Scientia Pharmaceutica www.scipharm.at

Research article Open Access

Molecular Mobility and Physical Stability of Amorphous Irbesartan

Garima CHAWLA, Arvind K. BANSAL *

Department of Pharmaceutical Technology (Formulations), National Institute of Pharmaceutical Education and Research (NIPER), Sector 67, Phase X, S.A.S. Nagar, Punjab-160 062, India.

* Corresponding author. E-mail: akbansal@niper.ac.in (A. K. Bansal)

Sci Pharm. 2009; 77: 695–709 doi:10.3797/scipharm.0806-09

Published: July 18th 2009 Received: June 11th 2008
Accepted: July 17th 2009

This article is available from: http://dx.doi.org/10.3797/scipharm.0806-09

Abstract

Amorphous systems have attracted considerable attention due to their favorable properties; however, their stability issues still pose a major challenge. The purpose of the present work was to investigate the role of molecular mobility and moisture in the physical stability of a selected pharmaceutical amorphous system. Irbesartan (IBS), a relatively stable glass, was chosen as the model drug, as it exhibits a good physical stability (resistance to crystallization) at temperatures below the glass transition (T_g-50 K). The amorphous system was annealed at temperatures 298 K (25 °C) and 313 K (40 °C) at 0 and 75 % RH to study the effect of temperature and moisture on its relaxation behavior. Differential scanning calorimetry (DSC) was used to characterize both the crystalline and the freshly prepared glass, and to monitor the extent of relaxation at temperatures below glass transition (Tg) as well as heat capacity changes as a function of temperature. Molecular relaxation time constant (τ) decreased drastically from 302 years to 68 hours with the increase in annealing temperature as determined by Kohlrausch-William-Watts (KWW) equation. IBS was found to be 'relatively' stable in the amorphous state and presented a challenge for temporal measurements. Hence, at low annealing temperatures, (T_g-50 K or below) initial relaxation time (τ^0) was estimated using the calorimetric based approach. Amorphous IBS was non-hygroscopic and retained its glassy nature under the accelerated stability conditions. The extent of relaxation in the amorphous drug in the presence of moisture was also estimated.

Keywords

Irbesartan • DSC • Amorphous form • Enthalpy relaxation • Molecular mobility • Stability

Introduction

A higher solubility as well as enhanced bioavailability of amorphous pharmaceuticals, in comparison to their crystalline counterparts, has generated a growing interest in the development and stabilization of the amorphous systems. However, the advantages of the amorphous systems cannot be fully exploited due to the physical and chemical instability inherent to these systems. Several studies have recognized the role of molecular mobility in time dependent nucleation, crystallization, chemical degradation and structural collapse of amorphous systems [1]. In the pharmaceuticals, these changes may adversely lead to alterations in the physicochemical properties and the bioavailability of the molecule during storage [2]. Physical characteristics like, dielectric, mechanical and optical related properties may also vary with time on storage [3].

The amorphous solids, which are metastable in nature, tend to spontaneously approach their equilibrium structure with time, through the phenomenon of structural relaxation or physical ageing. The factors contributing to this relaxation include the vibrational and rotational motions, and additionally, for the molecules in the supercooled region, translational motions, which involve a change in the locus of a given molecule [1]. This relaxation, which is enthalpic and/or volumetric in nature, is quantified in terms of the mean molecular relaxation time constant (τ) and the relaxation time distribution parameter (β) [4].

Amorphous pharmaceuticals having a glass transition temperature (T_g) below 350 K, relax significantly during storage and can even crystallize out. The amorphous forms of drugs like indomethacin and phenobarbital have shown crystallization at temperatures well below their respective glass transition temperatures, indicating a high molecular mobility of the amorphous solids [5–8]. In addition to the elevated storage temperatures, water has also been reported to be detrimental to the physical stability of the amorphous solids [9]. Water acts as a plasticizer for amorphous systems, causing an increase in the free volume and a reduction in the T_g of the system. Enhanced molecular mobility, caused by plasticization, has been proposed to be the underlying factor in the chemical and the physical instability of the amorphous pharmaceutical solids [10]. Therefore, it becomes imperative to perform an assessment of the molecular mobility to determine the suitable storage conditions for amorphous substances and their products.

Amorphous systems differ with each other in their behavior during storage, with some of the systems exhibiting a better kinetic ‘stability’. From a stability perspective, it is desirable that amorphous materials exhibit relaxation times comparable to, or greater than, their shelf life, which is generally 3 years for pharmaceuticals. The aim of this study was to characterize the behavior and performance of a ‘relatively’ stable amorphous system by taking irbesartan (IBS), as the model drug. IBS, 2-butyl-3-{[2'-(1*H*-tetrazol-5-yl)biphenyl-4-yl]methyl}-1,3-diazaspiro[4.4]non-1-en-4-one, is a potent long-acting non-peptide AII receptor antagonist with high specificity for the AT1 subtype, and used in the treatment of hypertension. The enthalpy relaxation of amorphous IBS was studied using differential scanning calorimetry (DSC) and, additionally, the role of moisture and temperature on the physical stability of amorphous IBS was also investigated.

