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Stability study of amorphous valdecoxib

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Abstract

Formulation of poorly water-soluble drugs in the most stable dosage form for oral delivery perhaps presents the greatest challenge to pharmaceutical industry. Physical transformation of drug substance into its more soluble but metastable amorphous form is one of the approaches for improving dissolution rate of such drugs. The present study utilizes technique of spray drying for preparation of solid dispersions (SDs) and includes stability study of the same. Valdecoxib (VLD), a prototype of poorly water-soluble drugs, has been the drug of choice. The hydrophilic carriers selected were polyvinylpyrrolidone K30 (PVP) and hydroxypropylcellulose (HPC). SDs and pure VLD in the form of spray dried powder (SDVLD) in comparison with pure drug and corresponding physical mixtures (PMs) were initially characterized and then subjected to stability testing at ambient temperature and relative humidity up to 3 months. During initial characterization, increase in saturation solubility and dissolution rate was observed in all samples. DSC and XRPD studies of SDVLD and SDs suggested generation of amorphous form of drug. IR spectroscopy revealed presence of hydrogen bonding in SDs. During stability testing, there was gradual decrease in saturation solubility and dissolution rate of SDs, over the period of 3 months. While, saturation solubility of SDVLD dropped drastically within 15 days and was almost comparable with pure VLD. SD PVP retained the amorphous form of drug throughout stability period, whereas SD HPC and SDVLD presented incidence of crystallinity after 1 month and 15 days, respectively. This was justified by enthalpy relaxation studies in which, amorphous VLD showed considerable relaxation of enthalpy at T_g, while it was totally suppressed in SD PVP and partly in SD HPC. The study thus definitely reveals tremendous potential of solid dispersions of valdecoxib with PVP, from stability point of view.

Keywords: Valdecoxib; Amorphous; Solid dispersion; Stability study; Enthalpy relaxation

1. Introduction

Spray drying technique often results in physical transformation of a drug substance leading to the formation of an amorphous or partially amorphous phase (Corrigan, 1995). Although amorphous phase is a high-

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energy state resulting in enhanced dissolution rate of poorly water-soluble drugs; from thermodynamical point of view, it is a metastable state and tends to revert back to the more stable crystalline state. In general, the stability of amorphous materials can be improved by storage well below the glass transition temperature (T_g) and by protection from plasticizer (e.g. water vapour), which can depress the T_g to below the storage temperature (Hancock and Zografi, 1997). An alternative strategy has been investigated whereby the material of interest is combined with an antiplasticizer (i.e. the material having higher T_g) in the form of an amorphous solid dispersion (SD) (Saleki-Gerhardt and Zografi, 1994; Shamblin et al., 1996). The combined system is expected to have a T_g that is situated somewhere between those of the individual components. The commonly used antiplasticizers are the hydrophilic organic polymers such as polyvinylpyrrolidone, polyethylene glycol and various cellulose derivatives like hydroxypropylmethylcellulose, hydroxypropylcellulose, etc. The presence of hydrophilic carrier prevents aggregation or agglomeration of individual drug particles exhibiting a high solid–liquid surface tension and also creates a microenvironment in which the drug solubility is high (Van den Mooter et al., 2001).

Since the 1960s, there have been more than 500 publications investigating various aspects of SDs, however, there are very few marketed products utilizing this technology (Serajuddin, 1999). This poor success rate has often been attributed to processing difficulties, cost of preparation and physical instability (Hancock and Zografi, 1994; Yoshioka et al., 1994; Leuner and Dressman, 2000). Also, it is often observed that the dissolution profile and mechanical strength of SDs can change over a period (Ford and Rubinstein, 1980; Dordunoo et al., 1997).

Valdecoxib (VLD) is a novel selective cyclooxygenase-2 inhibitor administered orally as an analgesic and anti-inflammatory drug. The chemical structure of VLD is shown in Fig. 1. It is a white crystalline powder, relatively insoluble in water and freely soluble in alkaline aqueous solutions (pH 12). The pK_a is around 10. Often such drugs show poor absorption and limited bioavailability. Therefore, improvements in solubility and/or dissolution rate of poorly water-soluble drugs through formation of SDs may lead to enhancement in their bioavailability (Chiou and Riegelman, 1970; Law et al., 1992; Yamamura and Rogers, 1996).

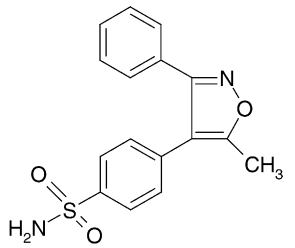

Fig. 1. Chemical structure of VLD.

In the present study, we have utilized the technique of spray drying to prepare SDs of VLD with two different hydrophilic carriers viz. polyvinylpyrrolidone K30 (PVP) and hydroxypropylcellulose-LF (HPC) (1:1, w/w). SDs and pure VLD in the form of spray dried powder (SDVLD) were characterized initially in comparison with pure drug and corresponding physical mixtures (PMs) in the same ratio and then subjected to stability testing at ambient temperature and relative humidity (30 °C/60% RH) up to 3 months. We have also performed the enthalpy relaxation studies (Shamblin and Zografi, 1998; Matsumoto and Zografi, 1999) of amorphous VLD and SDs to support the stability data.

2. Materials and methods

2.1. Materials

VLD was a generous gift from Astron Research Pvt. Ltd. (Ahmedabad, India). PVP (BASF Ludwigshafen, Germany) and HPC (Klucel-LF, Hercules Inc., Delaware, USA) were supplied by Get-Rid Pharmaceuticals Ltd. (Pune, India). All other chemicals and solvents were of reagent grade.

