Study on Mechanism for Amorphous Drug Stabilization Using Gelucire 50/13

Shamkant Laxman Shimpi,*[,a] Kakasaheb Ramoo Mahadik,[b] and Anant Raghunath Paradkar*[,c]

[a] *Formulation Research Division, APL Research Centre, Aurobindo Pharma Ltd.; Bachupally, Hyderabad–500070, India:* [b] *Department of Pharmaceutics, Bharati Vidyapeeth Deemed University, Poona College of Pharmacy; Erandwane, Pune–411 038, Maharashtra, India: and* [c] *Institute of Pharmaceutical Innovation, and IRC in Polymer Science and Technology, University of Bradford; Bradford, West Yorkshire, United Kingdom, BD7 1DP.*

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Methods of preparation and application of amorphous form are well established but it is equally important to note that devitrification of amorphous drugs has limited their applications. Present study was performed to investigate mechanism for amorphous drug stabilization using Gelucire in comparison with polyvinylpyrrolidone (PVP). Etoricoxib and celecoxib were taken as model drugs for this study, as etoricoxib has only proton accepting site for hydrogen bonding in comparison with celecoxib, which has both proton accepting and donating site. Solid dispersion of celecoxib with polyvinylpyrrolidone and Gelucire was prepared by spray drying and melt-granulation technique respectively. X-ray powder diffractometry and differential scanning calorimetry were used to study the physical state of the drug. Dissolution studies were performed to differentiate dissolution performance. Stability study samples were evaluated for physical state of the drug and dissolution performance. An IR study in correlation with molecular modeling was carried out to study the mechanism for stabilization. Dissolution of melt-granulation of amorphous celecoxib was improved significantly as compared to amorphous celecoxib and Celecoxib-PVP solid dispersion. Melt-granulation with lipid seemed to be more dominant than amorphization of drug for improving dissolution. Stability data revealed that PVP was significantly advantageous for amorphous form stabilization whereas Gelucire failed in case of Celecoxib. In contrast to this, our previous study revealed the stabilization ability of Gelucire for amorphous etoricoxib. Molecular modeling and IR studies revealed that H-bonding was predominant mechanism for stabilization. Out of two proposed mechanism for amorphous drug stabilization by lipids, H-bonding ability is more dominant than immobilization of molecule in lipid matrix.

Key words amorphous state; solid dispersion; Gelucire; mechanism; stabilization; molecular modeling

Preparation of solid dispersions to increase dissolution rate and bioavailability of poorly water-soluble drug is now well established.[1—3] Though there are many reports describing methods of preparation and application of amorphous form, it is equally important to note that devitrification of amorphous drugs has limited their applications to a great extent. The commercial use of such systems has been limited, primarily because of manufacturing difficulties and stability problems. Several attempts have been made to obtain and stabilize drugs in amorphous state. Solid dispersions (SDs) with various polymers like polyvinylpyrrolidone (PVP), hydroxypropylmethyl cellulose, hydroxypropylcellulose,[4,5] silicates like calcium silicate, silicon dioxide, magnesium aluminosilicate (Neusilin®),[6,7] cyclodextrins[8] and lipids[9,10] have been reported. These SDs were obtained using various techniques such as melt quenching, solvent evaporation, spray drying, milling, *etc.*

Spray drying technique has limitation in preparation of solid dispersions with polyethylene glycol (PEG) and lipid, due to low melting point of such material. Weuts *et al.*[11] have reported spray-drying technique for obtaining loperamide-PEG 6000 solid dispersion. But processing temperature had to be maintained low due to presence of PEG, which resulted product containing some proportion of crystalline drug. This residual crystallinity in the product was responsible for faster divitrification and deterioration in dissolution profile on storage. In our previous report we have demonstrated application of melt granulation of spray dried amorphous form with Gelucire in stabilization of amorphous etoricoxib (ET, Fig. 1a). This technique provides enhanced dissolution, stability, bioavailability and feasibility of compression into tablet. In this study, amorphous etoricoxib (AET) was prepared by spray drying technique, further its granules with Gelucire 50/13 were prepared by melt granulation. In 3-month stability study, melt granules of AET has performed well where etoricoxib-PVP SD (ET-PVP SD) was found to devitrify at faster rate. This failure can be attributed to absence of proton donating group in etoricoxib. Thus it was proposed that lipid melt granulation of amorphous form