Results and Discussion

Crystalline and amorphous forms of IBS

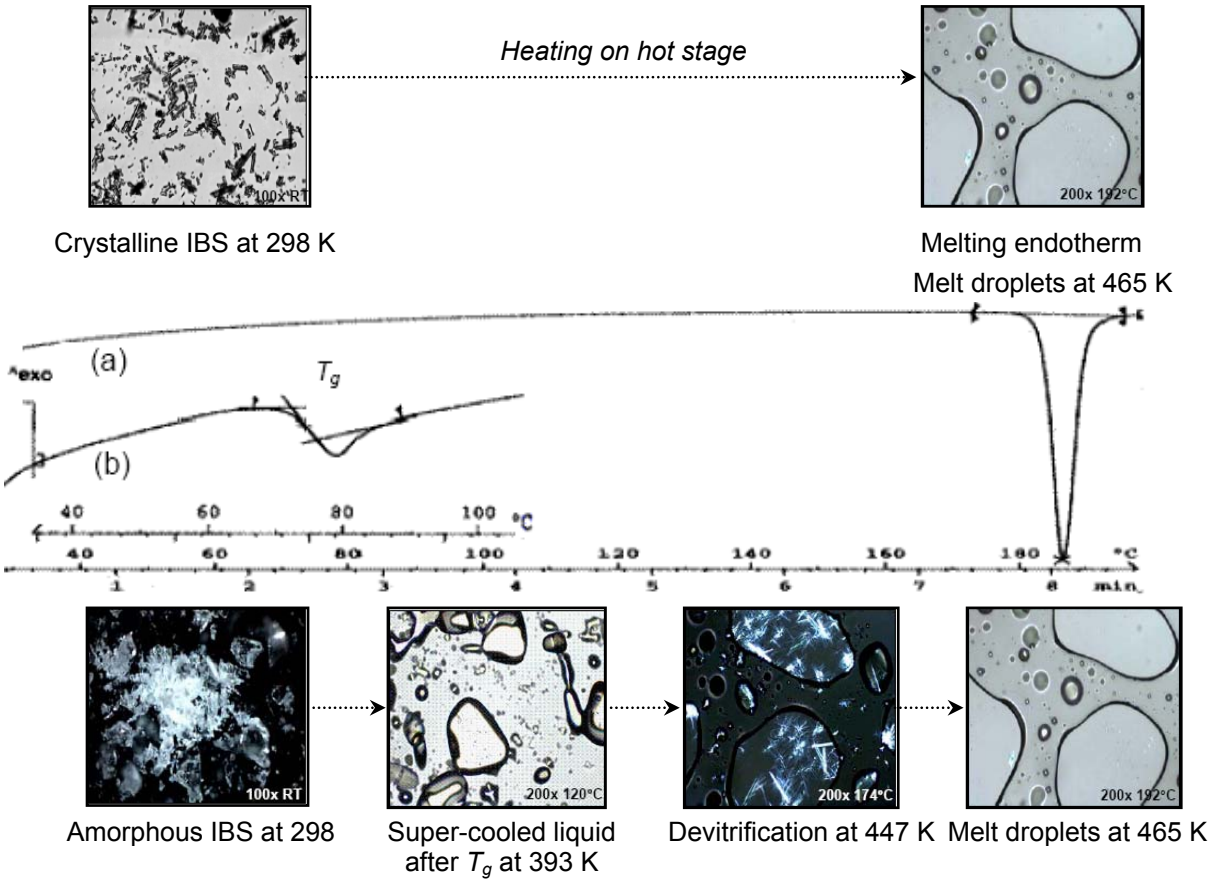


Fig. 1. DSC curves of crystalline and amorphous IBS at heating rate of 20 K/min with photomicrographs showing visual observations of thermal events on hot stage microscope. (a) Melting endotherm in crystalline IBS, (b) glass transition in amorphous form generated *in-situ* and photomicrographs of *ex-situ* amorphous IBS

DSC of the received sample of crystalline IBS, at a heating rate of 20 K/min, showed a single sharp fusion endotherm at 456 K-463 K ± 0.5 K having the heat of fusion (ΔH_f) equivalent to 107 J/g ± 2 J/g (Figure 1). The sharp fusion endotherm at 456 K in DSC, the powder X-ray diffraction (PXRD) pattern and the Fourier transfer infrared (FTIR) spectra revealed that the sample of crystalline IBS to be the polymorphic form A (low melting, metastable form) without any contamination from other polymorphic forms [11]. DSC of the *in situ* quench-cooled IBS exhibited a sigmoid shape endotherm (glass transition) at 344.7 K ± 1.0 K (onset T_g), which is a reflection of the gradual softening of a glass to its ultraviscous equilibrium liquid state. No other exothermic peak of crystallization or endothermic peak of melting was observed. Heating at a slower rate of 1 K/min, also did not result in the spontaneous crystallization of amorphous IBS, thereby, suggesting a lack of crystallization tendency of amorphous IBS. The *ex situ* quench-cooled amorphous product, on the other hand, exhibited a small melting peak at 451–461 K (ΔH_f = 14 J/g), after the glass transition, at a heating rate of 20 K/min. The moisture entrapped during the

preparation of the *ex situ* sample, might have contributed to this devitrification, as against the *in situ* sample, which was prepared in a dry nitrogen environment. Findings from the DSC analyses were corroborated with the observations of the hot stage microscopy (HSM). Under polarized light, amorphous IBS appeared as irregularly shaped particles, without anybirefringence because of loss of lattice order upon amorphization. IBS exhibited a T_g/T_m of 0.75 and, therefore, is expected to be a relatively good glass former [12]. Fragile molecules like acetaminophen and trimethoprim have lower values of 0.67 and 0.70, respectively, in comparison to a good glass former like ritonavir, which has a higher value of 0.82 [11]. This supports the enthalpy relaxation data, which exhibited a relatively 'stable' nature of amorphous forms of IBS (data shown later). The characteristics of IBS, such as, ease of glass formation and relatively low molecular mobility, make it a suitable for the development of a stabilized amorphous pharmaceutical delivery system.