2.2. Preparation of SDs and PMs

Samples of VLD, as such or in combination with PVP or HPC (1:1, w/w) were dissolved in sufficient amount of methanol to obtain clear solutions. Spray drying was carried out using laboratory scale spray dryer (Jay Instruments & Systems Pvt. Ltd., Mumbai, India) under following set of conditions: inlet temperature, 90 °C; outlet temperature, 70 °C; feed rate, 4–6 ml/min; atomization air pressure, 2 kg/cm^2; aspi-

ration, −300 mm WC. PMs of drug and polymer in the same ratio of 1:1 (w/w) were prepared by mixing VLD and PVP or HPC thoroughly for 5 min in a mortar until a homogeneous mixture was obtained. All the samples were passed through fine mesh (150 μm) and stored in desiccated environment until further study.

2.3. Initial characterization

The samples of pure VLD, SDVLD, SDs and corresponding PMs were subjected to initial characterization immediately after their preparation based on following parameters.

2.3.1. Drug content

SDs equivalent to 40 mg of VLD were weighed accurately and dissolved in suitable quantity of methanol. The drug content was determined at 240 nm by UV spectrophotometer (V-530, JASCO, Japan). Analysis of data was done using PCP-Disso software (V3, Pune, India).

2.3.2. Saturation solubility

To evaluate increase in solubility of VLD after spray drying (SDVLD or SDs) or only by the presence of hydrophilic polymer (PMs), saturation solubility measurements were carried out as follows: known excess (approximately 10 mg) of VLD was added to 10 ml of phosphate buffer (pH 7.4). Samples were rotated at 20 rpm in a water bath (37 °C) for 48 h. The samples were then filtered, suitably diluted and analyzed by UV spectrophotometer at 240 nm.

2.3.3. Dissolution rate

The dissolution studies were performed using USP 24 type II dissolution test apparatus (Electrolab TDT-06P, India). The samples equivalent to 40 mg VLD were placed in dissolution vessel containing 900 ml phosphate buffer (pH 7.4) maintained at 37 ± 0.5 °C and stirred at 100 rpm. Samples were collected periodically and replaced with a fresh dissolution medium. After filtration through Whatman filter paper no. 41, concentration of VLD was determined spectrophotometrically at 240 nm. Data was analyzed by PCP-Disso software.

2.3.4. Scanning electron microscopy (SEM)

Samples were mounted on a double faced adhesive tape and sputtered with thin gold–palladium layer by sputter coater unit (VG-Microtech, UK) and surface topography was analyzed with a Cambridge Stereoscan S120 scanning electron microscope (Cambridge, UK) operated at an acceleration voltage of 10 kV.

2.3.5. Differential scanning calorimetry (DSC)

DSC studies were carried out using Mettler-Toledo DSC 821^e instrument equipped with an intracooler (Mettler-Toledo, Switzerland). Indium/zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in aluminum pans and heated at a constant rate of 20 °C/min over a temperature range of 25–175 °C. Inert atmosphere was maintained by purging nitrogen gas at flow rate of 50 ml/min.

2.3.6. X-ray powder diffraction (XRPD)

The XRPD patterns were recorded on X-ray diffractometer (PW 1729, Philips, The Netherlands). The samples were irradiated with monochromatized Cu Kα radiation (1.542 Å) and analyzed between 2 and 50° (2θ). The voltage and current were used 30 kV and 30 mA, respectively. The range and the chart speed were 5×10^3 CPS and 10 mm/° (2θ), respectively.

2.3.7. Infrared (IR) spectroscopy

IR spectroscopy was performed on Fourier-transformed infrared spectrophotometer (V-5300, JASCO). The pellets of drug and KBr were prepared on KBr-press (Spectra Lab., India). The spectra were scanned over wave number range of 4000–400 cm^{-1}.

2.4. Stability study

The stability of SDVLD and SDs was monitored up to 3 months at ambient temperature and relative humidity (30 °C/60% RH). Periodically (initial, 7 and 15 days for SDVLD; initial, 1 and 3 months for SDs) samples were removed and characterized by saturation solubility and dissolution rate measurements along with presence of crystallinity by DSC and XRPD studies.

2.5. Enthalpy relaxation study

Pure VLD and its SDs were subjected to enthalpy relaxation study in DSC instrument. The instrumental specifications and operational parameters were similar as stated earlier with only few modifications in the heat-

ing and cooling cycles, which were as follows: in the first cycle, samples were heated 3 °C above the melting temperature of VLD at a constant rate of 20 °C/min and maintained at that temperature for about 1 min to standardize the thermal history. The samples were then cooled immediately in DSC instrument itself up to 25 °C, at a constant rate of −20 °C/min, to generate the amorphous form. In the subsequent heating cycle, the pronounced endothermic recovery peak, located at the end of the glass transition region, was analyzed. The samples were aged at 30 °C/60% RH for specified time period (16 h) and analyzed periodically (initial, 2, 4, 8 and 16 h) for enthalpy relaxation at T_g. Each time the heating run was continued until melting temperature of VLD to confirm any incidence of crystallization.

3. 3. Results and discussion

3.1. Initial characterization

3.1.1. Drug content

The drug content in spray dried SDs was found to be 100.8 and 98.7% (w/w) for PVP and HPC, respectively. Therefore, the spray drying method used in this study appears applicable for the preparation of SDs with high content uniformity.

3.1.2. Saturation solubility and dissolution rate

Pure VLD was characterized by 16.8 μg/ml of saturation solubility and only 7% drug release within 60 min in phosphate buffer (pH 7.4). All the test samples showed increase in drug solubility (Table 1) and dissolution rate (Fig. 2) over the pure VLD in the order: SDs > SDVLD > PMs. This may be due to an improved wettability of the drug particles (Leuner and Dressman, 2000; Broman et al., 2001), significant reduction in particle size during the formation of SD or the inherently higher rate of dissolution of the soluble polymer component of SD, which would pull along the more insoluble but finely mixed drug into the dissolution medium. Among SDs, SD PVP presented highest saturation solubility (51.4 μg/ml) and better drug release profile (71% drug released in 60 min) as compared to SD HPC. This may be due to the inherent differences between the two polymers in terms of dissolution rates, hydration and possible complexation of the drug with PVP or decrease in crystallinity of the coprecipitated drug. SDs and PMs exhibited initial high drug release up to 10-min time point over SDVLD and pure VLD, probably due to the presence of hydrophilic carrier, which caused improvement in wetting and initial rapid flux of the drug particles to the dissolution medium, which got reduced at subsequent time points.