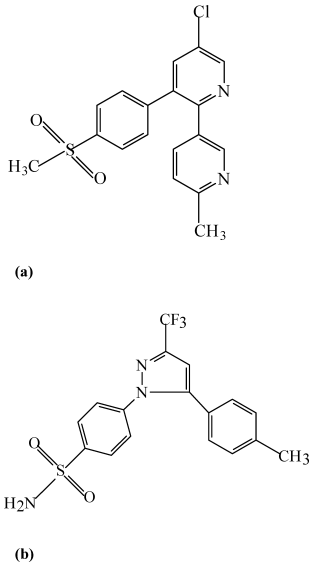

Fig. 1. Chemical Structure of Etoricoxib (a) and Celecoxib (b)

* To whom correspondence should be addressed. e-mail: arparadkar@rediffmail.com; shyam_5p@yahoo.com © 2009 Pharmaceutical Society of Japan

can be considered for drugs where PVP does not provide stabilizing ability either due to lack of interaction or insufficient anti-plasticizing effect. From the results, we had proposed two mechanisms, hydrogen bonding of drug with Gelucire and immobilization of the drug in the lipid matrix.

To test the proposed mechanism present study was designed. In the present study drug, from the same group of series, Celecoxib (CEL, Fig. 1b) was selected which has both proton accepting as well as donating groups in comparison with etoricoxib having only proton accepting group. Drug-PVP solid dispersion (CEL-PVP SD) and amorphous CEL (ACEL) was prepared by spray drying technique. Melt granules of ACEL were obtained with Gelucire 50/13 by melt granulation technique. Physicochemical characterization of the dispersions and melt granules was performed on the freshly prepared samples as well as on stability samples using X-ray diffraction study, differential scanning calorimetry, infrared spectroscopy and dissolution study. Molecular modeling study was carried out for the detailed explanation of mechanism in correlation with IR studies.

Experimental

Materials Celecoxib and etoricoxib was obtained as a gift sample from Lupin Ltd. (Pune, India) and Unichem Laboratories Ltd. (Mumbai, India) respectively. Gelucire® 50/13 (Stearoyl Macrogoglycerides EP, Gattefosse, France) and PVP (BASF, Germany) were supplied by Colorcon India (Mumbai, India) and Get-Rid Pharmaceuticals Pvt. Ltd. (Pune, India), respectively. All other chemicals were of analytical grade.

Methods. Preparation of Amorphous Form and SDs CEL alone or in combination with PVP (1 : 0.5, 1 : 1, 1 : 1.5) was dissolved in methanol. The solid concentration of the sample was kept just below the saturation level. The clear solution was spray dried using a spray drier (Jay Instruments & Systems Pvt. Ltd., Mumbai, India) under following set of conditions: flow rate, 10 ml/min; inlet temperature, 90 °C; outlet temperature, 70—75 °C; aspiration −200 mm WC and atomization air pressure, 1 kg/cm^2. The resulting solid powder was placed in a vacuum dryer for 24 h to remove residual solvent. AET and ET-PVP solid dispersion (ET-PVP SD) were prepared similarly using the spray drying technique.[9]

Preparation of Melt Granules Granules of ACEL (MG-ACEL) were prepared using the melt granulation (MG) technique. The drug : lipid ratios used to prepare the granules were 1 : 0.5 and 1 : 1 parts by weight. Gelucire 50/13 was melted at 60 °C. To the molten lipid, ACEL was added, mixed well and cooled to room temperature to obtain the solid mass. The mass was passed through 510 μm sieve to obtain uniform sized granules. Similarly melt granules of AET (MG-AET) was prepared.[9]

Drug Content SDs and melt granules equivalent to 5 mg of drug were weighed accurately and dissolved in suitable quantity of methanol. The drug content was determined spectrophotometrically at 254 nm (V-530, JASCO, Japan).