Kinetic behavior of amorphous IBS: enthalpy relaxation studies

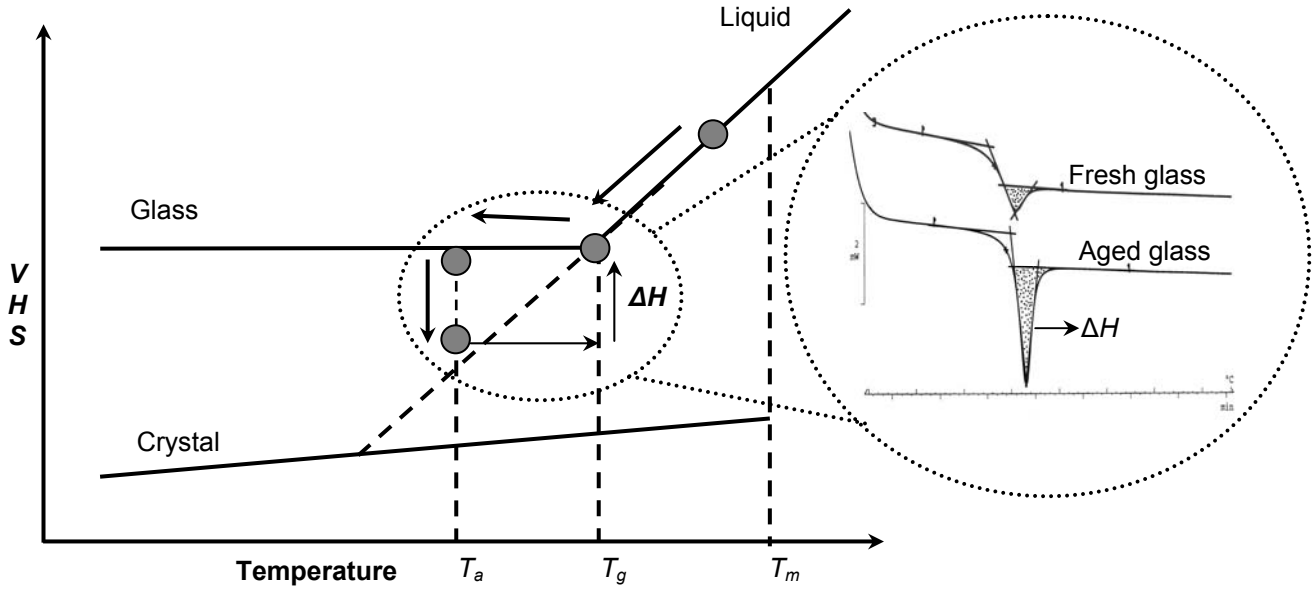


Fig. 2. Schematic representation of enthalpy or volume-temperature relation in amorphous solids during aging and its response in DSC. Inset represents freshly prepared and aged sample run on DSC, where area under endotherm associated with T_g is defined as enthalpy recovery Note: ΔH is the loss/recovered enthalpy, T_a is annealing temperature

Amorphous systems have poorer physical and chemical stability as compared to crystalline counterparts, owing to their thermodynamic (higher free energy, enthalpy and entropy) and kinetic properties (higher molecular represented by the molecular relaxation time constant) [13]. Both properties determine the crystallization tendency in the rubbery state. Greater molecular mobility has been regarded as the key factor responsible for their physical instability. Molecules in an amorphous system are said to be kinetically trapped

since the time scale of the long-range molecular mobility is much smaller than the experimental time scale. Therefore, the amorphous systems, formed due to quench cooling, have an excess of thermodynamic properties as compared to the corresponding supercooled liquid state. During aging at a particular temperature (T_a), an amorphous system loses this excess enthalpy as they move towards a more stable conformation (Figure 2). The amount of enthalpy, lost during storage, is recovered by the sample during its heating run in the DSC and is measured as an integral of the enthalpy recovery peak which accompanies the glass transition (Figure 2). This phenomenon of enthalpy relaxation reflects the molecular mobility in the glassy state.

Storage conditions, mainly temperature and humidity, have been reported to play a vital role in the physical stability of amorphous systems. The amorphous samples of IBS were aged at 298 K and 313 K with 0 % relative humidity (RH) (over P_2O_5), for different periods, to assess the effect of storage temperature on their stability. The total or maximum enthalpy change (ΔH_α) needed for a glass to relax to a supercooled liquid state increases linearly with decrease in degree of undercooling, as explained by equation (1)

Eq. 1. $\Delta H_\alpha = \Delta C_p(T_g - T_a)$

where ΔC_p is the change in the heat capacity at T_g, i.e., the difference in the heat capacity between the supercooled and glassy states and T_a is the storage temperature. Decrease in the enthalpy during structural relaxation is the sum of all the changes that occur with time and during the cooling and heating of a glass [3]. Heat capacity (C_p), a thermodynamic quantity that is experimentally determined, is an important parameter for the characterization of the amorphous form. C_p values of both the crystalline and the amorphous forms of IBS increased with increasing temperature; almost linearly in the crystalline IBS and hyperbolically in its amorphous form. Additional degrees of freedom in the amorphous state were reflected by the elevated heat capacities at all the temperatures. A characteristic step change at T_g, indicated an increase in the molecular specific volume.

Amorphous IBS showed significant relaxation (as seen in the DSC scan) upon storage at temperatures below T_g (344 K), confirming that the molecular motions below T_g could be measured using this thermal method. An increase in the storage temperature from 298 K to 313 K, led to a decrease in ΔH_α from 16.4 J/g to 10.5 J/g. The extent of material relaxation (Φ_t) was calculated from the maximum enthalpy recovery at any time (t) and temperature T_a, using equation (2),

Eq. 2. $\Phi_t = 1-(\Delta H_t / \Delta H_\alpha)$

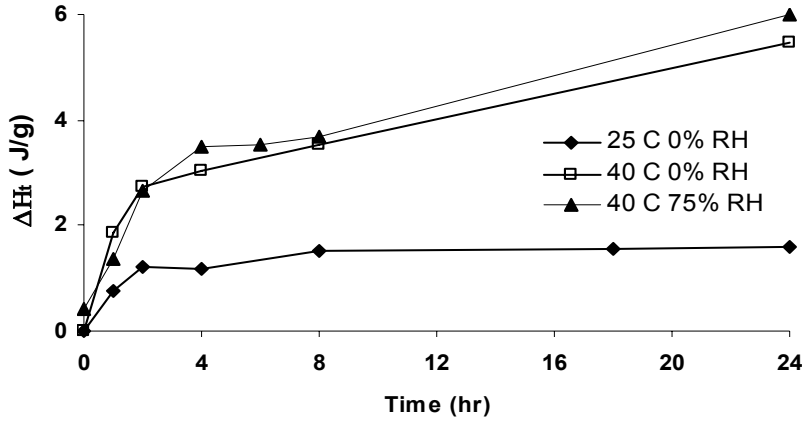
where ΔH_t is the measured enthalpy recovery at those particular conditions and Φ_t reflects the proportion of glass that has been relaxed over time t. A non-linear increase in ΔH_t was observed with an increase in the aging time (Figure 3a). However, the amount of enthalpy relaxed was dependent on the temperature of the aging studies. Relaxation was minimal when the storage temperature was well below T_g (i.e. 298 K), but increased when stored at 313 K. Enthalpy recovery increased from 1.9 J/g to 5.5 J/g with time (1 to 24 h) when the sample was stored at 313 K in contrast to marginal increase from 0.8 J/g to 1.6 J/g at 298

K. Greater the value of Φ_t, lesser is the relaxation of glass to pseudoequilibrium supercooled state. It was observed that the increase in the temperature by 15 K towards T_g decreased Φ_t from 0.9 to 0.5 (Figure 3b).