Table 1
Saturation solubility of different formulations of VLD tested in phosphate buffer (pH 7.4) at 37 °C

Type of formulation	Saturation solubility (μg/ml)[a]		
	Initial	1 Month	3 Months
Pure VLD	16.8 ± 0.4	–	–
SDVLD	38.4 ± 1.3	28.2 ± 1.9 (7 days)	22.7 ± 2.0 (15 days)
PM PVP	26.5 ± 1.1	–	–
PM HPC	17.9 ± 0.8	–	–
SD PVP	51.4 ± 1.9	43.5 ± 2.1	30.1 ± 1.6
SD HPC	46.2 ± 1.8	32.8 ± 1.6	22.6 ± 2.0

[a] Mean ± S.D., $n = 3$.

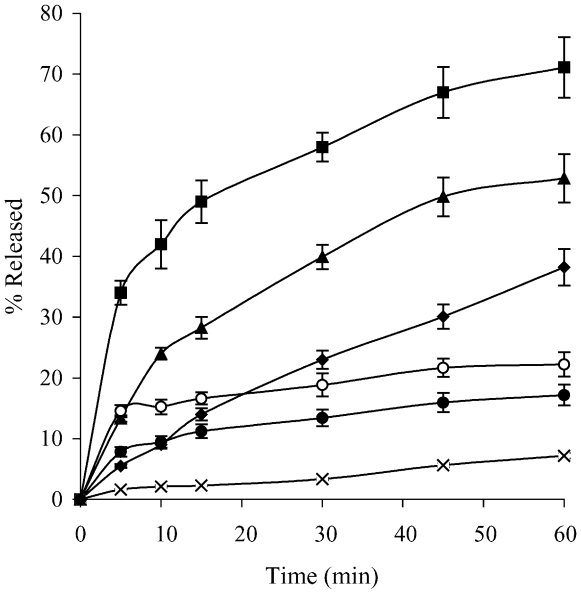

Fig. 2. Comparative dissolution profiles of different formulations of VLD. *Key*: (×) pure VLD; (♦) SDVLD; (◯) PM PVP; (●) PM HPC; (■) SD PVP; (▲) SD HPC.

3.1.3. SEM

The microphotographs of pure VLD, SDVLD and its SDs are shown in Fig. 3(a)–(d). Pure drug consisted

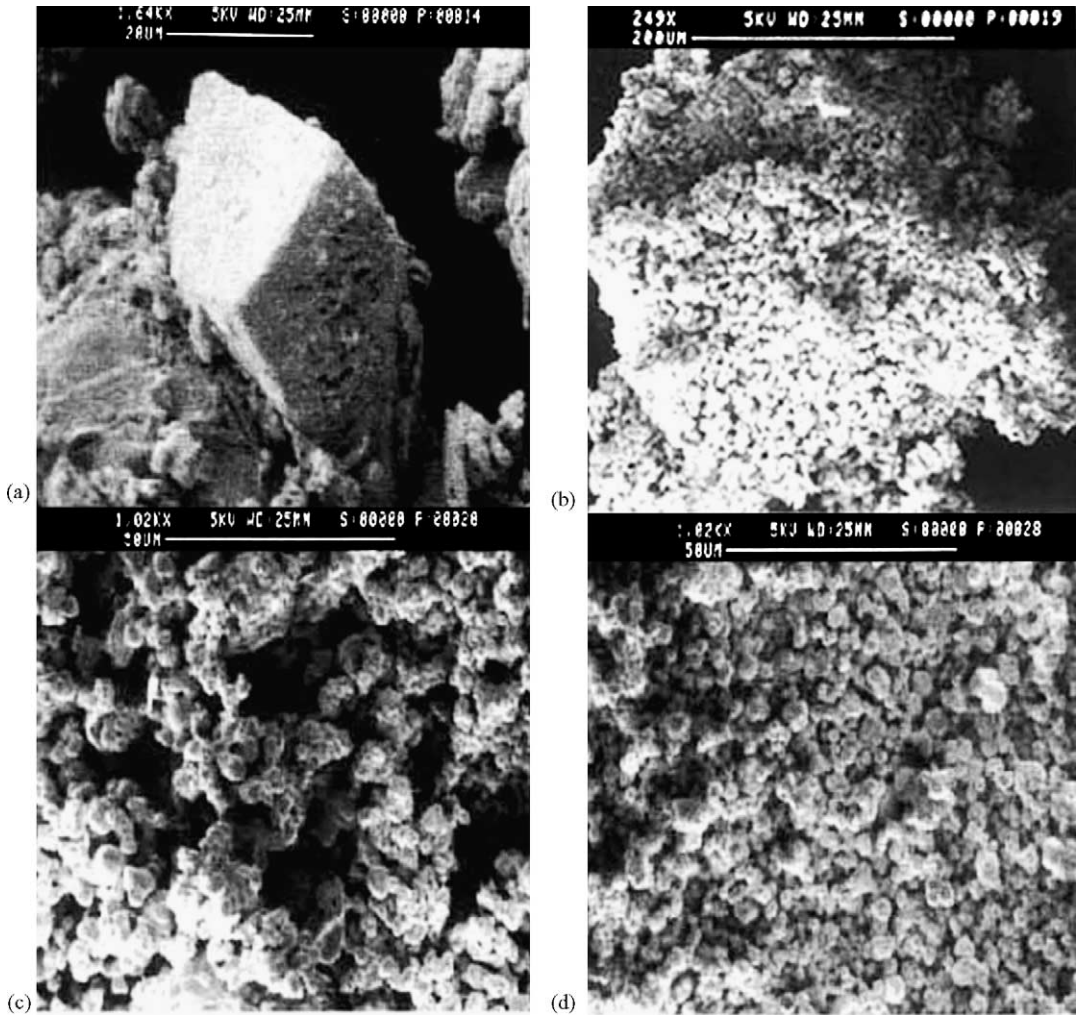

Fig. 3. Scanning electron microphotographs of different formulations of VLD. *Key*: (a) pure VLD; (b) SDVLD; (c) SD PVP; (d) SD HPC.