Thermogravimetric Analysis (TGA) In order to calculate the amount of residual solvent in the spray dried drug and solid dispersions, thermogravimetric analysis was performed using TA-60WS Thermogravimetric analyzer (Shimadzu Corporation, Japan). Samples (approximately 30—40 mg) were heated in platinum crucible in nitrogen atmosphere and the loss of weight as a function of temperature was recorded.

Differential Scanning Calorimetry (DSC) DSC studies were performed using Mettler-Toledo DSC 821° (Mettler Toledo, Switzerland) instrument equipped with an intracooler. Indium and Zinc standards were used to calibrate the DSC temperature and enthalpy scale. The samples were hermetically sealed in an aluminum pan and heated at a constant rate of 10 °C/min, over a temperature range of 25—180 °C. Inert atmosphere was maintained by purging nitrogen gas at the flow rate of 50 ml/min. Sample weights were in the range of 5 to 10 mg.

X-Ray Powder Diffraction (XRPD) X-Ray powder diffraction patterns were recorded on X-ray diffractometer (PW 1729, Philips, The Netherlands). The samples were irradiated with monochromatized Cu$K\alpha$ radiation (1.542 Å) and analyzed between 2 and 50 °2θ at ambient temperature. The voltage and current used were 30 kV and 30 mA, respectively. The range and the chart speed were 5×10^{-3} CPS and 10 mm/°2θ, respectively.

Diffuse Reflectance Infrared Fourier Transform Spectroscopy (DRIFTS) The DRIFTS spectra were obtained, after appropriate background subtraction; using an FT-IR spectrometer (FTIR-8400, Shimadzu Corporation, Japan) equipped with a diffuse reflectance accessory (DRS-8000, Shimadzu Corporation, Japan) and a data station. About 2—3 mg of the sample was mixed with dry potassium bromide and the samples were scanned from 4000—400 cm^{-1}.

Dissolution Studies Dissolutions studies (in triplicate) were carried out using USP 24 type II dissolution test apparatus (TDP-06P, Electrolab, India) with the agitation speed of 100 rpm in phosphate buffer (pH 6.8) maintained at 37±0.2 °C. Dissolutions studies were carried out with maintaining the sink condition. At appropriate time intervals, aliquots were withdrawn and replaced with a fresh dissolution medium. After filtration through Whatman filter paper No. 41, concentration of CEL was determined spectrophotometrically at 254 nm with suitable dilutions. Analysis of data was done using PCP-Disso V3 software (Poona College of Pharmacy, Pune, India).

Molecular Modeling All molecular modeling studies were performed on Intel Pentium IV 1.8 GHz computer running Windows 2000 using Material Studio software (Accelrys, U.S.A.). All the molecules were constructed using molecular builder. Polymers, lipids and drug molecules were constructed; partial charges were calculated and minimized. CEL molecules were placed randomly in the network of polymer chains and the system was minimized to reduce the steric clashes between the drug and polymer. The dynamics trajectories were then analyzed.

Stability Study The stability of samples was monitored up to 3-month at ambient temperature and relative humidity (30 °C/65% RH). Periodically samples were removed and characterized for dissolution along with the presence of crystallinity using DSC and XRPD studies.

Results and Discussion

Spray drying of drug alone and with PVP in various ratios (1 : 0.5, 1 : 1 and 1 : 1.5 parts by weight) was optimized on the basis of physical state of the powder. Percent yield for ACEL was 65—70% and 80—85% for CEL-PVP SD, whereas drug content was in the range of 90—94% w/w. ACEL was further processed to granules using melt granulation with Gelucire 50/13 in 1 : 0.5 and 1 : 1 ratio. The amount of PVP and Gelucire was optimized on the basis of physical state of the powder and *in vitro* dissolution performance, which is discussed further in respective sections. The amount of organic solvent in the dried particles was below the detection limit of TGA (<0.05% w/w).

