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Research Article

Physicochemical Investigations and Stability Studies of Amorphous Gliclazide

Shital Jondhale,[1] Satish Bhise,[2] and Yogesh Pore[1,3]

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Abstract. Gliclazide (GLI), a poorly water-soluble antidiabetic, was transformed into a glassy state by melt quench technique in order to improve its physicochemical properties. Chemical stability of GLI during formation of glass was assessed by monitoring thin-layer chromatography, and an existence of amorphous form was confirmed by differential scanning calorimetry and X-ray powder diffractometry. The glass transition occurred at 67.5°C. The amorphous material thus generated was examined for its *in vitro* dissolution performance in phosphate buffer (pH 6.8). Surprisingly, amorphous GLI did not perform well and was unable to improve the dissolution characteristics compared to pure drug over entire period of dissolution studies. These unexpected results might be due to the formation of a cohesive supercooled liquid state and structural relaxation of amorphous form toward the supercooled liquid region which indicated functional inability of amorphous GLI from stability point of view. Hence, stabilization of amorphous GLI was attempted by elevation of T_g via formation of solid dispersion systems involving comprehensive antiplasticizing as well as surface adsorption mechanisms. The binary and ternary amorphous dispersions prepared with polyvinylpyrrolidone K30 (as antiplasticizer for elevation of T_g) and Aerosil 200® and/or Sylysia® 350 (as adsorbent) in the ratio of 1:1:1 (*w*/*w*) using kneading and spray-drying techniques demonstrated significant enhancement in rate and extent of dissolution of drug initially. During accelerated stability studies, ternary systems showed no significant reduction in drug dissolution performance over a period of 3 months indicating excellent stabilization of amorphous GLI.

KEY WORDS: amorphous; gliclazide; solid dispersion; stability studies; T_g.

INTRODUCTION

Drug amorphization is an interesting and frequently being exploited one of the approaches for enhancement of physicochemical and biopharmaceutical characteristics of poorly aqueous soluble crystalline active pharmaceutical ingredients (APIs) (1–4). Due to inherent and thermodynamic stability of crystalline API, it is usually being preferred for the purpose of delivery by the formulation experts in a pharmaceutical industry (5–7). However, the possibility of existence of crystalline API in different polymorphic forms cannot be ruled out as this can be one of the reasons for low solubility and dissolution rate leading to inadequate and variable oral bioavailability, especially for poorly water-soluble compounds (8,9). The poor oral bioavailability often results in limited therapeutic response and reduced patient compliance.

The overall physicochemical and therapeutic performance of such drugs in terms of solubility, dissolution, and bioavailability can be improved by intentional solid-state modification (crystalline to amorphous/glassy state) (10–12). This can be achieved by condensation from the vapor state of solid, supercooling of the melt, mechanical activation of a crystalline mass (*e.g.*, during milling), and rapid precipitation from solution (*e.g.*, during freeze drying or spray drying) (13). The characteristics and significance of the amorphous state in pharmaceutical systems have been reviewed elegantly by Hancock and Zografi from manufacturability, bioavailability, therapeutic performance, and stability point of view (13). The advantages of glassy or vitreous state of solids are enhanced thermodynamic properties such as solubility, dissolution rate, and greater molecular motion as a result of high internal energy as compared to their crystalline form (11,13,14).

However, the high internal energy and specific volume of amorphous state relative to crystalline state can promote the amorphous state to undergo devitrification during processing (mechanical stress) or storage (temperature and humidity stress). Further, the presence of water vapor which acts as plasticizer with greater plasticizing effect on amorphous structure of solids can be expected to be an important factor influencing the properties of amorphous solids (12,13). Thus, the process of vitrification of solids is disfavored at these situations and needs their physical stabilization in solid state as well as during performance.

The stability of amorphous solids can be improved by storage at well below the glass transition temperature (T_g) and by protection from plasticizer (water vapor) (13,15). In an alternative approach, the amorphous material is formulated with an antiplasticizer with higher T_g in the form of an amorphous solid dispersion (16,17). The antiplasticizer is expected to stabilize the amorphous material by elevation of

[1] Department of Pharmaceutical Chemistry, Government College of Pharmacy, Karad, Maharashtra 415124, India.
[2] Sinhgad Institute of Pharmaceutical Sciences, Lonavala 410401, India.
[3] To whom correspondence should be addressed. (e-mail: yogeshvpore@rediffmail.com)

T_g. The hydrophilic polymers such as polyvinylpyrrolidone (PVP), hydroxypropyl methylcellulose, and polyethylene glycol are usually employed as antiplasticizers in the amorphous dispersions. The antiplasticizing effect of hydrophilic carriers such as PVP can be augmented by the incorporation of an adsorbent (third component) such as Aerosil® 200 or Sylysia® 350 which are nonporous and porous hydrophilic silica particles, respectively (18,19). In addition to the antiplasticizing effect, these polymers improve drug solubility by virtue of their hydrophilicity, by preventing the aggregation of individual particles and creating microenvironment in which the drug solubility is high (20).

Therefore, as a proof of concept, an attempt was made to improve physicochemical characteristics and stability of the amorphous gliclazide (GLI) that has been chosen as a model drug for the present study. Gliclazide [1-(3-azabicyclo (3, 3, 0) oct-3-yl)-3-*p*-tolylsulfonylurea] is a second-generation hypoglycemic sulfonylurea useful in the treatment of non-insulin dependent diabetes mellitus (21). The drug exhibits good tolerability, low incidence of hypoglycemic effect, low rate of secondary failure, and low rate of progression of diabetic retinopathy (22,23). Therefore, it is an effective long-term sulfonylurea therapy for treatment of type 2 diabetes mellitus (24). However, gliclazide appears to be a white crystalline powder with relatively low solubility in water. The p*K*a of gliclazide is 5.8. Gliclazide exhibits slow GI absorption rate and variable bioavailability (22).

Few attempts including cyclodextrin complexation (25,26) and crystalline dispersions without stability studies have been reported for improvement of solubility (24,27) and bioavailability of gliclazide (28). However, no ternary dispersion approach for improvement of solubility and bioavailability of gliclazide has been employed yet. Therefore, in this report, the generation and stabilization of glassy gliclazide was attempted along with its physicochemical performance.

MATERIALS AND METHODS

Materials

Gliclazide and PVP K30 were kindly provided as a gift samples from Indoco Remedies, Mumbai. Aerosil® 200 was obtained as a gift sample from Degussa Evonik, Mumbai, India. Sylysia® 350 was obtained as a gift sample from Fuji Silysia Chemical Ltd., Japan. All the reagents were of analytical grade. Double-distilled water was used throughout the experiment.

Methods

Preparation of an Amorphous State

The amorphous state of gliclazide was prepared by the melt quench technique. The crystalline form of GLI (GLIC) was taken in a steel container and was heated rapidly at its melting point. Then it was cooled suddenly in an intimate freezing mixture (mixture of an ice and sodium chloride) for about 1–1.5 h. The glassy GLI was collected and ground with the help of pestle on the butter paper protecting it from the moisture and immediately stored in a dessicator.

Thin-Layer Chromatography

Thin-layer chromatography was performed to detect the possible degradation during melting of the drug. The stationary phase used was silica gel G. A mixture of chloroform: benzene (40:10) was used as a mobile phase. The spots were visualized with the help of iodine vapors. The R_f value was calculated and checked each time.

Preparation of Solid Dispersions

The solid dispersions of amorphous gliclazide were prepared using kneading and/or spray-drying method with PVP K30 as a hydrophilic carrier. The amorphous state was prepared each time freshly at the time of preparation of dispersion followed by its purity checking by thin-layer chromatography. Aerosil®200 and Sylysia® 350 were used as ternary components for ternary dispersions.

Preparation of Binary and Ternary Amorphous Dispersions by Kneading Method

The amorphous gliclazide (GLIA) and PVP (1:1 ratio by weight) for binary and GLIA, PVP, and ternary component that is either Aerosil®200 or Sylysia® 350 (1:1:1 ratio by weight) were taken in a glass mortar and mixed uniformly to form physical mixture. The ethanol/water mixture (1:1 ratio) was added drop by drop to form paste, and this was kneaded uniformly and unidirectionally for about 1 h. The paste was dried in an oven at 40°C for about 12 h for binary and 2 h for ternary dispersion. After drying, product was passed through 60 mesh size sieve that is 250 μm and stored in dessicator until further study.