of some large crystals with fine particles or microparticles covering their surface, which may be generated due to micronization or any other size reduction process. SDVLD and SDs on the other hand looked like a matrix with spherical microparticles, indicating presence of amorphous form. Therefore, it is possible that the reduced particle size, increased surface area and the close contact between the hydrophilic carrier and the drug, may be responsible for the enhanced drug solubility and dissolution rate observed for the SDs (Jae-Young et al., 1999).

3.1.4. Thermal analysis and XRPD studies

Pure VLD showed a melting endotherm at 173.2 °C with enthalpy of fusion (ΔH) 96.53 J/g (Fig. 4). PMs revealed slight shift in the melting temperature of the drug along with significant decrease in ΔH (171.8 °C and 42.73 J/g for PM PVP and 172.6 °C and 26.18 J/g for PM HPC, respectively). In general, this decrease in ΔH may be due to combination of dilution of drug, miscibility of the two components on melting and interference from the water endotherm (at around 100 °C) associated with the hydrophilic carriers (Forster et al.,

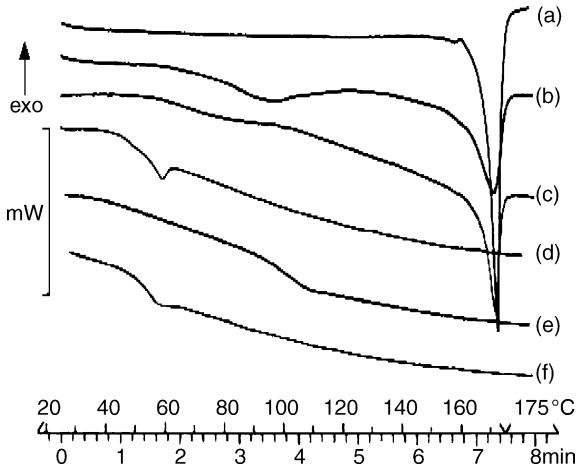

Fig. 4. Differential scanning calorimetry thermograms during initial characterization of different formulations of VLD. *Key*: (a) pure VLD; (b) PM PVP; (c) PM HPC; (d) SDVLD; (e) SD PVP; (f) SD HPC.

2001). The XRPD spectra (Fig. 5) of pure VLD and PM PVP were identical showing prominent diffraction peaks in the range of 12–36° (2θ), while in case of PM HPC there was significant decrease in intensity of some major VLD crystalline peaks (23.8, 22, 19.6, 15.6, 12° (2θ)) indicating partial loss of crystallinity. It was interesting to note that, PM HPC was superior to PM PVP in suppressing the crystallinity of VLD. This is because, ΔH for melting transition of VLD in PM HPC was considerably lower than that in PM PVP and also the XRPD profile of PM HPC revealed decrease in intensity of peaks characteristic of VLD crystallinity.

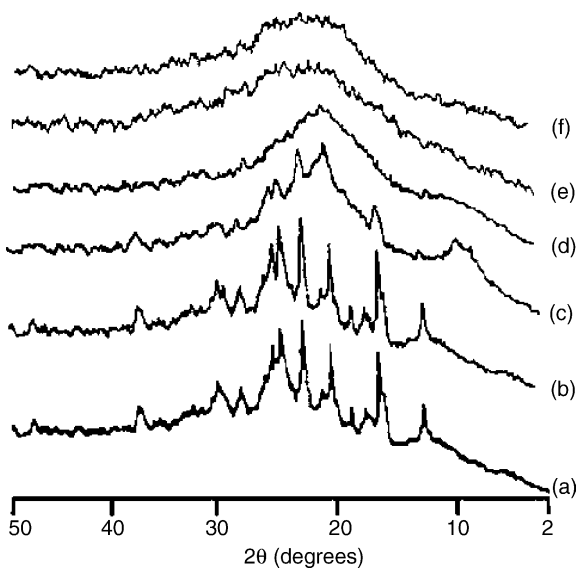

Fig. 5. X-ray powder diffraction patterns during initial characterization of different formulations of VLD. *Key*: (a) pure VLD; (b) PM PVP; (c) PM HPC; (d) SDVLD; (e) SD PVP; (f) SD HPC.

The thermograms of SDVLD and SDs did not show the melting transition; instead a T_g appeared at 54.5, 103.5 and 55 °C for SDVLD, SD PVP and SD HPC, respectively. This clearly indicated the existence of amorphous state of the drug, which was also confirmed by XRPD showing a halo, characteristic to amorphous form. Formation of SD with HPC had no significant effect on the T_g of amorphous drug, as the T_g of mixture was almost similar to the SDVLD. This could be attributed to the absence of a characteristic T_g in the thermogram of pure HPC (not shown). This was in line with previous studies (Kararli et al., 1990; Fitzpatrick et al., 2002) that the dynamic mechanical analysis (DMA) did not demonstrate a primary T_g for HPC. The polymer was shown by hot stage microscopy to melt at 190–195 °C. On the other hand, the shift in T_g of SD PVP could be related to the ability of PVP to increase the T_g of binary mixture. It is well documented that PVP can inhibit crystallization of the amorphous state of drug only if the mixing of two components occurs on a molecular level (Broman et al., 2001). Therefore, as a measure of determining goodness of mixing, the observed T_g value of SD PVP was compared with that of predicted T_g value obtained by fitting the data in Couchman–Karasz (C–K) equation (Eq. (1)) (Couchman and Karasz, 1978):

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

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 heat capacity at T_g.

