scan. A similar kind of thermal response has been postulated for the complexing effect of cyclodextrins on ketoprofen (Mura et al 1999b) and econazole (Mura et al 1999a). All these results confirmed the complex-forming ability of PVP and meglumine with celecoxib in the amorphous state.

Further, the asymmetry index (A_s) (Bonora et al 2000) of these melting endotherms was measured as an indicator of molecular interaction.

$$A_s = [(T_{ons} - T_i)/(T_{end} - T_i)]_{CEL-additive\ amorphous\ system} / [(T_{ons} - T_i)/(T_{end} - T_i)]_{crystalline\ celecoxib} \quad (5)$$

Referring to the DSC plot, T_{ons} (onset temperature) is the temperature of the intercept between the baseline and the tangent to the descending part of the graph at its inflection point, and T_{end} (endset temperature) is the same, but refers to the rising part of the calorimetric peak. The temperature T_i is of the interception point of the two previous tangents and its value is the same or very close to T_m. According to this definition, $A_s > 1$ denotes a skewing to a lower temperature, and $A_s < 1$ denotes a skewing to a higher temperature. Melting endotherms for all celecoxib–meglumine binary systems and celecoxib–PVP–meglumine ternary systems were significantly asymmetric, with A_s values higher than 1, signifying their skewness towards lower temperatures as compared with that for crystalline celecoxib. This pointed toward greater strengths of interaction (Kim et al 1985) between celecoxib, PVP and meglumine than within the individual components.

Spectral analysis of celecoxib–meglumine and celecoxib–PVP–meglumine amorphous systems

Vibrational spectroscopy has been extensively used to investigate interactions between the components of solid dispersions (Doherty & York 1987; Taylor & Zografi 1997; Matsumoto & Zografi 1999; Khougaz & Clas 2000; Broman et al 2001). The mixing of two components at the molecular level is expected to cause changes in the oscillating dipole of the molecules, which will manifest itself as changes in the frequency and bandwidth of interacting groups in the spectrum (Silverstein & Webster 2002).

The FTIR spectrum of meglumine showed multiple O-H and N-H stretching vibration bands in the region of 3400–2800 cm^{-1}. Due to the overlapping of this absorption region with N-H stretching vibration of celecoxib, the C-O stretching vibrations of meglumine were explored for studying possible interactions. The possible participation of the -OH groups of meglumine in H-bonding with

Table 1 Effect of PVP and meglumine content on crystallization exotherm and melting endotherms in celecoxib–PVP–meglumine ternary systems

PVP content (% w/w)	Crystallization		Melting					
	T_c (°C)	ΔH_c (J g^{-1})	Peak 1			Peak 2		
			T_m (°C)	ΔH_m (J g^{-1})	A_s	T_m (°C)	ΔH_m (J g^{-1})	A_s
5% w/w Meglumine content								
0	86.8 ± 0.3*	49.7 ± 0.8*	—	—	—	159.6 ± 0.1*	78.5 ± 0.6*	1.3 ± 0.2*
5	107.0 ± 0.5*	45.0 ± 1.0*	145.2 ± 0.4	33.7 ± 0.3*	4.8 ± 0.5*	158.7 ± 0.2*	24.5 ± 0.3*	3.3 ± 0.5*
10	114.0 ± 0.4*	13.6 ± 0.3*	145.1 ± 0.2	18.1 ± 0.1*	3.8 ± 0.2*	156.4 ± 0.5*	1.2 ± 0.2*	2.8 ± 0.3*
20	—	—	—	—	—	149.4 ± 0.4*	0.4 ± 0.1*	2.5 ± 0.1*
10% w/w Meglumine content								
0	77.3 ± 0.1*	43.2 ± 0.6*	—	—	—	154.9 ± 0.2*	70.6 ± 0.5*	3.7 ± 0.1*
10	113.1 ± 0.4*	5.1 ± 0.1*	142.4 ± 0.2	11.0 ± 0.7	3.4 ± 0.3	153.7 ± 0.3*	1.11 ± 0.4*	2.7 ± 0.3*
20	—	—	—	—	—	145.9 ± 0.5*	0.2 ± 0.0*	1.6 ± 0.2*
20% w/w Meglumine content								
0	75.6 ± 0.2	12.3 ± 0.5	—	—	—	150.8 ± 0.1*	67.0 ± 0.8*	2.6 ± 0.3*
10	—	—	135.9 ± 0.3	1.9 ± 0.9	2.3 ± 0.2	147.0 ± 0.2*	0.4 ± 0.1*	2.3 ± 0.1*

Values are reported as mean ± s.d., n = 3. *$P < 0.05$.

electron-donating centres of celecoxib will weaken the C-O bond of meglumine, which can be expected to result in peak shifts. The C-O stretching vibrations were seen as multiple sharp bands at 1017, 1050, 1075, 1098 and 1120 cm^{-1} for meglumine.