Preparation of Binary and Ternary Amorphous Dispersions by Spray-Drying Method

Freshly prepared amorphous gliclazide in combination with PVP K30 (1:1 ratio by weight) in binary dispersion and with PVP K30 and either Aerosil® 200 or Sylysia® 350 (1:1:1 ratio by weight) in ternary dispersions was dissolved in sufficient amount of chloroform to obtain clear solutions. Spray drying was carried out using laboratory-scale spray dryer (Labultima, LU 222 Advanced, Mumbai, India) under the following set of conditions: inlet temperature 65°C, outlet temperature 40°C, cool temperature 30°C, feed rate 10 mL/min, atomization air pressure 2 kg/cm^2, and aspiration rate 60 mBar. All the spray-dried products were collected and stored in a dessicator until further study. The codes of all systems are mentioned in Table I.

Initial Characterization

The samples of pure crystalline GLI, amorphous GLI, and all the solid dispersions (binary and ternary by both methods) were subjected to initial characterization immediately after their preparation based on the parameters below.

Table I. Codes for All Systems

Sr. No.	System	Code
1	Pure crystalline drug	GLIC
2	Amorphous gliclazide	GLIA
3	Binary dispersion by kneading method	GLIKN1
4	Binary dispersion by spray-drying method	GLISD2
5	Ternary dispersion with Aerosil® 200 by kneading method	GLIAKN3
6	Ternary dispersion with Aerosil® 200 by spray-drying method	GLIASD4
7	Ternary dispersion with Sylysia® 350 by kneading method	GLISKN5
8	Ternary dispersion with Sylysia® 350 by spray-drying method	GLISSD6

Fourier Transformed Infrared Spectroscopy

Fourier transformed infrared spectroscopy (FTIR) spectra were obtained using FTIR spectrophotometer (model: Jasco V550, Japan). The samples were prepared into KBr disks. The numbers of scans before FT was performed were 20. The scanning range was kept from 4,000 to 400 cm^{-1}.

Differential Scanning Calorimetry

Thermal analysis of GLIC, GLIA, and all solid dispersions (SDs) was carried out on a differential scanning calorimeter (model: Q600 V20.9 Build 20, TA Instruments). The sample (4.5–6 mg) was sealed in an aluminum pan and heated in the nitrogen atmosphere (flow rate 40 ml/min) at the scanning rate of 10°C/min in the range of 25–200°C.

X-ray Powder Diffractometry

The X-ray powder diffractometry (XRPD) data of pure GLI, amorphous GLI, PVP K30, and all solid dispersion systems were recorded on a X-ray diffractometer (model: Philips Analytic X-Ray—PW 3710, Philips, Almelo, the Netherlands) with tube anode Cr over the interval 5–50°/2θ.

Drug Content Studies

SDs equivalent to 5 mg of GLI were accurately weighed and dissolved in 5 mL of methanol and volume adjusted to 50 mL with distilled water. Then it was filtered and the drug content was determined at 228 nm by using UV–visible spectrophotometer (UV-1700 Pharmaspec, SHIMADZU, Japan).

Dissolution Rate Studies

The dissolution medium for pure drug and formulations was optimized, and the phosphate buffer solution (pH 6.8) was selected as a dissolution medium for all the systems. The dissolution rate studies were conducted in 900 mL of phosphate buffer solution (pH 6.8) at 100 rpm maintained at 37 ± 0.5°C in dissolution apparatus using the paddle method (Disso 2000, LabIndia, India). Forty milligrams of drug or its equivalent amount of dispersion was added to dissolution medium, and the samples were withdrawn at 2, 5, 10, 15, 20, 25, 30, 45, 60, and 90 min time intervals and the dissolution medium was replaced with the same amount as sampled.

The samples were immediately filtered through 0.45 μm membrane filter, suitably diluted, and analyzed spectrophotometrically at 227.5 nm. The data obtained from dissolution studies were statistically analyzed.

Stability Studies

The amorphous gliclazide and all solid dispersions were subjected to the accelerated stability testing for the period of 3 months as per the ICH guidelines at 40°C/75% RH. Periodically (initial, 1 and 3 months for all systems) samples were removed and characterized by dissolution rate measurements along with the presence of crystallinity by differential scanning calorimetry (DSC) and XRPD studies.

RESULTS AND DISCUSSION

Appearance of an Amorphous State

The state of gliclazide which was formed after melt quench technique was completely transparent and brittle in the appearance. The amorphous nature of the drug was further confirmed by DSC and XRPD studies.

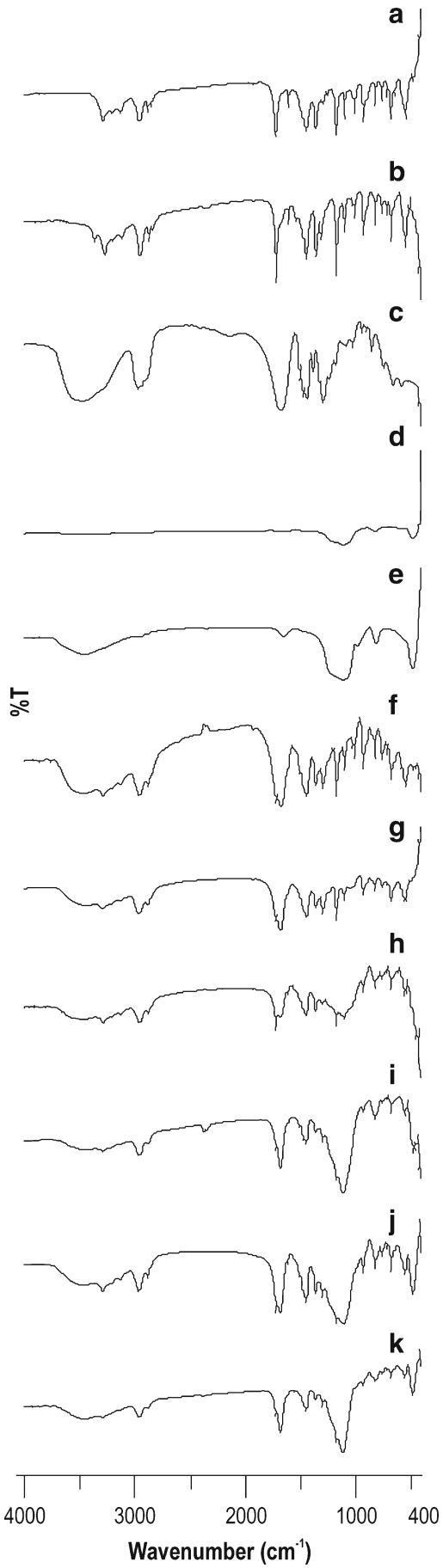
Thin-Layer Chromatography

It was performed to check whether any degradation has occurred during melting of the drug. It was found that no degradation occurred during processing. The R_f value of both crystalline as well as formed amorphous state was found to be identical, and the value obtained each time was around 0.97. No additional spot was observed in the amorphous state run indicating the absence of degradation of the drug.

Initial Characterization

Fourier Transformed Infrared Spectroscopy

Figure 1 illustrates the FTIR spectra of pure GLI (crystalline), amorphous GLI, PVP K30, ternary components (Aerosil®200 and Sylysia® 350), and all solid dispersion systems. The IR spectrum of GLIC (Fig. 1 A) presents characteristic peaks at 3,273.57 and 3,192.58 cm^{-1} (N–H amide stretch), 3,112.55 cm^{-1} (C–H aromatic stretch), 2,949.59 cm^{-1} (C–H aliphatic stretch–asymmetric), 2,867.63 cm^{-1} (C–H aliphatic stretch–symmetric), 1,709.59 cm^{-1} (C=O, amide carbonyl stretch), 1,595.81 cm^{-1} (N–H amide bend), 1,590 and 1,473.35 cm^{-1} (C=C aromatic



◀ **Fig. 1.** FTIR spectra of all systems. *A* GLIC, *B* GLIA, *C* PVP K30, *D* Aerosil®200, *E* Sylysia® 350, *F* GLIKN1, *G* GLISD2, *H* GLIAKN3, *I* GLIASD4, *J* GLISKN5, and *K* GLISSD6

stretch), 1,348 cm^{-1} (S=O sulfonyl stretch), 1,240.97 cm^{-1} (C–N ring stretch, heterocyclic), and 811.885 cm^{-1} (*p*-phenyl group in fingerprint region).