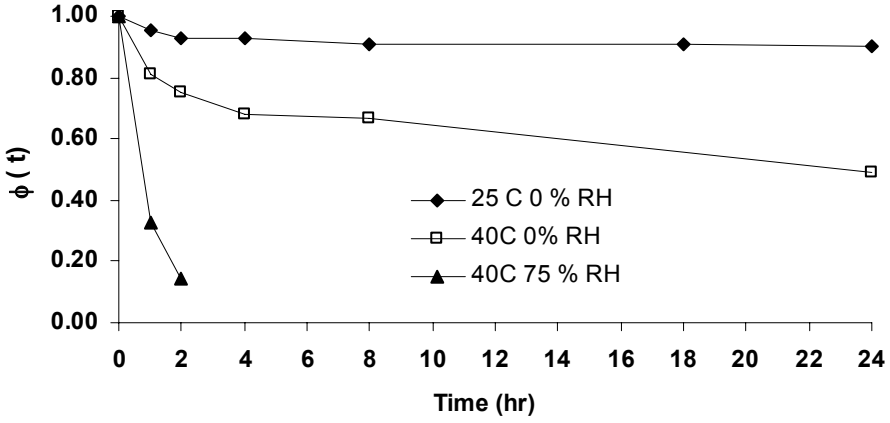
The portion of the glass relaxed was used to express mobility in terms of the average relaxation time (τ) and the 'stretching parameter'/relaxation constant (β) by fitting the data to the non-exponential Kohlrausch–William–Watts (KWW) equation (3)

Eq. 3. $\Phi(t) = \exp - (t / \tau)^{\beta}$

As described previously in the literature, the data was fitted to a stretched exponential function using non-linear regression with the assumption that there are multiple relaxation processes with a distribution of relaxation times [1]. An iterative non-linear regression algorithm based on the Levenberg-Marquardt method was used to obtain the best fit for β and τ values using initial parameters τ = 100 s and β = 0.5.



(a)



(b)

Fig. 3. (a) Enthalpy lost with time on structural relaxation of amorphous IBS annealed for 24 h at different storage conditions, (b) Proportion of glass relaxed with aging time at different annealing conditions

Table 1 lists the calculated parameters expressing mobility. At T_g, τ is typically about 100-200 s [14]. At temperatures below T_g, the apparent activation energy for molecular rearrangement varies according to the sample history, but is typically significantly less than that at temperatures above T_g, where glass exhibits a typically non-Arrhenius τ [1]. Amorphous IBS exhibited a very high τ value of 302 years at 298 K. However, as seen in table 1, an increase in the storage temperature led to a significant drop in the τ and the half-life ($t_{1/2}$) of amorphous IBS. The τ value decreased from 302 to 67.5 years with an increase in the temperature. The half-life ($t_{1/2}$), defined as the time for which $\Delta H_{recovery}$ reaches half its theoretical maximum was determined using the KWW equation. Amorphous IBS exhibited $t_{1/2}$ of 45 years and was also found to be dependent on the storage temperature. As the storage temperature increased and approached T_g, $t_{1/2}$ reduced from years to hours (25 h).

Another parameter called the 'Deborah number' was calculated. The Deborah number can be used to assess performance of amorphous pharmaceuticals since it is an index of the relative molecular mobility in context of the product stability. It is the ratio of τ to reference time (t_{ref}). The reference time for the product stability of pharmaceuticals is taken as three years and the values of Deborah number greater than unity indicate stable systems for the reference time frame. IBS exhibited a very high Deborah number at temperatures 298 K (100.5) and it again showed a significant dependence on the storage temperature (Table 1).

The study clearly highlights, that IBS forms a 'stable' glass in comparison to other pharmaceuticals. Amorphous IBS has pharmaceutical advantages which were highlighted in a previous study by the authors, where amorphous IBS showed a 2.5 folds increase in the solubility over the crystalline form [11]. Thus, amorphous IBS can be used to design a stable drug product exhibiting an enhanced solubility.

Tab. 1. KWW relaxation time constant, stretching parameter and other mobility parameters of amorphous IBS annealed at 298 and 313 K

Condition	Φ_{24hr}	β	τ	Deborah No.	$t_{50\%}$
298 K/0 %RH	0.9	0.19	302 (years)	100.5	45 (years)
313 K/0 %RH	0.5	0.37	67.5 (hours)	0.003	25 (hours)

Molecular mobility in 'sluggish' amorphous systems

It can be seen from Table 1 that the molecular mobility is too sluggish to be measured on the experimental time scale, especially at aging temperatures well below T_g, thus resulting in a relaxation time in years. A recent study by Mao *et al.*, had exposed the limitation of the commonly used KWW method to predict mobility of 'relatively' stable molecules with high T_g and at aging temperatures T_g-50 K. The concept of initial relaxation time (τ^0) has been discussed for cases where the relaxation process was too sluggish [15]. Therefore, τ^0 for IBS was calculated using the fragility parameters D (strength parameter), m (steepness parameter), and γC_p. The fragility parameters D and m were calculated from the temperature dependence of activation energy (ΔE_{Tg}) through the Vogel–Tamman–Fulcher

(VTF) relationship (equation 4 and 5) with m_{min} of 16 [16]. The ratio of the difference between the specific of liquid and glass to the difference between the specific heat of liquid and crystalline form (equation 6) was used in calculating γC_p. The limits for γC_p have been defined as $0 \leq \gamma C_p \leq 1$, where $\gamma C_p = 1$ corresponds to a strong glass and $\gamma C_p = 0$ corresponds to a fragile glass. In case of IBS, γC_p value of 0.63 suggested it to be a moderately strong glass [17, 18]. The activation energy of structural relaxation at T_g was calculated from the heating rate dependence of T_g. Graph was plotted between the log of heating rate vs. inverse of midpoint T_g to obtain ΔE_{Tg} (data not shown).