The possibility of an interaction between celecoxib and meglumine was initially tested at a 1:1 molar ratio. FTIR analysis of celecoxib–meglumine (1:1 molar ratio) binary system showed a negligible shift in the C-O stretching vibration bands of meglumine, signifying no interaction between the two species when present in 1:1 molar ratio (≅ 2:1 w/w). Thus, a high content of meglumine in the binary system had a tendency to self-associate, and neglect the celecoxib for participation in H-bonding.

Hence, the interaction between celecoxib and meglumine was studied using celecoxib–meglumine (9:1 w/w) binary system, which was also used to compare the relative solubilities of binary and ternary systems (Bansal et al 2002). The characteristic vibration bands of meglumine were found to overlap under those of celecoxib due to its high content. Spectral subtraction procedure (Doherty & York 1987) facilitated the assessment of spectral responses of meglumine, after subtracting the spectrum of amorphous celecoxib from that of the binary system. The C-O stretching vibration bands of meglumine were found to broaden and shift to lower wavenumbers of 1083 and 1106 cm^{-1} in the binary system. This shift of C-O stretching vibration band was indicative of an increase in the C-O bond length due to participation of the -OH group of meglumine in H-bonding with celecoxib. Thus, meglumine exhibited H-bonding with celecoxib at 9:1 w/w (4.6:1.0 molar ratio) composition rather than at 2:1 w/w (1:1 molar ratio) composition, implying that use of meglumine in a lower amount (on weight basis) in binary systems will favour H-bonding with celecoxib, with possible implications on celecoxib solubility or stability.

To ascertain the H-bonding between celecoxib and meglumine in the presence of PVP, the study was extended to FTIR analysis of celecoxib–PVP–meglumine (7:2:1 w/w) ternary system. The C-O stretching vibrations of meglumine were again found to be submerged under the spectrum of celecoxib, which was solved by subtraction of the spectrum of amorphous celecoxib from that of the ternary system. The C-O stretching vibration bands were found to broaden and shift to lower wavenumbers of 1073 and 1106 cm^{-1}, thereby confirming the complexation between celecoxib and meglumine, even in the presence of PVP.

Amorphous celecoxib showed a shift to a higher wavenumber for the N-H stretching vibration band, and to a lower wavenumber for the S=O stretching vibration band (Chawla et al 2003), as compared with crystalline celecoxib. These spectral shifts pointed to alteration of intermolecular H-bonding between -N-H and -S=O groups of celecoxib in the crystalline and amorphous phases. In the celecoxib–meglumine (9:1 w/w) binary system, as well as the celecoxib–PVP–meglumine (7:2:1 w/w) ternary system, the N-H and S=O stretching vibration bands of celecoxib were observed at positions characteristic for amorphous celecoxib. These results implied that the celecoxib–meglumine amorphous systems were multi-phasic with both celecoxib–celecoxib and celecoxib–meglumine in H-bonded states.

Computer simulation of celecoxib–meglumine amorphous system

Computer simulation has been an efficient tool for gaining a deeper understanding of molecular interactions between drug and additives (Piel et al 2001; Langer et al 2003). In this study, computer simulation was used as an adjunct to the results of FTIR studies, to confirm the molecular interactions between celecoxib and meglumine. Apart from the inter-molecular interaction between two randomly oriented celecoxib molecules, H-bonding was also observed between celecoxib and meglumine molecules (Figure 3A). Various H-bondings evident between celecoxib and meglumine were -S=O...H-O- (O...H-O 2.729 Å, O...H 1.805 Å) (Figure 3B), -C-F...H-O- (F...H-O 2.804 Å, F...H 2.078 Å) and -N...H-O- (N...H-O 3.046 Å, N...H 2.384 Å) (Figure 3C). Thus, meglumine exhibited extensive H-bonding with all possible H-bond acceptors in the celecoxib molecule, with the -S=O group being the most favoured one exhibiting a moderate-strength H-bond (Jeffrey 1997). This extensive H-bonding between the two species appears to regulate the mobility of celecoxib molecules in amorphous systems, and provides the advantage of high solubility.