In case of GLIA (Fig. 1 B), slight shift in few characteristic peaks was observed with no major difference in overall spectrum. The IR spectra of all solid dispersion systems showed disappearance of some peaks of gliclazide as well as shifting of some peaks to lower wavenumber.

The binary dispersion systems GLIKN1 and GLISD2 (Fig. 1 F, G) showed almost all peaks with low peak intensity as compared with pure and amorphous form of drug. Both GLIKN1 and GLISD2 showed broadening of amide stretching vibration (N–H) and amide carbonyl stretching vibration (C=O) peaks characteristic of gliclazide.

However, peaks such as C–H aromatic stretching and C–H aliphatic stretching vibrations (symmetric) completely disappeared in ternary dispersion systems (Fig. 1 H–K). This might be due to the ternary component present in the system (Aerosil®200 and Sylysia® 350) which contains silanol groups in them which have high potential to form strong hydrogen bonding with other groups of the gliclazide.

All other peaks appearing of GLI in the spectrum were having less intensity which indicates strong physical interaction between drug and polymer. However, absence of any additional peak in all dispersion systems indicated that no chemical interaction occurred between GLI, polymer PVP K30, as well as ternary components (29).

Thermal Analysis

Differential scanning calorimetry, a powerful tool, was employed to observe thermal behavior of amorphous gliclazide and its corresponding solid dispersion systems initially as well as during aging (Fig. 2). DSC thermogram of pure gliclazide showed a sharp melting endotherm at 171.5°C with an enthalpy of fusion (ΔH) 540.39 J/g (Fig. 2 A) indicating its crystalline nature. PVP K30 exhibited a broad endotherm at 83.79°C as a result of loss of moisture. The absence of melting endotherm and appearance of T_g at 175°C clearly revealed the amorphous nature of PVP K30 (http://scholar.lib.vt.edu/theses/available/etd-42198-113329/unrestricted/ch3-5.pdf).

The thermograms of amorphous gliclazide and its corresponding kneaded and spray-dried binary systems with PVP did not produce melting transitions; instead, a T_g appeared at 67.52°C and 126°C for amorphous gliclazide and binary kneaded and spray-dried dispersions, respectively (Fig. 2 B–D). In all cases, the glass transitions were assigned to the midpoint temperature of the range of temperature during the transition (30). The kneaded ternary dispersions incorporated with Aerosil® 200 and/or Sylysia® 350 also did not show melting transition. However, it could be possible to assign T_g around 127°C in both the thermograms (Fig. 2 E, G). The thermograms of spray-dried ternary dispersions with Aerosil® 200 and/or Sylysia® 350 showed the absence of melting transitions (Fig. 2 F, H). However, they should indicate T_g. Interestingly, no such transitions were detected in both the cases. This could be possibly attributable to the

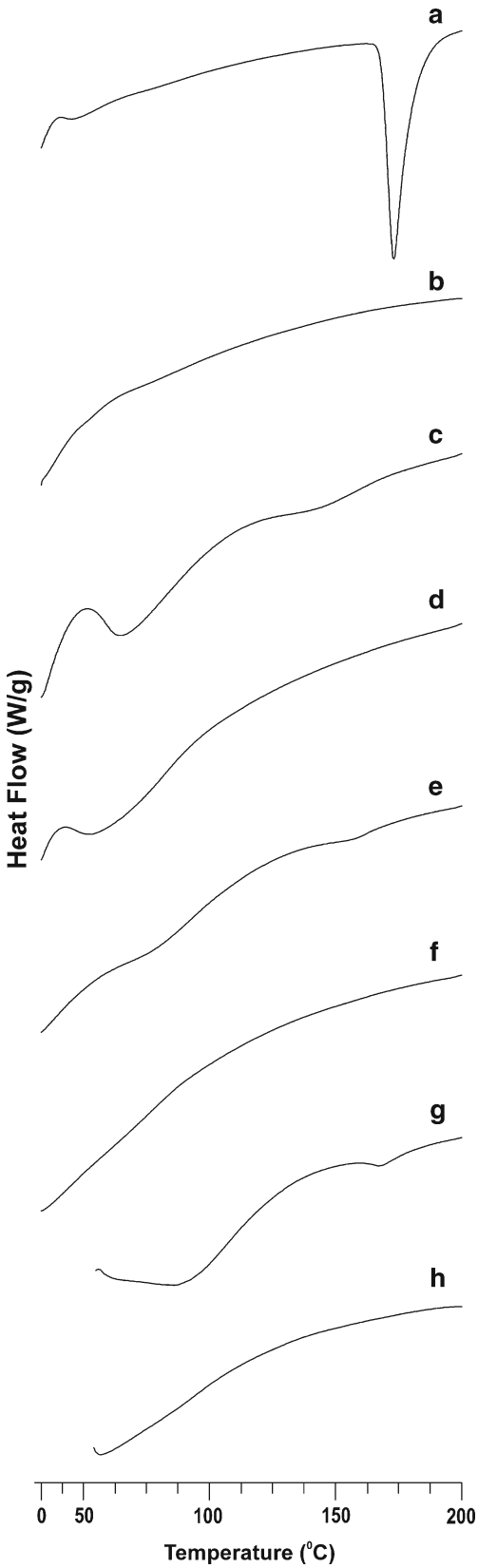


Fig. 2. Initial DSC spectra of all systems. *A* GLIC, *B* GLIA, *C* GLIKN1, *D* GLISD2, *E* GLIAKN3, *F* GLIASD4, *G* GLISKN5, and *H* GLISSD6

masking of the thermodynamic transitions by Aerosil® 200 and/or Sylysia® 350 in spray-dried ternary systems (12).

The absence of thermodynamic transitions by Aerosil® 200 and/or Sylysia® 350 could be confirmed from the DSC thermograms of binary systems where the elevation of T_g of gliclazide due to formation of solid dispersion was detected. The observed T_g value was also compared with that of the predicted value obtained by fitting the data in Couchman–Karasz (C–K) Eq. 1 (31).

$$T_g = \frac{w_1\ T_{g1} + k\ w_2\ T_{g2}}{w_1 + k\ w_2} \quad (1)$$

where w_1 and w_2 are weight fractions of each component and T_{g1} and T_{g2} are their corresponding T_g values. K in C–K equation; a thermodynamic model is defined as follows:

$$K = \frac{\Delta C_{p2}}{\Delta C_{p1}} \quad (2)$$

where ΔC_p is the difference in the heat capacity at T_g.

The observed T_g of SDPVP (126°C) was found to be nearer to the predicted T_g of SDPVP (121°C). Further, there was only a single T_g observed throughout the temperature range of DSC run. This suggested perfect miscibility of drug and polymer indicating formation of uniform SDs.

X-ray Powder Diffraction Studies

The XRPD spectra of GLIC, GLIA, PVP K30, and all SD systems are shown in Fig. 3. The XRPD spectra of pure gliclazide clearly suggest the crystalline nature of the drug showing prominent diffraction peaks in the range of 10–30° (2θ) values (Fig. 3 A). The XRPD spectra of PVP K30 show the amorphous nature clearly having a halo, characteristic to amorphous form (Fig. 3 B).

The GLIA exhibited halo pattern in XRPD which was characteristic to its glassy state as confirmed from the DSC thermogram (Fig. 2 B). The little peaks which were visible inidated the transformation of some crystalline traces to amorphous form (Fig. 3 B). In case of SD systems (binary and ternary), all XRPD spectra showed the amorphous nature as there were no diffraction peaks observed for any SD; instead, a halo pattern attributed to the amorphous form was observed (12,15,32) (Fig. 3 D–I).

The XRPD spectra of spray-dried systems (both binary and ternary) were very fine indicating the effectiveness of the method. These results obtained were also supported by DSC analysis as there was no melting endotherm observed while T_g was observed which is characteristic to an amorphous form.

Drug Content

Percentage drug content of all formulations was found to be in the range of 96.7±1.2% (n=3 for each formulation).

Dissolution Rate Studies

Dissolution profiles of GLIC, GLIA, and all solid dispersion systems are presented in Fig. 4. The release profiles were expressed as percent milligrams released *vs.* time (minutes).