Eq. 4. $m = \Delta E_{Tg} / 2.303RT_g$
Eq. 5. $D = \ln m^2_{min} / (m - m_{min})$
Eq. 6. $\gamma C_p = (C^l_p - C^g_p) / (C^l_p - C^c_p)$
Eq. 7. $\tau^0 = \tau \exp [(DT_0) / T - T_0(T/T_g)^{\gamma Cp}]$

where T_0 in this case is

Eq. 8. $T_0 = T(1 - m_{min}/m)$ and

τ_0 is approximately 10^{-14} s.

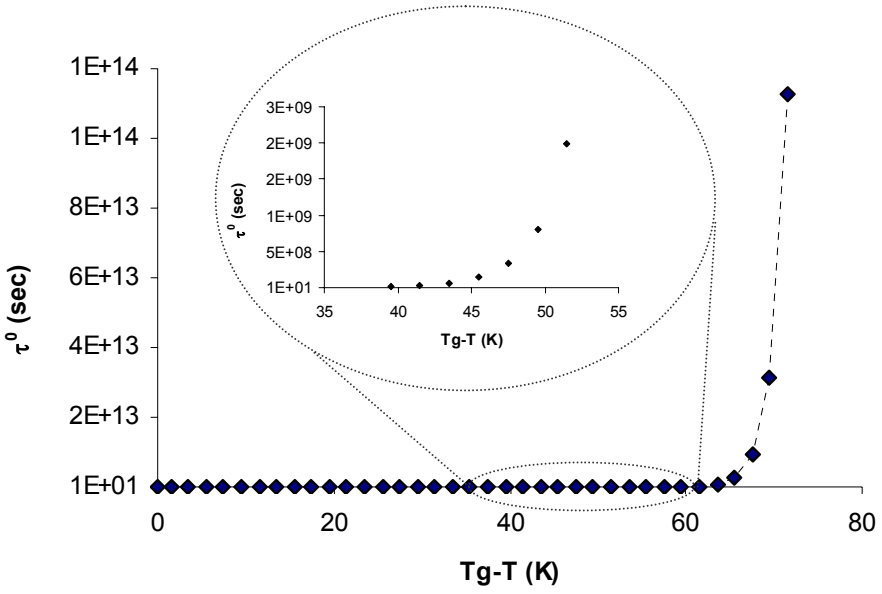


Fig. 4. Estimated τ^0 values of amorphous IBS plotted as a function of difference of annealing temperature to T_g. Note: The inset shows the τ^0 values of amorphous IBS at temperatures 40–50 K lower than T_g.

At T_g, material exhibited the expected magnitude of relaxation time i.e. 100 s. As the temperatures fell below T_g, τ^0 began to diverge and at temperatures 40 to 50 K below T_g the value of τ^0 differed by more than one order of magnitude (Figure 4). For IBS, T_0 was calculated to be 260.8 K and τ^0 at this temperature was 6.3 years. T_0 is the temperature of

infinite τ (zero mobility), and acts as a better guide than T_g for selecting the storage temperature. As expected the values obtained using KWW equation were about one magnitude higher than this method. This is because τ^0 estimates the initial relaxation time, whereas KWW equation gives average relaxation time over the entire storage period. Using equation 7, and assuming 3 years to be the shelf life of a pharmaceutical product, the storage temperature of glassy IBS was calculated to be 300 K. T_0 value for the majority of amorphous solids lies near to refrigeration temperature, whose maintenance becomes impractical during the different stages of product development, handling and storage. IBS on the other hand, would be stable for 3 years when stored at 300 K, a temperature very much near the room temperature.

Role of moisture in stability of amorphous systems

The role of water as a plasticizer was made clear when IBS was aged in 75 % RH at 313 K (ICH accelerated stability condition). The samples were subjected to DSC to obtain ΔH_t as the area of the recovery peak accompanying T_g. The samples, in the DSC, were heated to temperatures above melting point of the crystalline substance to ascertain the absence of crystalline character. T_g values were found to be 345 K, 321 K and 318 K after 0, 2 and 6 h of exposure, respectively, and Φ_t became 0.15 within 2 h, in contrast to 0.75 at 313 K in 0 % RH.

The role of water as a plasticizer was also studied on T_0 (or T_K) using the VTF equation using shear viscosity [17] and calculated from equation 9

Eq. 9. $T_0 = T_g / (1+ D/2.303(17))$

where 17 corresponds to $\log(\eta_g/\eta_0)$. T_0 was predicted to be 275 K and 272.4 K, at 321 K and 318 K, respectively, and the difference between T_g-T_0 was approximately 50 K at all the three T_g values (345 K, 321 K and 318 K). Criticality of the plasticization effect depends on the extent to which T_g is reduced by the absorbed water as well as the intrinsic dynamic properties of the glass, as reflected by its fragility (D).

Hygroscopicity Studies of Crystalline and Amorphous IBS

Amorphous systems have been known to demonstrate an ‘excess’ of thermodynamic properties (enthalpy, entropy, and free energy) relative to their crystalline counterparts [19]. On the one hand, these ‘excess’ properties bestow enhanced solubility, improved bioavailability and better compressibility, however, on the other hand, they are responsible for their physical instability by way of devitrification. Usually the higher hygroscopicity of the amorphous system in comparison to the crystalline drug can further enhance devitrification. Typically, crystalline materials adsorb vapors in smaller quantities at their surface. In contrast, amorphous systems absorb vapors in relatively large amounts (even up to 100 % by weight) [20]. It has been shown in the previous studies, that even a small amount of amorphous material, embedded within a largely crystalline matrix, preferentially absorbs water vapor. This amplifies the local water content and a corresponding plasticization of the amorphous structure [10, 20]. Thus, relative humidity is an important factor influencing the solid-state properties of glassy systems.