The predicted T_g of SD PVP (102.4 °C) was in close agreement with the observed value (103.5 °C). Also, there was only a single T_g observed over the entire tem-

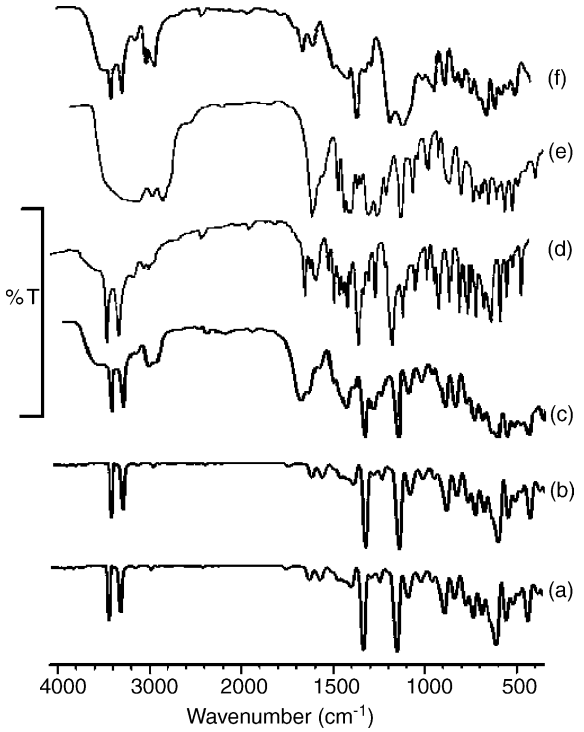

Fig. 6. Infrared spectra during initial characterization of different formulations of VLD. *Key*: (a) pure VLD; (b) SDVLD; (c) PM PVP; (d) PM HPC; (e) SD PVP; (f) SD HPC.

perature range of DSC measurements. This indicated perfect miscibility of drug and polymer in the SDs.

3.1.5. IR spectroscopy

The interaction between the drug and the carrier often leads to identifiable changes in the IR profile of SDs. IR spectra of SDVLD, SDs and PMs were compared with the standard spectrum for VLD (Fig. 6). The presence and absence of characteristic peaks associated with specific structural characteristics of the molecule was noted. The spectrum of pure VLD presented characteristic signals at 3375.2 and 3249.8 cm^{-1} (N–H stretching vibrations), 1620.1 cm^{-1} (C=N stretching vibrations), 1332.7, 1153.4 and 1093.6 cm^{-1} (S=O stretching vibrations), respectively. In case of SDVLD, slight shift in few characteristic peaks was observed with no major difference in overall spectrum. The spectra of PMs were equivalent to the addition spectrum of polymer and crystalline drug. This indicated that no interaction occurred with simple physical mixing of drug and polymer. The spectrum of SD PVP presented significant broadening of N–H stretching vibration peaks characteristic of VLD and C=O stretching vibration peak (1680 cm^{-1}) characteristic of PVP. Similarly, the spectrum of SD HPC revealed slight shift along with decrease in intensity of both N–H and S=O stretching vibration peaks of VLD and hydroxyl stretching vibration peak (3466.4 cm^{-1}) of HPC. These observations indicated possibility of intermolecular hydrogen bonding via N–H group of VLD and carbonyl group of PVP or N–H as well as S=O groups of VLD and hydroxyl groups of HPC. Thus, VLD in the form of SD, exhibited better H-bonding interaction with HPC than PVP. In the low frequency region (1000–400 cm^{-1}) of the spectra of SDs, the peaks characteristic of VLD were almost unchanged. This indicated that although the drug molecule is hydrogen bonded with the polymer through sulfonamide group, the overall symmetry of the molecule is not significantly affected.

3.2. Stability and enthalpy relaxation studies

The results from saturation solubility, dissolution rate, DSC and XRPD studies provide an insight into the accelerated stability of SDVLD and its SDs. The choice of appropriate storage condition during accelerated stability study is necessary to predict the long-term stability of amorphous formulations (Nair et al., 2002). The temperature during storage has been reported to influence the rate of transformation of the amorphous to crystalline form. Storage above T_g will lead to a relatively rapid conversion to the crystalline form due to the high mobility of the amorphous form above their T_g (Hancock et al., 1995). The humidity during storage is also extremely important considering the hygroscopic nature of hydrophilic polymers. Absorbed moisture can act as a plasticizer and reduce the T_g of amorphous substance and lead to further instability (Schmitt et al., 1996; Shalaev and Zografi, 1996). For the present study, ambient temperature and relative humidity (30 °C/60% RH) were selected.

During stability, there was gradual decrease in saturation solubility (Table 1) and dissolution rate (Figs. 8 and 9) of SDs, over the period of 3 months. While, saturation solubility of SDVLD dropped drastically within 15 days and was almost comparable with pure VLD. Consequently, dissolution rate also decreased to around 20% released within 60 min (Fig. 7). This could be ex-

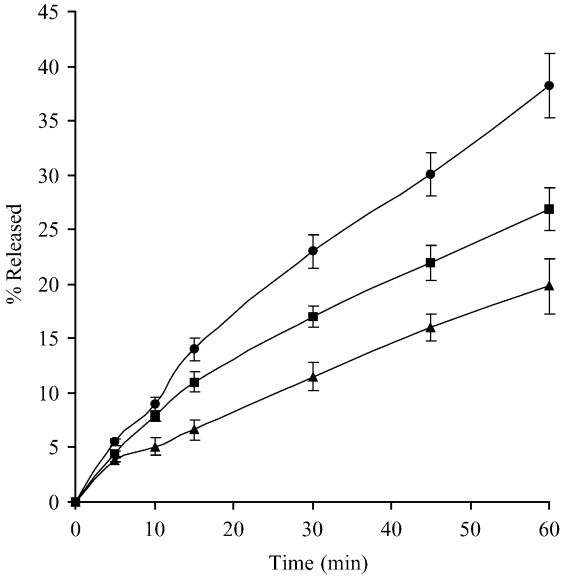

Fig. 7. Dissolution profile of SDVLD during stability study at different time intervals. *Key*: (●) initial; (■) 7 days; (▲) 15 days.