It was observed that all formulations have significantly improved dissolution rate as compared to crystalline drug as well as amorphous state (p<0.001). The % Drug dissolved at 2

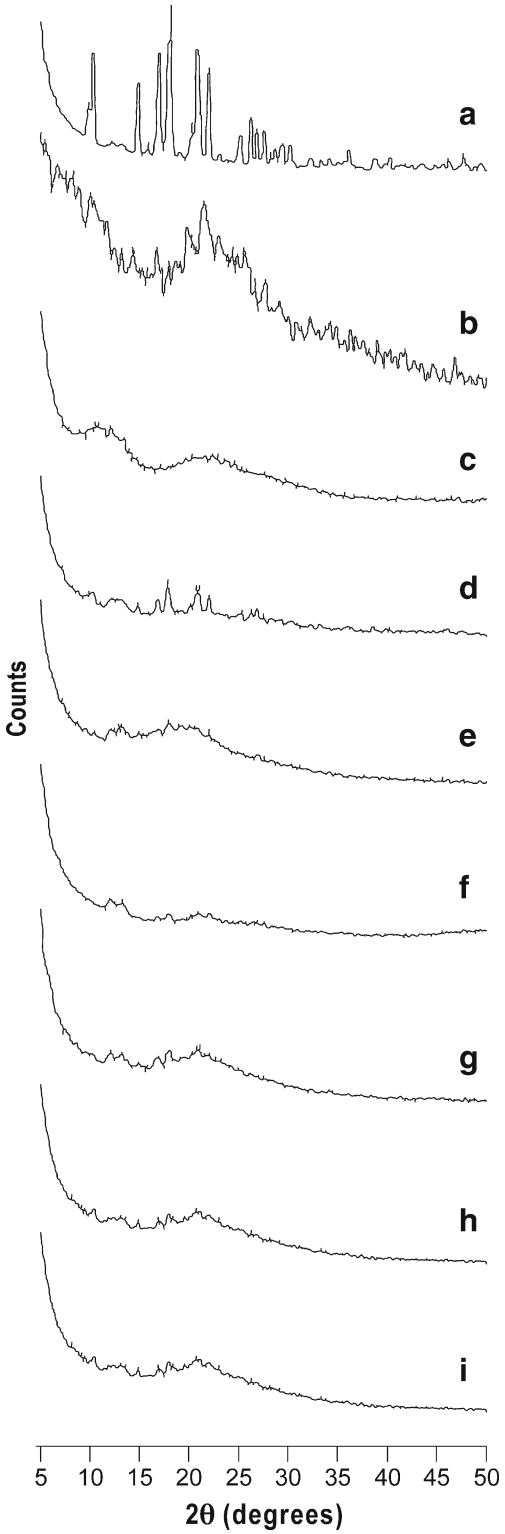


Fig. 3. Initial XRPD spectra of all systems. *A* GLIC, *B* GLIA, *C* PVP K30, *D* GLIKN1, *E* GLISD2, *F* GLIAKN3, *G* GLIASD4, *H* GLISKN5, and *I* GLISSD6

and 5 min (DP_2 and DP_5) and dissolution efficiency (DE_2) values of pure drug and all formulations are shown in Table II. The statistical analysis of DE values has shown significant improvement in dissolution profile of GLI at 2mins (DE_2) ($p<0.001$).

The crystalline GLI was characterized by around 100% drug release within 90 min in phosphate buffer (pH 6.8). Unexpectedly, amorphous GLI was found to be unable to improve the dissolution characteristics over pure drug. It showed only 23% drug release within 90 min. This surprising result might be because of the formation of a cohesive supercooled liquid state below their T_g value through the equilibrium and the material experiences gradual loss in energy (enthalpy relaxation). So, attainment of 100% crystallinity would require longer time. This could be the possible reason for poor dissolution characteristics of an amorphous state (12,33,34). In case of binary systems, 100% release of drug was obtained at 15 and 10 min for kneaded (GLIKN1) and spray-dried systems (GLISD2), respectively.

In case of ternary systems with Aerosil®200, 100% drug release occurred at 5 and 2 min for kneaded (GLIAKN3) and spray-dried SDs (GLIASD4), respectively. In case of ternary systems with Sylysia® 350, 100% drug release was obtained at 2 min for both kneaded (GLISKN5) and spray-dried SDs (GLISSD6). Within ternary systems, dispersions containing Sylysia® 350 as ternary component (GLISKN5 and GLISSD6) showed slight better results over systems containing Aerosil® 200 (GLIAKN3 and GLIASD4), but no significant difference was observed within them when compared statistically ($p>0.05$).

All the solid dispersion systems were very effective over crystalline as well as amorphous state in improving rate and extent of dissolution. Within these systems, ternary systems were much better in performance over binary systems. Within two methods employed to prepare the dispersions, i.e., kneading and spray drying, spray-dried systems showed faster dissolution than the kneaded product.

The better dissolution profile of binary solid dispersion systems over pure drug could be due to an improved wettability of the drug particles (15,35,36), significant reduction in particle size during formation of SD, as well as naturally higher rate of dissolution from the hydrophilic carrier (PVP K30) as the presence of hydrophilic carrier prevents aggregation and agglomeration of individual drug particles exhibiting a high solid–liquid surface tension and also creates a microenvironment in which the drug solubility is high (15,20) and stabilization of an amorphous state.

In case of ternary dispersion systems along with the abovementioned reasons, use of a ternary component (either Aerosil®200 or Sylysia® 350) could be one of the major reason in dramatic improvement in rate and extent of dissolution as both are hydrophilic in nature. The slightly better performance observed of Sylysia® 350 might be because of its porous nature (18,19). The silica particles (Aerosil®200 and Sylysia® 350) are fine silicon dioxide particles characterized by the large specific surface area with a high affinity with water (hydrophilic) molecules. The silanol groups (–Si–OH) on their surfaces impart good aqueous wettability and dispersibility and can interact with the adsorbate through hydrogen bond formation. In addition to that, drugs adsorbed onto high-surface area carriers are known to assume an amorphous state, and the activity in amorphous state is higher than that in crystalline state leading to improved dissolution (37,38). The better dissolution performance of spray-dried systems over kneaded systems might be due to the larger reduction in particle size during formation of SD.

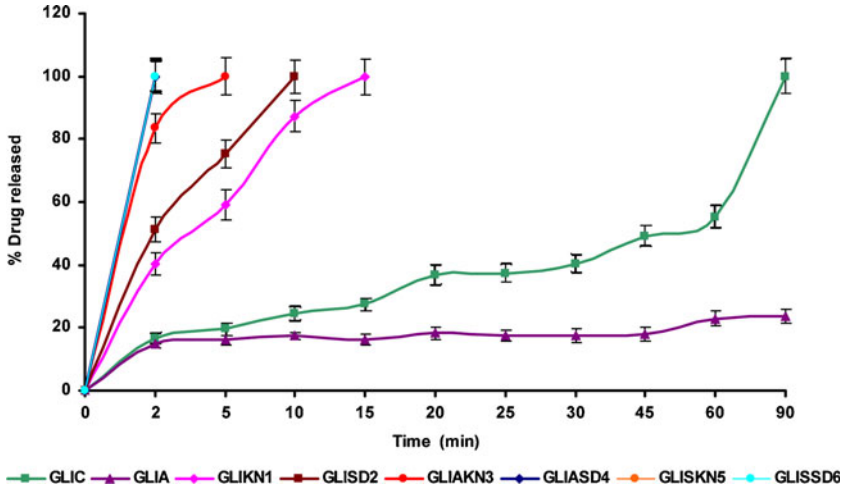


Fig. 4. Initial dissolution profile of all systems including pure drug in phosphate buffer (pH 6.8) at 37±0.5°C

Stability Studies

Thermal Analysis

It is well understood that amorphous drugs formulated in a solid dispersion tend to undergo devitrification process upon storage at high temperature and humidity. Therefore, effect of aging on performance of amorphous gliclazide was investigated by performing accelerated stability studies up to 3 months as per ICH guidelines (40°C/75% RH) (39).