DSC thermograms of CEL samples are shown in Fig.2. CEL showed melting endotherm at 162.3 °C. ACEL showed change in heat capacity at 51 °C indicating glass transition temperature (T_g), followed by recrystallization exotherm at 111 °C and melting endotherm at 165 °C. DSC pattern of the 3-month stability sample of ACEL showed melting peak at 161.8 °C, which indicated devitrification of amorphous form during stability. Thermograms of CEL-PVP SD (1 : 1) showed T_g at 81 °C, recrystallization exotherm and a melting endotherm was absent. This indicated that for complete amorphization of CEL, 1 part of PVP was sufficient; therefore CEL-PVP SD (1 : 1) was used for further studies. Whereas in our earlier study, PVP required for complete amorphization of ET was 1.5 parts.[9] The reason for this difference might be H-bond forming ability of PVP with CEL than ET. During stability CEL-PVP SD showed T_g at slightly lower temperature (74—76 °C) than initial sample without any melting peak of CEL. It shows that PVP has shown stabilizing ability for CEL during stability.

The DSC pattern of initial sample of MG-ACEL showed broad melting peak of the Gelucire 50/13 at 55 °C followed by low intensity melting peak of CEL at 165 °C. The T_g peak might have been overlapped with the melting peak of the

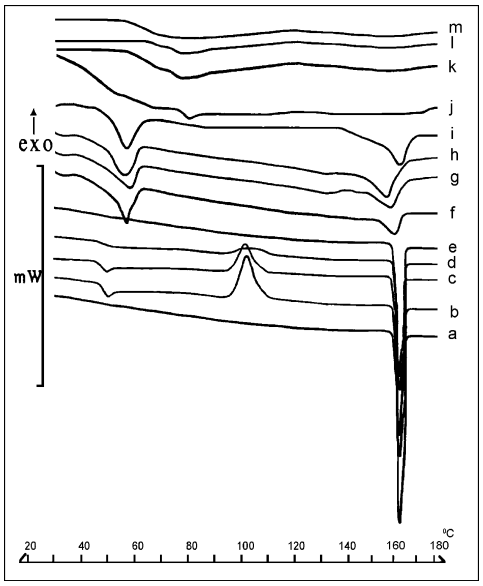

Fig. 2. DSC Curves of Initial and Stability Samples of CEL

Key: CEL (a); ACEL, initial (b); ACEL, 10-d (c); ACEL, 1-month (d); ACEL, 3-months (e); MG-ACEL 1 : 0.5, initial (f); MG-ACEL 1 : 0.5, 10-d (g); MG-ACEL 1 : 0.5, 1-month (h); MG-ACEL 1 : 0.5, 3-months (i); CEL-PVP SD 1 : 1, initial (j); CEL-PVP SD 1 : 1, 10-d (k); CEL-PVP SD 1 : 1, 1-month (l); CEL-PVP SD 1 : 1, 3-months (m).

lipid.[12] This was in accordance with our earlier study with etoricoxib. The appearance of the CEL melting peak might be due to conversion of amorphous to crystalline state in the DSC. Reports also suggested that when the melt was held for $>$3 min, crystal growth occurred due to plasticizing effect.[12] In contrast to this, crystalline nifedipine at low concentration in solid dispersion did not show any characteristics of the crystalline nifedipine. One of the reason could be that nifedipine might have been converted to metastable amorphous form, or might have dissolved in the matrix system to form a solid solution, or might exist in microcrystalline form in the system.[13] The solid dispersion of the cinnarizine in Gelucire 50/13, showed no melting peak of cinnarizine at low concentration ($\leq$30% w/w). The imprecise outcomes in these reports concluded that DSC is unsuitable for determining the degree of crystallinity for systems containing lipid or low melting component.[14] DSC thermogram of MG-ACEL 3-month stability sample showed melting peak of Gelucire and CEL similar to initial sample.

The XRPD pattern of CEL showed sharp and defined diffraction peaks (Fig. 3), whereas ACEL and CEL-PVP SD exhibited a diffused halo pattern. This indicated complete conversion of CEL to amorphous form. Among CEL diffraction peaks, 16.1, 19.4, 27.2, 30.1 °2θ were considered to be the important peaks for stability evaluation because these peaks appeared first, when the samples started to recrystallize. Devitrification of drug was studied using DSC and XRPD along with dissolution studies over a period of 3-months. XRPD patterns of CEL, ACEL, CEL-PVP SD, MG-ACEL and stability samples at different time periods are shown in Figs. 3 and 4. XRPD patterns for 10-d stability sample of ACEL has shown occurrence of crystallinity, which subsequently increased on storage.