plained on the basis of DSC and XRPD studies. After 7 days of storage, DSC observations of SDVLD revealed presence of endotherm associated with T_g attributed to enthalpy relaxation (Fig. 10), but still absence of melting transition. Slight changes in XRPD spectrum were also observed (Fig. 11). There was appearance of very low intensity peaks at 35.6, 23.8 and 15.6° (2θ), characteristic to crystalline VLD. However, after 15 days of storage, both DSC and XRPD observations characteristic to crystalline drug, confirmed the destabilization of amorphous state of VLD.

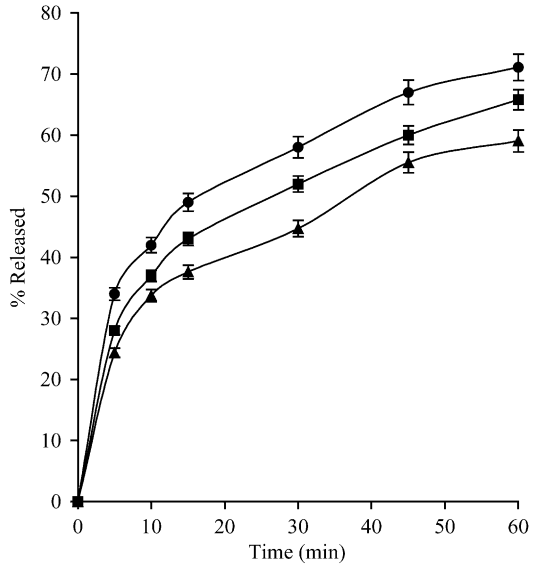

Fig. 8. Dissolution profile of SD PVP during stability study at different time intervals. *Key*: (●) initial; (■) 1 month; (▲) 3 months.

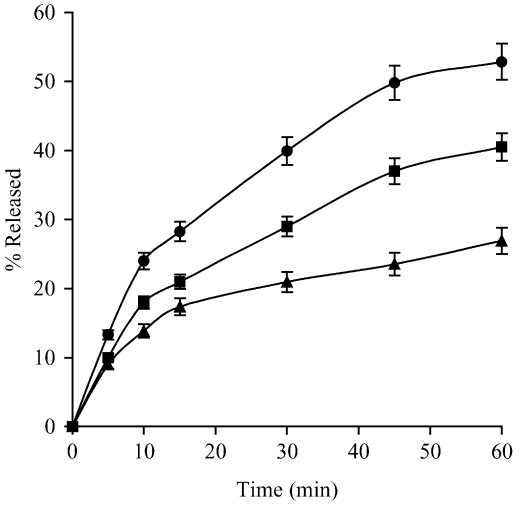

Fig. 9. Dissolution profile of SD HPC during stability study at different time intervals. *Key*: (●) initial; (■) 1 month; (▲) 3 months.

The DSC and XRPD observations (Figs. 10 and 11, respectively) of both the SDs after 1 month were identical, indicating presence of amorphous form of VLD. A broad endotherm around 90–100 °C in DSC was observed, which could be attributed to the loss of absorbed moisture by the polymer during storage at higher relative humidity. Similarly, at the end of 3 months, DSC and XRPD observations of SD PVP were identical with that of 1 month, indicating its physical stability. While, SD HPC presented incidence of crystallinity, as the DSC thermogram (Fig. 10) revealed considerable shift in melting transition of VLD (160 °C, ΔH 17.95 J/g) and XRPD spectrum (Fig. 11) showed appearance of peaks characteristic of VLD crystallinity. Saturation solubility of SD HPC also dropped to 22 μg/ml, which was almost comparable with pure VLD.

The improved stability of SD PVP over SD HPC and SDVLD could be best explained by the enthalpy relaxation studies (Shamblin and Zografi, 1998; Matsumoto and Zografi, 1999; Zhou et al., 2002; Hilden

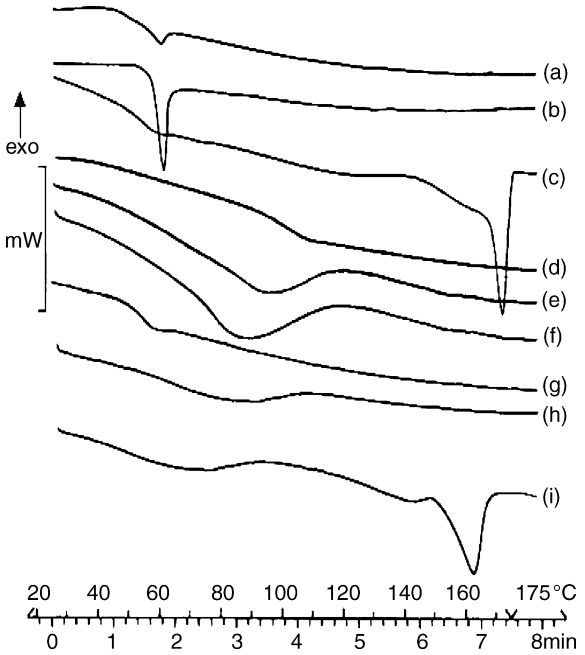

Fig. 10. DSC profiles of SDVLD and SDs during stability study at different time intervals. *Key*: (a) SDVLD initial; (b) SDVLD 7 days; (c) SDVLD 15 days; (d) SD PVP initial; (e) SD PVP 1 month; (f) SD PVP 3 months; (g) SD HPC initial; (h) SD HPC 1 month; (i) SD HPC 3 months.