Based on the initial characterization, it could be seen that SDs were more beneficial as compared to pure amorphous gliclazide in terms of physicochemical properties. Therefore, SDs were also subjected further for accelerated stability studies. It has been well documented that the temperature during storage influences the rate of devitrification process (amorphous to crystalline form) of glassy material (15). Storage conditions above T_g permits a relatively rapid conversion to the crystalline form due to the high mobility of the amorphous form above their T_g (40). The humidity during storage is another important factor affecting the hygroscopic nature of hydrophilic polymers. The plasticizing effect of absorbed moisture can reduce the T_g of amorphous substance and lead to further instability (41,42). Thus, appropriate storage conditions (aging) are necessary to be selected during accelerated stability studies.

Table II. The Initial Dissolution Data of Pure GLI, Amorphous GLI, and Its All SD Systems

Sr. No.	System	DP_2 (%)[a]	DP_5 (%)[a]	DE_2 (%)[a]
1	GLIC	16.7±1.7	19.56±1.9	8.35±0.85
2	GLIA	15.1±1.6	16.1±1.5	7.45±0.89*
3	GLIKN1	40.23±3.4	59.02±4.7	20.11±1.7**
4	GLISD2	51.1±3.9	75.29±4.5	25.53±1.95**
5	GLIAKN3	83.46±4.7	100±5.8	41.73±2.37**
6	GLIASD4	100±4.8	–	50±2.35**
7	GLISKN5	100±5.4	–	50±2.7**
8	GLISSD6	100±4.9	–	50±2.45**

DP_2 drug dissolved at 2 min (percent), DP_5 drug dissolved at 5 min (percent), DE_2 dissolution efficiency at 2 min (percent)
*$p>0.05$, no significant difference compared to GLIC; **$p<0.001$, significant difference compared to GLIC and GLIA
[a] Mean±SD ($n=3$)

DSC thermograms of the samples subjected to accelerated stability testing are shown in Fig. 5 for 1 and 3 months, respectively. Amorphous gliclazide on aging after a period of 1 month clearly displayed a T_g around 67–70°C along with weekly intensified broad melting endotherm at 156.6°C (ΔH= 267.12 J/g) indicating partial devitrification of amorphous gliclazide and incidence of crystallinity (Fig. 5 A). The effect has been observed to be more pronounced after 3 months where a small T_g around 55–57°C (Fig. 5 H) was detected. The melting endotherm at 155.6°C (ΔH=211.35 J/g) was more intensified indicating transformation of amorphous to crystalline form of drug. The lowering of T_g was clearly due to absorption of moisture by amorphous gliclazide during aging.

All binary systems (kneaded and spray dried) aged at 1 and 3 months did not show melting transitions (no incidence of crystallinity) in their thermograms indicating the presence of amorphous state of gliclazide in dispersions (Fig. 5 B, C, I, J). A broad endotherm in the range of 126.6–131.2°C was observed in all binary systems which could be attributable to the loss of moisture by the polymer during storage at higher relative humidity (15). Alternatively, the appearance of broad endotherm in the range of 126.6–131.2°C associated with T_g could be due to enthalpy recovery of SD indicating structural relaxation of amorphous form toward the supercooled liquid region (15). The structural relaxation of amorphous SD was greater in case of kneaded binary SD in comparison to all other binary systems aged up to 3 months. The kneaded ternary systems incorporated with Aerosil® 200 and/or Sylysia® 350 aged up to 1 and 3 months exhibited some incidences of crystallinity in the form of a very small melting endotherm in the range of 157.5–162.5°C. Unlike binary systems, spray-dried ternary systems experienced no such incidences of crystallinity or relaxation endotherm associated with T_g in their DSC thermograms (Fig. 5 D–G, K–N) indicating greater stabilization of amorphous state of gliclazide in these ternary systems.

It is well-known that the stability of amorphous solids can be improved by storage at well below the glass transition temperature (T_g). However, amorphous substances aging at

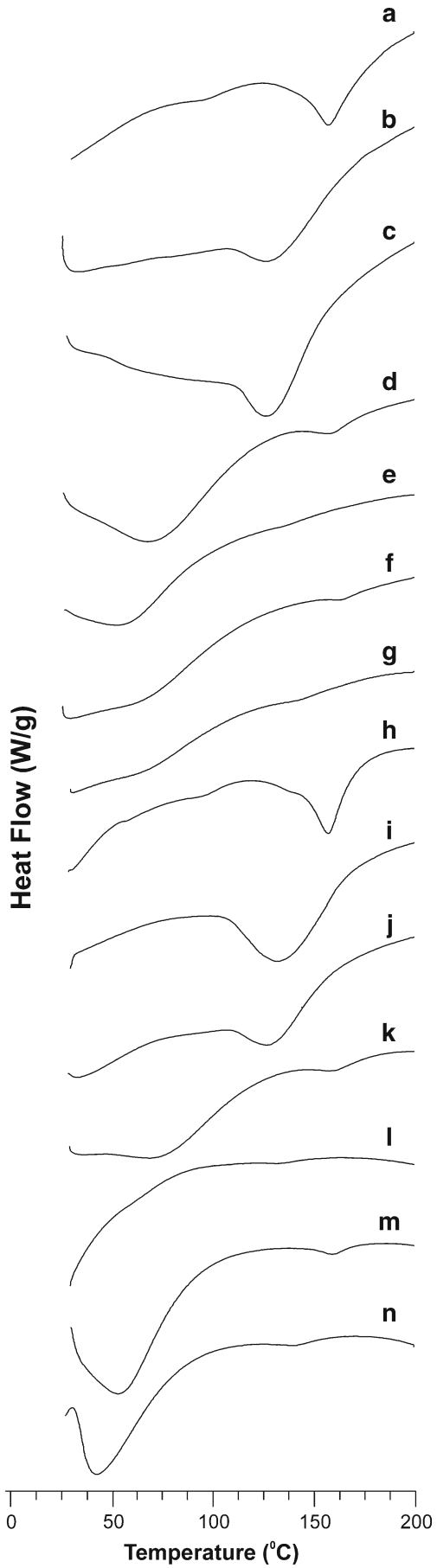


Fig. 5. DSC thermograms during stability studies (after 1 and 3 months). *A–G* DSC spectra after 1 month. *H–N* DSC spectra after 3 months. *A* GLIA, *B* GLIKN1, *C* GLISD2, *D* GLIAKN3, *E* GLIASD4, *F* GLISKN5, *G* GLISSD6, *H* GLIA, *I* GLIKN1, *J* GLISD2, *K* GLIAKN3, *GLIASD4, M GLISKN5, and N GLISSD6*

a temperature below T_g may show crystallization of amorphous state via the equilibrium supercooled liquid state. The material experiences progressive loss in energy in the form of enthalpy due to the effect of molecular motions occurring at prevailing conditions, which brings it toward a more stable crystalline state. This loss of enthalpy is recovered by the material at T_g during its heating run in DSC and can be measured with time (12,15,32,33) as an enthalpy relaxation process. It is well documented that both the amorphous drug alone and its corresponding SDs require approximately the same total enthalpy change to reach the supercooled equilibrium state. However, the rate at which the samples approach the relaxed state is significantly lowered for the SDs, which contains high molecular weight polymers (15,43). Based on the comparative assessment of stabilization potential of various binary and ternary dispersion systems including pure amorphous gliclazide, it could be possible to report that the amorphous gliclazide aged at 40°C/75% RH up to 3 months showed incidences of crystallinity with decrease in T_g. On the contrary, all binary dispersion systems with PVP aged at identical conditions exhibited no incidences of crystallinity; instead, the size of the endotherm associated with T_g was increased indicating an increase in enthalpy recovery and structural relaxation of amorphous form toward the supercooled liquid region. All ternary dispersion systems with PVP and adsorbent aged at 40°C/75% RH up to 3 months exhibited neither any incidences of crystallinity nor any incidence of relaxation endotherm associated with T_g reflecting enthalpy changes for ternary systems were considerably less than amorphous gliclazide alone. The excellent stabilization of amorphous state of gliclazide up to 3 months was achieved in spray-dried ternary systems of Aerosil® 200 among all the formulations ever studied which was also reflected in dissolution experiments.