Figure 4 shows the XRPD pattern for the MG-ACEL and CEL-PVP SD. The XRPD pattern of the MG-ACEL showed

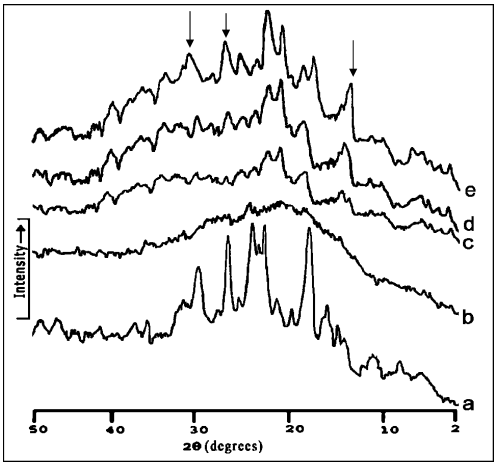

Fig. 3. XRPD Pattern of Initial and Stability Samples of ACEL

Key: CEL (a); ACEL, initial (b); ACEL, 10-d (c); ACEL, 1-month (d); ACEL, 3-months (e).

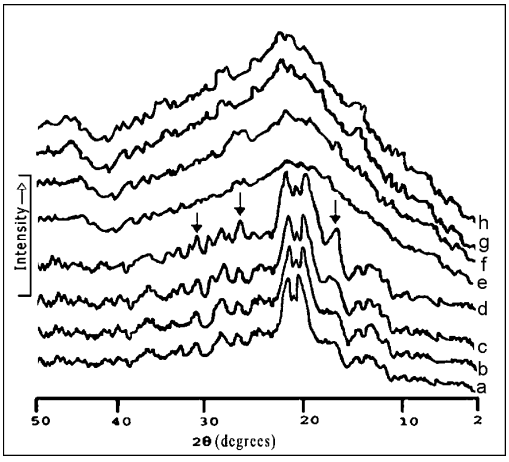

Fig. 4. XRPD Pattern of Initial and Stability Samples of MG-ACEL and CEL-PVP SD

Key: MG-ACEL, initial (a); MG-ACEL, 10-d (b); MG-ACEL, 1-month (c); MG-ACEL, 3-months (d); CEL-PVP SD 1 : 1, initial (e); CEL-PVP SD 1 : 1, 10-d (f); CEL-PVP SD 1 : 1, 1-month (g); CEL-PVP SD 1 : 1, 3-months (h).

characteristic peaks at 19.26 and 23.5 °2θ, attributed to Gelucire 50/13.[13] Initial sample of MG-ACEL showed absence of CEL peaks, which indicated that melt granulation did not affect the physical state of ACEL. Characteristic peaks of CEL were observed during 3-month stability study, which was reflected through decreased dissolution profile. CEL-PVP SD was found to be stable over the 3-month storage. No characteristic peaks corresponding to CEL were observed during stability study. PVP has shown its stabilizing ability through interaction with CEL. In contrast to this observation our previous report has shown efficacy of Gelucire in stabilization of AET when processed by MG. FT-IR and molecular modeling data was generated for both drugs with Gelucire and PVP as stabilizers to elucidate the mechanism.

Comparative dissolution profiles of initial samples in phosphate buffer (pH 6.8) are shown in Fig. 5. Amorphization showed significant increase in dissolution rate as compared to crystalline form. ACEL showed 42% dissolution in 60 min, whereas it was only 20% for crystalline CEL. Dissolution profile for CEL-PVP SD (1 : 1) was significantly high (67%) as compared to ACEL, whereas MG-ACEL showed

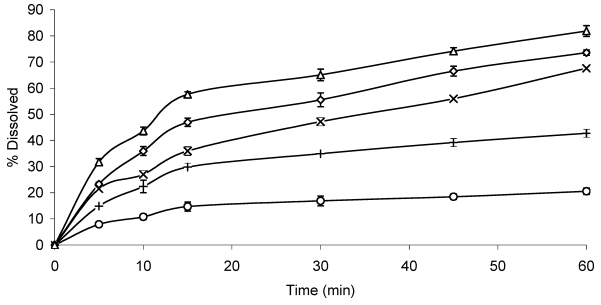

Fig. 5. Comparative *in Vitro* Dissolution Profile of Initial Samples
Key: CEL (○); ACEL (+); CEL-PVP SD (×); MG- CEL (◇); MG-ACEL (△).