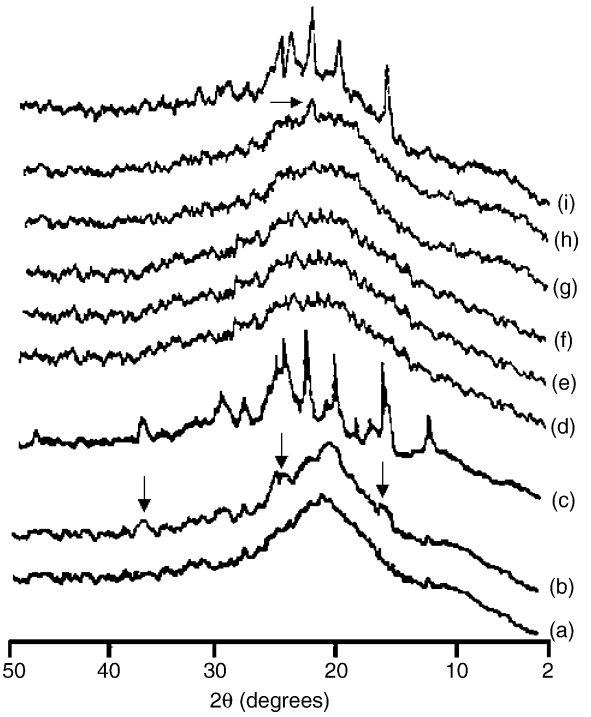

Fig. 11. XRPD profiles of SDVLD and SDs during stability study at different time intervals. *Key*: (a) SDVLD initial; (b) SDVLD 7 days; (c) SDVLD 15 days; (d) SD PVP initial; (e) SD PVP 1 month; (f) SD PVP 3 months; (g) SD HPC initial; (h) SD HPC 1 month; (i) SD HPC 3 months.

and Morris, 2004). Amorphous substances aging at a temperature below T_g, show crystallization of glassy state via the equilibrium supercooled liquid state. The material experiences gradual loss in energy in terms of enthalpy because of the effect of molecular motions occurring at prevailing conditions, which drive it towards a more stable crystalline state. This loss of enthalpy is recovered by the sample at T_g during its heating run in DSC and can be measured with time, which in turn reflects the molecular mobility or in other words the crystallization rate of unstable glassy amorphous systems. This technique has been used previously to compare the molecular mobility of polymers (Cowie and Ferguson, 1989) and single component amorphous materials of pharmaceutical importance, including carbohydrates (Shamblin et al., 1998), indomethacin (Matsumoto and Zografi, 1999) and proteins (Duddu et al., 1997). It is reported that, the total enthalpy change required to reach the supercooled equilibrium state is approximately the same for both, the amorphous drug alone and its SDs. However, the rate at which the samples approach the relaxed state is reduced significantly for the SDs, which contains high molecular weight polymers (Shamblin and Zografi, 1998).

A comparative assessment of stabilization capacity of two polymers was obtained by measuring the structural relaxation of the amorphous drug in their presence and absence. The samples of amorphous VLD aged at 30 °C/60% RH for 16 h presented no incidence of crystallinity (Fig. 12), but the size of endothermic peak accompanying T_g experienced gradual enhancement with time, reflecting an increase in enthalpy recovery and structural relaxation of amorphous form towards the supercooled liquid region (Fig. 13). On the contrary, SD PVP exhibited gradual decrease in T_g from 103.5 to 72 °C within 16 h (Fig. 15) without incidence of relaxation endotherm accompanying T_g (Fig. 14). While, SD HPC exhibited considerable decrease in T_g from 55 to 38 °C, i.e. almost equal to the aging temperature (Fig. 15), along with incidence of small relaxation en-

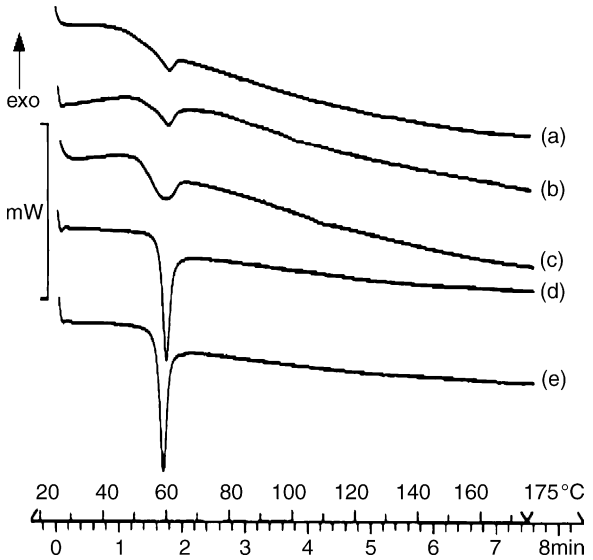

Fig. 12. Enthalpy relaxation study of amorphous VLD at different time intervals. *Key*: (a) initial; (b) 2 h; (c) 4 h; (d) 8 h; (e) 16 h.

dotherm associated with T_g after 2 h, without any further relaxation up to 16 h (Fig. 16). Thus, from the enthalpy relaxation study, it can be concluded that the enthalpy changes for the SDs were significantly less than

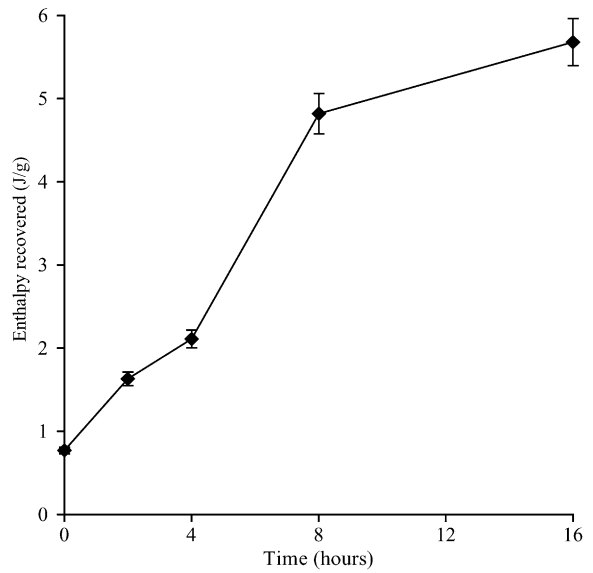

Fig. 13. Graph of enthalpy recovered with respect to time for amorphous VLD aged at 30 °C/60% RH up to 16 h.