Thus, the improved stability of amorphous gliclazide in spray-dried ternary SDs could be explained on the basis of combination of several effects: (a) elevation of T_g (126°C), which was well above the storage temperature; (b) hydrogen bonding between the drug and the polymer and possibly also between drug and silanol groups of Aerosil® 200 and/or Sylysia® 350 (data not shown); (c) antiplasticizing effect of the polymer which was further augmented by the presence of an adsorbent; (d) entrapment of the drug particles in the polymer matrix during solvent evaporation. The rapid evaporation of solvent during formation of SD resulted in increased viscosity of the system leading to a decrease in drug mobility; (e) freezing of drug particles in the polymer matrix as a result of complete solvent evaporation; (f) inhibition of crystal lattice formation as a result of existence of drug particles as a separate entity in random fashion comparable to the liquid state, which is characteristic of amorphous form (44); and (g) adsorption on the surface of amorphous Aerosil® 200 and/or Sylysia® 350. Their hydrophilic nature enables preferential

adsorption of moisture on its surface thereby acting as a buffer for SD system of drug and polymer (12).

XRPD Studies

For all the systems subjected for accelerated stability study (40°C/75% RH), XRPD analysis was done after 1 and 3 months (Fig. 6). After 1 month, the GLIA showed some incidences of crystallinity showing peaks at 10.5°, 17.9°, 18.2°, and 20.8° (2θ) values which were prominent but were having less intensity as compared to crystalline form (Fig. 6 A). After 3 months, the significant devitrification of the drug has been observed by appearance of prominent peaks having higher intensities which confirms the deterioration of an amorphous state of gliclazide (Fig. 6 H). These results were also supported by DSC study in which a small endotherm was observed at its melting temperature.

In case of binary systems, after 1 month, slight incidences in crystallinity were observed for both kneaded and spray-dried systems (Fig. 6 B, C) while after 3 months, marked crystalline character was observed showing characteristic peaks of pure gliclazide (Fig. 6 I, J). In case of ternary systems, all were quiet stable after 1 month showing a halo pattern. However, some crystalline traces were evident as a result of aging of the samples up to 1 month (Fig. 6 D–G).

After 3 months, some incidences of slight crystallinity were observed for ternary kneading system with Aerosil® 200 and both SDs with Sylysia®, but the rate of devitrification process was very less as no incidence of melting endotherm has been observed in DSC (Fig. 6 K, M, N).

The spray-dried ternary system with Aerosil®200 did not show any incidences of crystallinity, and the halo pattern of amorphous form was observed even after 3 months. This obviously suggests the excellent stabilization of glassy state in this system (Fig. 6 L). The significant devitrification of the amorphous drug (GLIA) during stability study was because of the higher humidity during accelerated stability studies which acts as a plasticizer and destabilizes the system (13,15).

In case of binary SDs, rate of devitrification process was less than drug as PVP K30 acts as an antiplasticizer (6), but the system failed to protect the amorphous state. This might be because of lower concentration used of polymer, more pronounced effect of plasticizer (humidity) (15).

In case of ternary systems, use of an adsorbent augmented the antiplasticizing property of PVP K30 by protecting the system from moisture (12). All systems were purely in amorphous state after 1 month. After 3 months, slight incidences of crystallinity were observed but were not significant which were supported by an absence of melting endotherms in DSC thermograms.

The spray-dried ternary system with Aerosil®200 has been well stabilized after 3 months also. The successful stabilization of the amorphous state in ternary systems might be

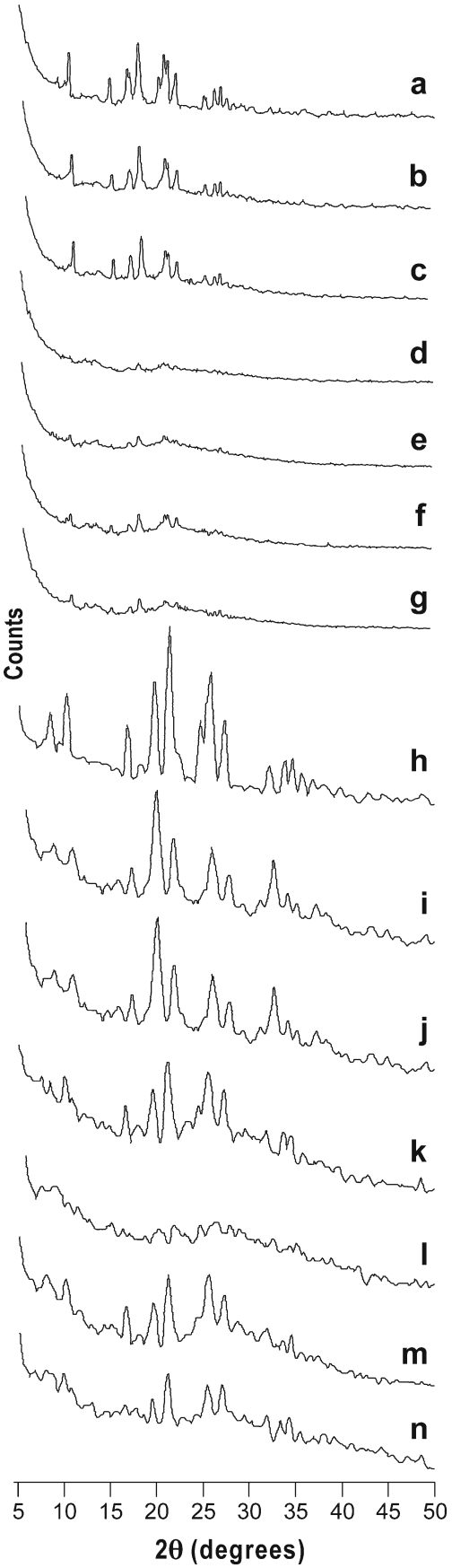


Fig. 6. XRPD spectra during stability studies (after 1 and 3 months). *A–G* XRPD spectra after 1 month. *H–N* XRPD spectra after 3 months. *A* GLIA, *B* GLIKN1, *C* GLISD2, *D* GLIAKN3, *E* GLIASD4, *F* GLISKN5, *GLISSD6, H GLIA, I GLIKN1, J GLISD2, K GLIAKN3, L GLIASD4, M GLISKN5, and N GLISSD6*

attributed to the antiplasticizing effect of the polymer which was further augmented by the presence of an adsorbent.

Dissolution Rate Studies

Dissolution profiles of GLIC, GLIA, and all solid dispersion systems are presented in the Fig. 7a, b. The release profiles were expressed as percent milligrams released *vs.* time (minutes). During stability studies, dissolution performance of all the systems was monitored after 1 and 3 months.

It was observed that all formulations have significantly retained dissolution rate as compared to amorphous state ($p<0.001$). The % Drug dissolved at 2 and 5 min (DP_2 and DP_5) and dissolution efficiency (DE_2) values of pure drug and all formulations are shown in Tables III and IV. The statistical analysis of DE values has shown significant improvement in dissolution profile of gliclazide at 2 min (DE_2) ($p<0.001$) after 1 and 3 months as well during accelerated stability studies.

After 3 and 1 months, the dissolution of GLIA was about 27.4% and 51% at 90 min, respectively. This slight increase in dissolution (not significant) might be because of conversion of an amorphous state into crystalline one during accelerated stability testing. This reason could also be supported by DSC and XRPD pattern of GLIA after 1 month. The DSC thermogram showed small endotherm at 156.61°C and in XRPD pattern peaks were observed. But there was no complete conversion of drug to crystalline form (Figs. 5 A and 6 A). This could be the reason that dissolution profile of GLIA after 1 and 3 months was intermediate between amorphous and crystalline state. This result clearly indicated the necessity of stabilization of glassy state.

Among the binary dispersions, kneaded SD (GLIKN1) showed 100% drug release at 45 min after 1 month while it failed to give 100% release even at 90 min after 3 months. The release was around 58% only. The spray-dried SD (GLISD2) showed around 100% release at 15 min after 1 month while same value shifted to 30 min after 3 months.