In this study, both, crystalline and amorphous IBS, were exposed to a high humidity condition in open vessels, and the weight gain was observed at regular intervals. The weight gain for the crystalline and amorphous material was estimated by subtracting with the weight gain shown by the excipients alone. Based on the observations, it was found that the crystalline sample did not exhibit any significant weight gain (0.0006 % w/w increase) with and without the excipients. After 7 days of exposure, though the amorphous IBS exhibited weight gain higher than the crystalline form (0.0088 % w/w increase) but it was not significant. The solid sample retained its amorphous nature as confirmed by the halo pattern of the PXRD and its non-birefringent behavior under polarized light. The low moisture uptake and the ability to retain the amorphous state can be attributed to the hydrophobic nature of the molecule [21]. This non-hygroscopic nature of amorphous IBS further strengthens its case as a good molecule for amorphous delivery.

Critical water content (W_c), i.e. the water content at which T_g of the system is lowered to the storage temperature (T_{ST}), was calculated using equation 10 for T_{ST} 298 K and 313 K [22].

Eq. 10. $$W_c = [1 + T_{g\rho}(T_{ST+} - 135) / 135(T_g - T_{ST})]^{-1}$$

where ρ is the density of the material assumed to be 1.2 g/ml for pharmaceuticals.

The critical water content, W_c, decreased from 8.5% w/w to 5.5% w/w with an increase in the temperature from 298 K to 313 K, respectively. Also, IBS exhibited very low absorption of water at 298 K (0.0088 % w/w) in comparison to W_c. Thus, amorphous IBS can be considered non-hygroscopic in nature.

Further, hygroscopicity studies of physical mixtures of amorphous IBS and excipients (lactose, microcrystalline cellulose, pregelatinized, starch, cross carmellose sodium, magnesium stearate, and silicon dioxide) also did not show any weight gain. This highlights that amorphous IBS would pose no problem due to hygroscopicity when converted into a solid dosage form.

Physical Stability Studies

Stability of quench-cooled IBS was monitored for three months when subjected to accelerated conditions as per the ICH stability guidelines (313 K / 75% RH). Stability samples were characterized by PXRD after 7, 15, 30, 60 and 90 days. Amorphous form of IBS was found to be stable for a period of three months. After 90 days of the studies, no peaks were observed in the PXRD pattern suggesting that, the sample did not crystallize on storage at 313 K / 75 % RH (Figure 5). The FTIR spectra of the stability samples also exhibited characteristic peaks of the amorphous form at 2960 (C-H triplet, aromatic), 1726 (-C=O), 1627 (-C=N), 1560 (-C=C, aromatic), 1439 (-N=N) and 1420 cm^{-1} (α-CH_2). Even though there was a decrease in T_g from 345 K to 321 K to 318 K in 0 to 2 to 6 h and $\sqrt{t}$ became 0.15 within 2 h at 75 % RH (as seen in the earlier section), crystallization was not seen in amorphous IBS in the presence of moisture. The results were concordant with the solubility studies reported earlier by the authors where complete devitrification occurred after 6 h of complete immersion of amorphous sample into the dissolution medium [11].

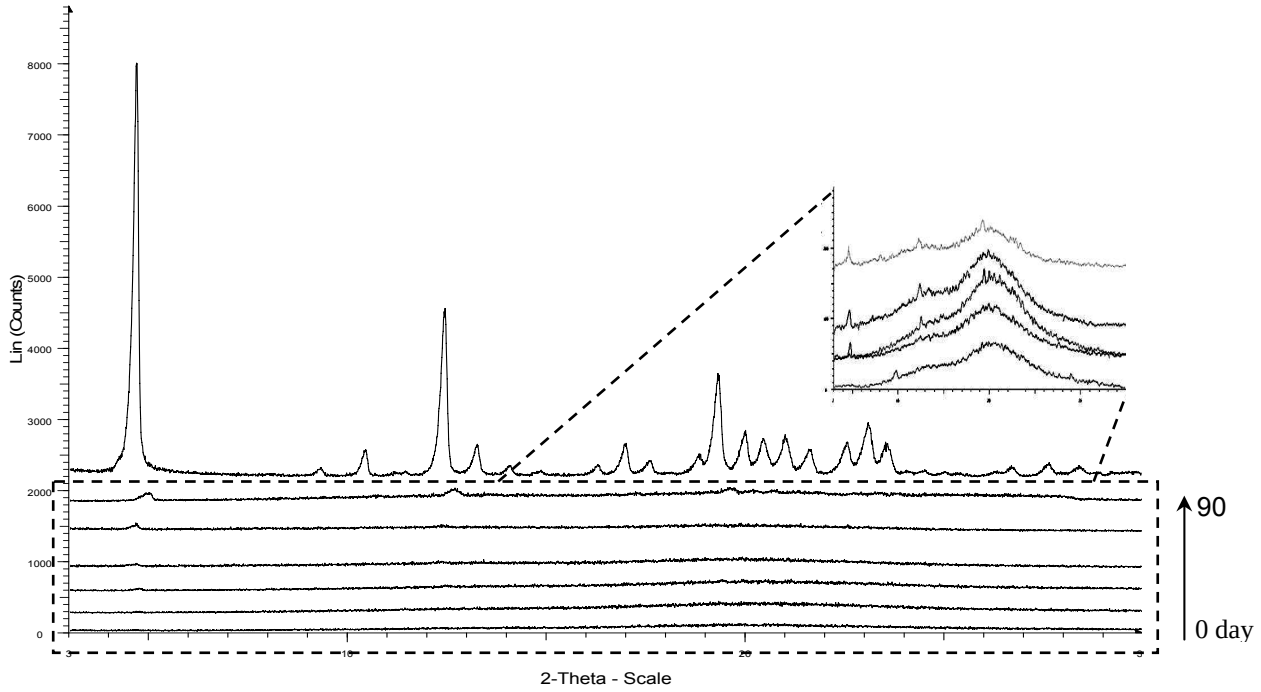


Fig. 5. PXRD patterns of amorphous IBS when stored at 313 K/ 75 % RH in stability chamber in comparison to pure crystalline form. Inset depicts zoomed pattern of amorphous IBS samples at different intervals (0, 15, 30, 60, and 90 day bottom to top).