Conclusions

The amorphous phase is characterized by high molecular mobility, even below the T_g, thus hampering its biopharmaceutical advantage of a higher dissolution rate, due to devitrification on storage. Attempts were made to retain or augment the solubility advantage of the amorphous form of celecoxib with the use of additives. Meglumine was found to complex with celecoxib, as evidenced by thermal, spectroscopic and molecular modelling studies.

A comparison of T_g values showed that 20% w/w PVP in a celecoxib–PVP binary system enhanced the T_g of amorphous celecoxib from 58.1 to 75.7°C, thus exhibiting an anti-plasticizing effect with enhanced amorphous-form stability. On the other hand, 10% w/w meglumine in a celecoxib–meglumine binary system reduced it to 49.1°C, indicating the plasticization effect of meglumine. A combination of 20% w/w PVP and 10% w/w meglumine in a celecoxib–PVP–meglumine ternary system showed T_g value of 65.2°C. Thus, PVP masked the plasticizing effect of meglumine in the amorphous ternary system. Further, an extensive H-bonding between celecoxib and meglumine, shown by molecular modelling studies, postulated a greater complexation between the two species, favouring the stability and solubility of amorphous celecoxib.

Meglumine exhibited a synergistic effect on enhancing the solubility of amorphous celecoxib (Bansal et al 2002). The solubility-enhancing effect of meglumine was specific to the amorphous form of celecoxib, as no enhancement in

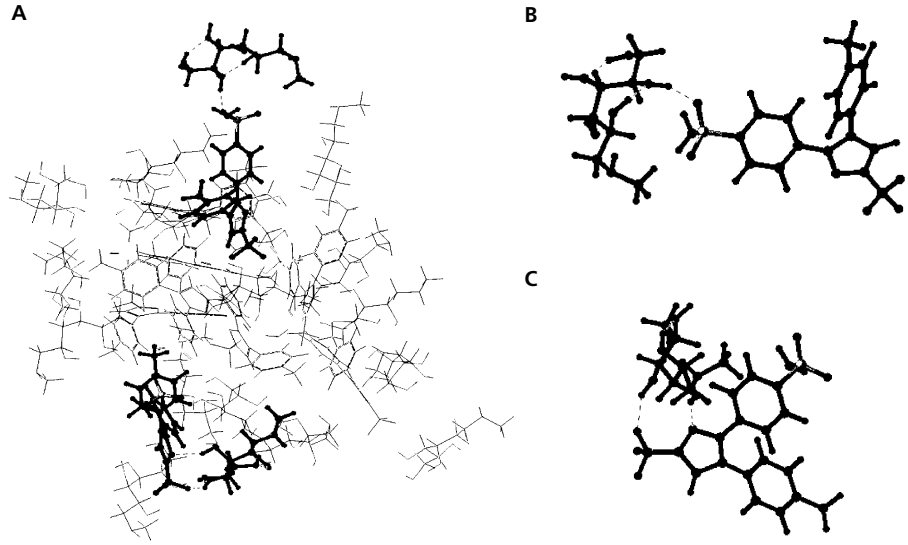

Figure 3 Stereoview of intermolecular associations between celecoxib and meglumine. A. Cluster of celecoxib and meglumine molecules in complexed state. B. Interaction of -S=O of celecoxib with -O-H of meglumine. C. Interaction of -C-F and 2-*N* of pyrazole ring of celecoxib with -O-H of meglumine. The H-bonding is represented by dotted lines between the interacting groups of celecoxib and meglumine molecules in the figures.

solubility was observed for physical mixtures with crystalline celecoxib. The presently observed complexation of meglumine with celecoxib is thus a reflection of the enhanced solubilization capacity of meglumine for amorphous celecoxib. This phase-specific interaction of meglumine with celecoxib could be due to the inaccessibility of molecular conformation conducive to complexation in the crystalline form, which was easily available in the disordered arrangement of the amorphous state. Despite its plasticization tendency, the specific chemical interaction of meglumine with celecoxib was able to limit the mobility of drug molecules, and retain the stabilization effect of PVP. Thus, in the ternary composition of celecoxib–PVP–meglumine, PVP can be labelled as the stabilizer and meglumine as the solubilizer for amorphous celecoxib.

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