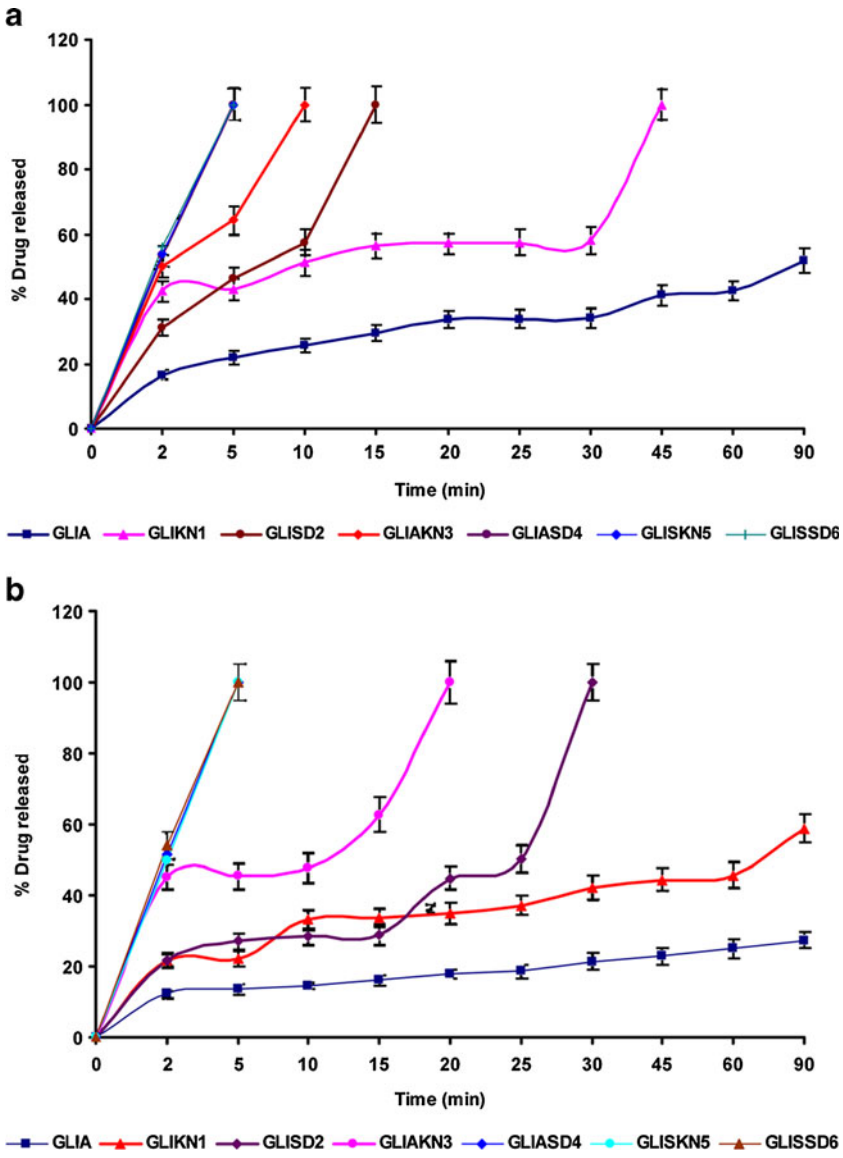


Fig. 7. **a** Drug release profile of all systems after 1 month in phosphate buffer (pH 6.8) at 37±0.5°C. **b** Drug release profile after 3 months in phosphate buffer (pH 6.8) at 37±0.5°C

Table III. The Dissolution Data of Amorphous GLI and its SD Systems after 1 Month in Phosphate Buffer (pH 6.8) at 37±0.5°C

Sr. No.	System	DP_2 (%)[a]	DP_5 (%)[a]	DE_2 (%)[a]
1	GLIA	16.63±1.4	22.08±2.1	8.32±0.7
2	GLIKN1	42.35±3.1	43.11±3.4	21.18±1.55*
3	GLISD2	31.24±2.4	46.11±3.4	15.62±1.2*
4	GLIAKN3	50.14±3.2	64.39±4.4	25.07±1.6*
5	GLIASD4	53.3±33.61	100±4.9	26.65±1.55*,**
6	GLISKN5	54.1±3.5	100±5.7	27.03±1.75*
7	GLISSD6	55.9±3.6	100±5.3	27.96±1.78*,**

DP_2 drug dissolved at 2 min (percent), DP_5 drug dissolved at 5 min (percent), DE_2 dissolution efficiency at 2 min (percent)
*$p<0.001$, significant difference compared to GLIA; **$p<0.05$, significant difference compared to GLIAKN3
[a] Mean±SD ($n=3$)

Among ternary systems with Aerosil®200, after 1 month, kneaded SD (GLIAKN3) showed 100% drug release at 10 min while spray-dried SD (GLIASD4) showed same release at 5 min. But after 3 months, kneaded SD (GLIAKN3) showed around 100% drug release at 20 min while spray-dried system (GLIASD4) showed same release at 5 min that was same as that of 1 month. Between the two dispersions with Sylysia® 350, no difference in dissolution profile was found as after 1 as well as 3 months the drug release obtained was 100% at 5 min for both kneaded SD (GLISKN5) and spray-dried SD (GLISSD6).

From obtained results, it can be stated that the binary systems were quite stable up to 1 month especially spray-dried system but crystallization process had been initiated at that time. This can also be supported by results obtained from DSC and XRPD study, while after 3 months, the kneaded system failed to give 100% drug release and dissolution of spray-dried SD has also lowered.

The poor dissolution rate of binary systems after accelerated stability studies might be because of the temperature and humidity conditions used during study. The temperature during storage also influences the rate of devitrification process (amorphous to crystalline form) of glassy material (15). The greater amount of moisture content may have the plasticizing effect on the system so as to reduce its performance (13,15). The moisture uptake by the system will depress the glass transition temperature of PVP and exposure to elevated temperature and humidity may result in a change in the PVP from the glassy to rubbery state. This conversion produces a change in the dissolution profile (45). Between the two binary systems, spray-dried dispersion showed better drug release profile over dispersion by kneading method. This indicates that better stability can be achieved in case of spray-drying method. The results obtained for binary systems indicate that there is necessity of protection of the amorphous state from the plasticizing effect of moisture which aids the devitrification process. On the other hand, all the ternary dispersion systems proved significantly better in dissolution profile over binary systems and amorphous form.

Table IV. The Dissolution Data of Amorphous GLI and its SD Systems after 3 Months in Phosphate Buffer (pH 6.8) at 37±0.5°C

Sr. No.	System	DP_2 (%)[a]	DP_5 (%)[a]	DE_2 (%)[a]
1	GLIA	12.17±1.1	13.42±1.3	6.08±0.6
2	GLIKN1	21.54±1.9	22.08±2.1	10.77±0.95*
3	GLISD2	21.81±1.8	27.1±2.3	10.9±0.97*
4	GLIAKN3	45.2±3.4	45.35±3.7	22.51±1.7*
5	GLIASD4	51.28±3.7	100.6±6.1	25.64±1.85*,**
6	GLISKN5	49.6±3.5	100±5.7	24.8±1.75*
7	GLISSD6	54.01±3.9	100±5.1	27±1.9*

DP_2 drug dissolved at 2 min (percent), DP_5 drug dissolved at 5 min (percent), DE_2 dissolution efficiency at 2 min (percent)
*$p<0.001$, significant difference compared to GLIA; **$p<0.01$, significant difference compared to GLIAKN3
[a] Mean±SD ($n=3$)

The reason behind these results lies in the use of a ternary component (either Aerosil® 200 or Sylysia® 350) which is used as an adsorbent (moisture protectant) in the present study. It causes protection of the product from the effect of moisture during aging thus augmenting the antiplasticizing effect of PVP. All the ternary systems were almost equally effective in improvement in dissolution rate except kneaded system with Aerosil®200 as no significant difference was found between them when compared statistically. This can be attributed to the porous nature of Sylysia® over Aerosil®200, and spray-drying technique was found effective over kneading method.

CONCLUSION

The present investigation demonstrated successful physical transformation of crystalline GLI to its intact glassy (amorphous) state which could be one of the approaches for improvement of physicochemical and biopharmaceutical characteristics of poorly water-soluble drugs. Interestingly, amorphous GLI could not offer any advantage over crystalline GLI in terms of physicochemical performance. This could be due to formation of a cohesive equilibrium supercooled liquid state below its T_g suggesting the need for stabilization of amorphous GLI. Therefore, stabilization of an amorphous GLI was attempted via formation of binary and ternary SDs systems and achieved up to satisfactory level. The excellent dissolution rates obtained for ternary dispersions initially and even after 3 months were attributed to the elevation of T_g due to antiplasticizing effect of PVP K30 and adsorbent used which could also be supported by results obtained from thermal analysis and XRPD studies. However, enthalpy relaxations studies are necessary in order to access the structural relaxation of amorphous GLI. Further, SDs should be examined for their biopharmaceutical performance by conducting *in vivo* studies.