Experimental

Materials

IBS (purity > 99 %) was gifted by Dr Reddy's Labs, (Hyderabad, India). All compounds were obtained in their purest grade and used as received without any further purification.

Methods

Preparation of amorphous form

'In situ' preparation of amorphous form: Amorphous form of the drugs was prepared by quench cooling the melt within the differential scanning calorimetric instrument (Mettler Toledo 821e DSC, Mettler Toledo, Switzerland), operated with STAR^e software (version 5.1), and equipped with an intracooler. 4–6 mg of crystalline drug was taken and sealed in an aluminum pan with a pinholed lid. The samples were heated from 298 K to 15-20 K above the melting temperature at a heating rate of 20 K/min under nitrogen purge (80 ml/min) and held at that temperature isothermally for 1 min within the instrument. The molten sample was then cooled to 298 K at a rate of 20 K/min. The cell constant and the temperature calibration was conducted using high-purity standards of naphthalene, 4-nitrotoulene, indium and zinc.

'Ex situ' preparation of amorphous form: Amorphous form of drug was prepared by melting the drug in a stainless steel beaker on a hot plate (Sonar®, Associated Scientific Technologies, India), and subsequently quench cooling the melt over crushed ice. The

quench-cooled product was ground and sieved (BSS No. 60, mesh size 250 μm) (Sonar®, Associated Scientific Technologies, India). It was then subjected to PXRD (D8 Advance, Bruker, Madison, USA) and polarized light microscopy (DMLP, Leica, Germany), immediately after preparation, to ascertain the absence of the crystalline form. HPLC analysis (Shimadzu Corporation, Kyoto, Japan) confirmed that no degradation had occurred during the procedure. These *ex situ* samples were prepared for the hygroscopicity and the physical stability studies.

Heat capacity measurements

The constant pressure C_p, of the amorphous and crystalline forms of the drug was measured using DSC in accordance with the ASTM method. The C_p measurements involved three runs: null curve (no reference and sample pan), blank curve (empty reference and sample pan) and measuring curve (reference pan and sample pan with sample). Sapphire was used as the heat capacity standard and C_p of the sample was obtained by referencing with the C_p of sapphire. C_p was calculated by taking into consideration the heat flow of the sample, the actual heating rate of the sample (corrected amplitude) and the sample mass. For the amorphous material, C_p was calculated at T_g onset (C_p glass) and at T_g endset (C_p liquid). Data used in the study was averaged from a minimum of three runs.

Enthalpy relaxation/molecular mobility studies

Amorphous form of IBS was prepared *in situ* as described previously and heated to the selected aging temperature. Amorphous IBS was aged at 298 and 313 ± 0.5 K under 0 % RH over P_2O_5 for 24 h. Amorphous IBS was also aged at 313 K under 75 % RH. At various time points, the samples were subsequently cooled in a DSC at a heating rate of 20 K/min and then reheated to obtain the recovered enthalpy (ΔH_t) as the area of the recovery peak accompanying T_g. The area of the endothermic peak at T_g was measured by constructing a tangent to the line of heat flow after T_g and extrapolating it to other side to enable the measurement of accurate enthalpy changes over the phase transformation. Samples were heated to temperatures well above melting point of crystalline substances to ascertain absence of crystalline character.

Hygroscopicity studies of crystalline and amorphous IBS

Hygroscopicity studies were performed with pure crystalline IBS, amorphous IBS and with their physical mixtures with excipients used in innovator formulation (lactose, microcrystalline cellulose, pregelatinized, starch, cross carmellose sodium, magnesium stearate, and silicon dioxide) (www.rxlist.com). Accurately weighed quantity of samples were placed in 'boats' made of aluminum foil (thickness of 0.04 mm) laminated with polyethylene (150 gauge) (M/s. Rototech, India), and stored uncovered, in a dessicator maintained with 95 % humidity using a saturated salt solution at 298 K. The samples were weighed at regular intervals for a period of 7 days to observe any weight gain due to moisture. The excipients, without the crystalline or amorphous drug sample, were also placed individually under the same hygroscopicity conditions, as controls.

Physical Stability Studies

The physical stability of quench-cooled IBS was monitored for three months under accelerated stability studies as per the International Conference on Harmonization (ICH)

guidelines at 313 K/ 75 % RH (ICH Harmonized Tripartite Guideline Q1A(R2), 1993). The samples were packed in thermally sealed pouches (Heat sealer, JTC, India) made of polyethylene laminated aluminum foil of thickness 0.04 mm, and charged in the stability chamber (KBF 720, WTC Binder, Germany). Periodically (0, 7, 15, 30, 60, and 90 days), the samples were removed and examined for solid-state transitions by PXRD, FTIR spectroscopy (using KBr pellet method) and polarized light microscopy.

Conclusion

Amorphous systems are an effective strategy in the pharmaceutical dosage form development and its importance is growing further due to the increasing number of insoluble molecules being pushed into the drug development pipeline. Physical instability due to devitrification and chemical degradation are the major setbacks impeding their commercialization.

Amorphous IBS, which shows a good physical stability, is a potential candidate for the development of a drug product. It exhibited sluggish molecular mobility and was found to be resistant to moisture-mediated plasticization. Favorable properties of amorphous IBS such as a high T_g value (greater than the room temperature), relatively 'slow' devitrifying behavior, good glass forming tendency and a reasonable stability, makes this system amenable for further exploitation. Theoretically, 'relatively' stable molecules like those studied would require only solubilizers and not antiplasticizing additives for making a stable and an effective delivery system. By understanding the relationship between the glassy behavior and product performance characteristics of these materials, it is, possible to select formulation strategies on a more rational basis.