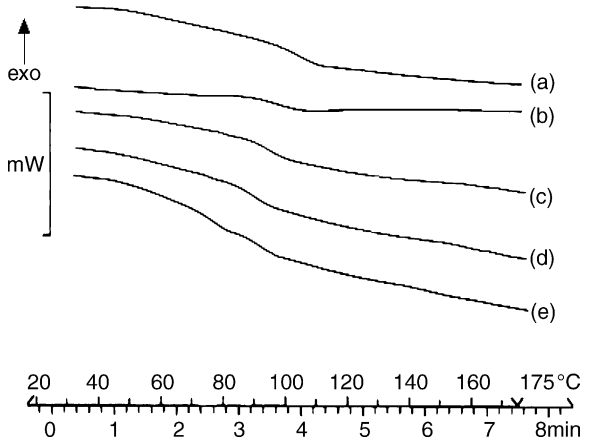

Fig. 14. Enthalpy relaxation study of SD PVP at different time intervals. *Key*: (a) initial; (b) 2 h; (c) 4 h; (d) 8 h; (e) 16 h.

the amorphous VLD alone. This could be attributed to either alone or combination of following reasons: (1) dilution effect of the polymer; (2) antiplasticizing effect of the polymer; and (3) interactions occurring at molecular level, like hydrogen bonding or any other weak electrostatic bonding between the two compo-

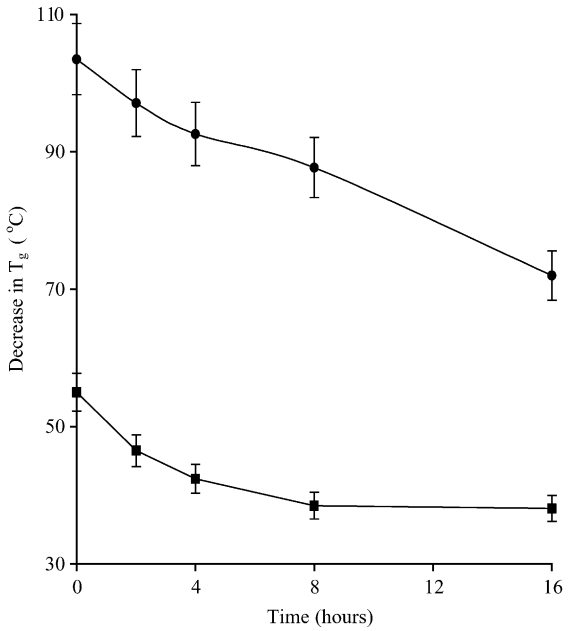

Fig. 15. Graph of decrease in T_g with time for the SDs aged at 30 °C/60% RH up to 16 h. *Key*: (●) SD PVP; (■) SD HPC.

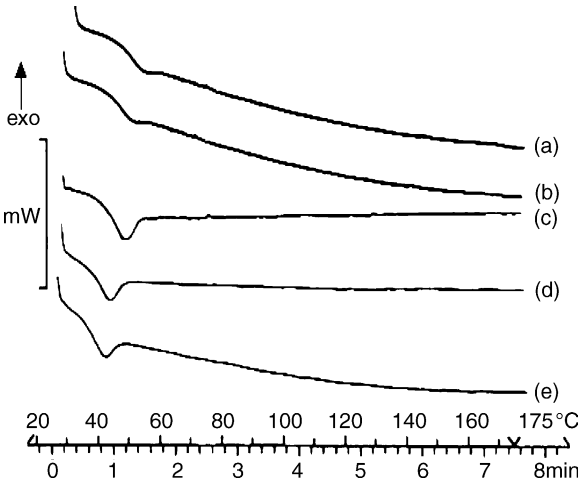

Fig. 16. Enthalpy relaxation study of SD HPC at different time intervals. *Key*: (a) initial; (b) 2 h; (c) 4 h; (d) 8 h; (e) 16 h.

nents of SD. However, as compared to SD PVP, even though SD HPC had T_g value almost similar to amorphous VLD, the molecular mobility of the system was reduced to the extent that it could inhibit further relaxation of enthalpy after 2 h. Also as stated earlier in IR spectroscopy, SD HPC had presented evidence of sufficient hydrogen bonding, which could retain the amorphous form of VLD at least for 1 month during stability.

4. Conclusions

Improving the solubility and dissolution characteristics of poorly water-soluble drugs is important to achieve better bioavailability. The physical transformation of crystalline drug substance into its more soluble but metastable amorphous form is one of the approaches in this direction. In present study, initial characterization confirmed the presence of amorphous form of VLD in all samples obtained by technique of spray drying. Further, SD formulations performed better than corresponding PMs and SDVLD in improving the saturation solubility, dissolution rate and suppressing crystallinity of VLD. During stability testing, there was gradual decrease in saturation solubility and dissolution rate of SDs, over the period of 3 months. While, saturation solubility of SDVLD dropped drastically within 15 days and was almost comparable with pure VLD. SD PVP retained the amorphous form of drug throughout stability period, whereas SD HPC and SDVLD presented incidence of crystallinity after 1 month and 15 days, respectively. This was justified by enthalpy relaxation studies in which, amorphous VLD showed considerable relaxation of enthalpy at T_g, while it was totally suppressed in SD PVP and partly in SD HPC. The study thus definitely reveals tremendous potential of solid dispersions of valdecoxib with PVP, from stability point of view.

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