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REFERENCES

1. Chauhan B, Shimpi S, Paradkar A. Preparation and characterization of etoricoxib solid dispersions using lipid carriers by spray drying technique. AAPS Pharm Sci Tech. 2005;6(3):E405–12.
2. Shimpi SL, Chauhan B, Mahadik KR, Paradkar A. Stabilization and improved *in vivo* performance of amorphous etoricoxib using Gelucire 50/13. Pharm Res. 2005;22:1727–34.
3. Chauhan B, Shimpi S, Paradkar A. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. Eur J Pharm Sci. 2005;26:219–30.
4. Shimpi S, Mahadik K, Takada K, Paradkar A. Application of polyglycolized glycerides in protection of amorphous form of etoricoxib during compression. Chem Pharm Bull. 2007;55:1448–51.
5. Paul EL, Tung HH, Milder M. Organic crystallization processes. Powder Technol. 2005;150:133–43.
6. Byrn SR, Pfeiffer RR, Stowell JG. Solid-state chemistry of drugs. West Lafayette: SSCI; 1999.
7. Brittain H, editor. Polymorphism in pharmaceutical solids, vol. 95. New York: Marcel Dekker; 1999.
8. Llinas A, Goodman JM. Polymorph control: past, present and future. Drug Discov Today. 2008;13:198–210.
9. Yadav AV, Shete AS, Dabke AP, Kulkarni PV, Sakhare SS. Co-crystals: a novel approach to modify physicochemical properties of active ingredients. Indian J Pharm Sci. 2009;71:359–70.
10. Craig DQM, Royall PG, Kett VL, Hopton ML. The relevance of the amorphous state to pharmaceutical dosage forms: glassy drugs and freeze dried systems. Int J Pharm. 1999;179:179–207.
11. Lian Y. Amorphous pharmaceutical solids: preparation, characterization and stabilization. Adv Drug Deliv Rev. 2001;48:27–42.
12. Pokharkar VB, Mandpe LP, Padamwar MN, Ambike AA, Mahadik KR, Paradkar A. Development, characterization and stabilization of amorphous form of a low Tg drug. Powder Technol. 2006;167:20–5.
13. Hancock BC, Zografi G. Characteristics and significance of the amorphous state in pharmaceutical systems. J Pharm Sci. 1997;86:1–12.
14. Paradkar AR, Chauhan B, Yamamura S, Pawar AP. Preparation and characterization of glassy celecoxib. Drug Dev Ind Pharm. 2003;29(7):739–44.
15. Ambike AA, Mahadik KR, Anant Paradkar A. Stability study of amorphous valdecoxib. Int J Pharm. 2004;282:151–62.
16. Saleki-Gerhardt A, Zografi G. Non-isothermal and isothermal crystallization of sucrose from the amorphous state. Pharm Res. 1994;11:1166–73.
17. Shamblin SL, Huang EY, Zografi G. The effects of colyophilized polymeric additives on the glass transition temperature and crystallization of amorphous sucrose. J Therm Anal. 1996;47:1567–79.
18. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of amorphous indomethacin with fine porous silica particles by using spray-drying method. Int J Pharm. 2005;293:155–64.
19. Takeuchi H, Nagira S, Yamamoto H, Kawashima Y. Solid dispersion particles of tolbutamide prepared with fine silica particles by the spray-drying method. Powder Technol. 2004;141:187–95.
20. Mooter VG, Wuyts M, Blaton N, Busson R, Grobet P, Augustijns P, Kinget R. Physical stabilization of amorphous ketoconazole in solid dispersions with polyvinylpyrrolidone K25. Eur J Pharm Sci. 2001;12:261–9.
21. Reynolds JEF, editor. Martindale: the extra pharmacopoiea, 30th ed. London: The Pharmaceutical; 1993. p. 279–80
22. Palmer KJ, Brogden RN. Gliclazide, an update of its pharmacological properties and therapeutic efficacy in NIDDM. Drugs. 1993;46:92–125.
23. Harrower AD. Comparison of efficacy, secondary failure rate and complications of sulfonylurea. J Diabetes Complicat. 1994;8:201–3.
24. Biswal S, Sahoo J, Murthy PN. Physicochemical properties of solid dispersions of gliclazide in polyvinylpyrrolidone K90. AAPS Pharm Sci Tech. 2009;10(2):329–34.
25. Ozkan Y, Atay T, Díkman N, Isimer A, Aboul-Enein YH. Improvement of water solubility and *in vitro* dissolution rate of gliclazide by complexation with β-cyclodextrin. Pharm Acta Helv. 2000;74:365–70.
26. Winters S, York P, Timmins P. Solid state examination of a gliclazide: beta-cyclodextrin complex. Eur J Pharm Sci. 1997;5:209–14.
27. Biswal S, Sahoo J, Murthy PN, Giradkar PR, Avari JG. Enhancement of dissolution rate of gliclazide using solid dispersions with polyethylene glycol 6000. AAPS Pharm Sci Tech. 2008;9(2):563–70.
28. Hong SS, Lee SH, Lee YJ, Chung SJ, Lee MH, Shim CK. Accelerated oral absorption of gliclazide in human subjects from a soft gelatin capsule containing a PEG 400 suspension of gliclazide. J Control Release. 1998;51:185–92.
29. Ford JL. The current status of solid dispersions. Pharm Acta Helv. 1986;61(69):69–88.
30. Lukas K, LeMaire PK. Differential scanning calorimetry: fundamental overview. Resonance. 2009;14(8):807–17.
31. Couchman PR, Karasz FE. A classical thermodynamic discussion on the effect of composition on glass-transition temperatures. Macromolecules. 1978;11:117–9.
32. Hilden LR, Morris KR. Physics of amorphous solids. J Pharm Sci. 2004;93(1):3–12.
33. Shamblin SL, Zografi G. Enthalpy relaxation in binary amorphous mixtures containing sucrose. Pharm Res. 1998;15 (12):1828–34.
34. Matsumoto T, Zografi G. Physical properties of solid molecular dispersions of indomethacin with poly (vinylpyrrolidone) and poly (vinylpyrrolidone-co-vinyl acetate) in relation to indomethacin crystallization. Pharm Res. 1999;16(11):1722–8.
35. Christian L, Dressman J. Improving drug solubility for oral delivery using solid dispersions. Eur J Pharm Biopharm. 2000;50:47–60. doi:10.1016/S09396411(00)00076-X.
36. Broman E, Khoo C, Taylor LS. A comparison of alternative polymer excipients and processing methods for making solid dispersions of a poorly water-soluble drug. Int J Pharm. 2001;222:139–51.
37. Miura H, Kanebako M, Shirai H, Nakao H, Inagi T, Terada K. Influence of particle design on oral absorption of poorly water-soluble drug in a silica particle-supercritical fluid system. Chem Pharm Bull. 2011;59:686–91.
38. Wang L, Cui FD, Sunada H. Preparation and evaluation of solid dispersions of nitrendipine prepared with fine silica particles using the melt-mixing method. Chem Pharm Bull. 2006;54:37–43.
39. Nair R, Gonen S, Hoag SW. Influence of polyethylene glycol and povidone on the polymorphic transformation and solubility of carbamazepine. Int J Pharm. 2002;240:11–22.
40. Hancock BC, Shamblin SL, Zografi G. Molecular mobility of amorphous pharmaceutical solids below their glass transition temperature. Pharm Res. 1995;12:799–806.
41. Shalaev EY, Zografi G. How does residual water affect the solid-state degradation of drugs in the amorphous state? J Pharm Sci. 1996;85:1137–41.
42. Schmitt E, Davis CW, Long ST. Moisture dependent crystallization of amorphous lamotrigine mesylate. J Pharm Sci. 1996;85:1215–9.
43. Shamblin SL, Taylor LS, Zografi G. Mixing behavior of colyophilized binary systems. J Pharm Sci. 1998;87:694–701.
44. Sethia S, Squillante E. Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm. 2004;272:1–10.
45. Fitzpatrick S, McCabe JF, Petts CR, Booth SW. Effect of moisture on polyvinylpyrrolidone in accelerated stability testing. Int J Pharm. 2002;246:143–51.