Acknowledgements

Garima Chawla acknowledges the financial assistance provided by Council for Scientific and Industrial Research (CSIR), Govt. of India as Senior Research Fellowship for the study. Assistance provided by Central Instrumentation Laboratory, NIPER, India is also gratefully acknowledged.

Authors' Statement

Competing Interests

The authors declare no conflict of interest.

References

[1] Hancock BC, Dalton CR, Pikal MJ, Shamblin SL.
A pragmatic tool of a simple calorimetric method for determining the fragility of some amorphous pharmaceutical materials.
Pharm Res. 1998: 15: 762–767.
doi:10.1023/A:1011931305755

[2] Hancock BC.
Disordered drug delivery: destiny, dynamics and the Deborah number.
J Pharm Pharmacol. 2002; 54: 737–746.
doi:10.1211/0022357021778989

[3] Gunawan L, Johari GP, Shankar RM.
Structural relaxation of acetaminophen glass.
Pharm Res. 2006; 23: 967–979.
doi:10.1007/s11095-006-9898-0

[4] Shamblin SL, Hancock BC, Dupuis Y, Pikal MJ.
Interpretation of relaxation time constants for amorphous pharmaceutical systems.
J Pharm Sci. 2000; 89: 417–427.
doi:10.1002/(SICI)1520-6017(200003)89:3<417::AID-JPS12>3.0.CO;2-V

[5] Andronis V, Yoshioka M, Zografi G.
Effect of absorbed water on crystallization of of indomethacin from the amorphous state.
J Pharm Sci. 1997; 86: 346–351.
doi:10.1021/js9602711

[6] Aso Y, Yoshioka S, Kojima S.
Relationship between crystallization rates of amorphous nifedipine, phenobarbital, anf flopropione, and their molecular mobility as measured by their ^{1}H NMR relaxation times.
J Pharm Sci. 2000; 89: 408–416.
doi:10.1002/(SICI)1520-6017(200003)89:3<408::AID-JPS11>3.0.CO;2-#

[7] Fukuoka E, Matika M, Yamamura S.
Glassy state of pharmaceuticals. III. Thermal properties and stability of glassy pharmaceuticals and their binary glassy systems.
Chem Pharm Bull. 1989; 37: 1047–1050.

[8] Yoshioka M, Hancock B, Zografi G.
Crystallization of indomethacin from the amorphous stet below and above its glass transition temperature.
J Pharm Sci. 1994; 83: 1700–1705.
doi:10.1002/jps.2600831211

[9] Oksanen C, Zografi G.
Molecular mobility in mixtures of absorbed water and solid poly(vinylpyrolidone).
Pharm Res. 1993; 10: 791–799.
doi:10.1023/A:1018988506336

[10] Ahlneck C, Zografi G.
The molecular basis of moisture effects on the physical and chemical stability of drugs in the solid state.
Int J Pharm. 1990; 62: 87–95.
doi:10.1016/0378-5173(90)90221-O

[11] Chawla G, Bansal AK.
A comparative assessment of solubility advantage from glassy and crystalline forms of a water-insoluble drug.
Eur J Pharm Sci. 2007; 32: 45–57.
doi:10.1016/j.ejps.2007.05.111

[12] Law B, Krill SL, Schmitt EA, Fort JJ, Qiu Y, Wang W, Porter WR.
Physicochemical considerations in the preparation of amorphous ritonavir-poly(ethylene glycol) 8000 solid dispersions.
J Pharm Sci. 2001; 90: 1015–1025.
doi:10.1002/jps.1054

[13] Zhou D, Zhang GGZ, Law D, Grant DJW, Schmitt EA.
Physical stability of amorphous pharmaceuticals: Importance of configurational thermodynamic quantities and molecular mobility.
J Pharm Sci. 2002; 91: 1863–1872.
doi:10.1002/jps.10169

[14] Ediger MD, Angell CA, Nagel SR.
Supercooled liquids and glasses.
J Phys Chem. 1996; 100: 13200–13212.
doi:10.1021/jp953538d

[15] Mao C, Chamarthy SP, Byrn SR, Pinal R.
A calorimetric method to estimate molecular mobility of amorphous solids at relatively low temperatures.
Pharm Res. 2006; 23: 2269–2276.
doi:10.1007/s11095-006-9071-9

[16] Hancock B, Shamblin S.
Molecular mobility of amorphous pharmaceuticals determined using differential scanning calorimetry.
Thermochim Acta. 2001; 380: 95–107.
doi:10.1016/S0040-6031(01)00663-3

[17] Bohmer R, Ngai KL, Angell CA, Plazek DJ.
Nonexponential relaxations in strong and fragile glass formers.
J Chem Phys. 1993; 99: 4201–4209.
doi:10.1063/1.466117

[18] Shamblin SL, Tang X, Chang L, Hancock BC, Pikal MJ.
Characterization of the time scales of molecular motion in pharmaceutically important glasses.
J Phys Chem B. 1999; 103: 4113–4121.
doi:10.1021/jp983964+

[19] Yu L.
Amorphous pharmaceutical solids: preparation, characterization and stabilization.
Adv Drug Del Rev. 2001; 48: 27–42.
doi:10.1016/S0169-409X(01)00098-9

[20] Hancock BC, Zografi G.
Characteristics and significance of the amorphous state in pharmaceutical systems.
J Pharm Sci. 1997; 86: 1–12.
doi:10.1021/js9601896

[21] Drooge D, Hinrichs W, Visser M, Frijlink H.
Characterization of the molecular distribution of drugs in glassy solid dispersions at the nano-meter scale, using differential scanning calorimetry and gravimetric water vapour sorption techniques.
Int J Pharm. 2006; 310: 220–229.
doi:10.1016/j.ijpharm.2005.12.007

[22] Royall PG, Craig DCM, Doherty C.
Characterisation of moisture uptake effects on the glass transitional behavior of an amorphous drug using modulated temperature DSC.
Int J Pharm. 1999; 192: 39–46.
doi:10.1016/S0378-5173(99)00270-7