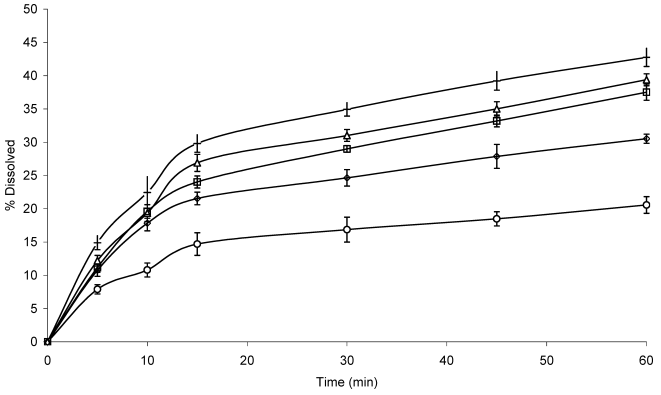

Fig. 6. *In Vitro* Dissolution Profile of Initial and Stability Samples
Key: CEL (○); ACEL, Initial (+); ACEL, 10-d (△); ACEL, 1-month (□); ACEL, 3-months (◇).

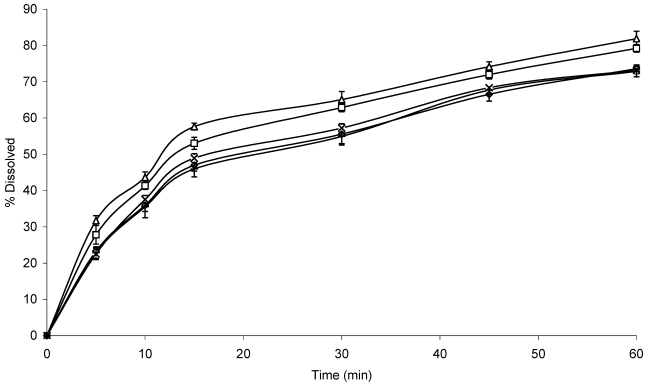

Fig. 7. *In Vitro* Dissolution Profile of MG-CEL and MG-ACEL Initial and Stability Samples
Key: MG-CEL (◇); MG-ACEL, initial (△); MG-ACEL, 10-d (□); MG-ACEL, 1-month (×); MG-ACEL, 3-months (+).

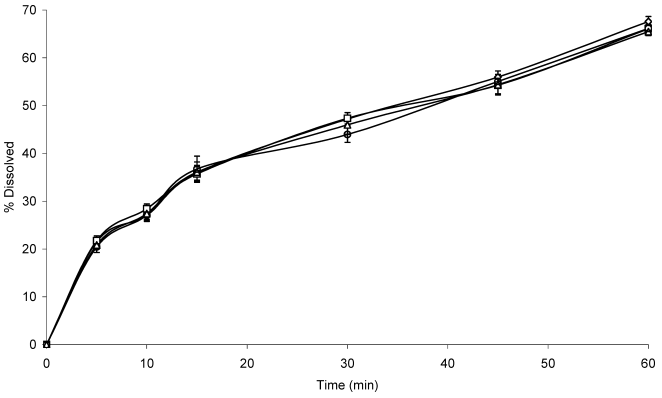

Fig. 8. *In Vitro* Dissolution Profile of CEL-PVP SD Initial and Stability Samples
Key: initial (◇); 10-d (□); 1-month (△); 3-months (○).

81% drug dissolution in 60 min. Insignificant change in dissolution profile of MG-ACEL 1 : 0.5 and 1 : 1 ratios was observed. Though Gelucire increased dissolution of drug, increase in Gelucire proportions did not have any significant effect. Dissolution of melt granules of crystalline CEL (MG-CEL) was carried out to study whether amorphization or MG with lipid contributed for the improvement in dissolution. MG-CEL showed higher dissolution (73%) than CEL (20%), this clearly indicated that Gelucire played an important role in improvement of dissolution rate of drug. Whereas there was slight improvement in dissolution of MG-ACEL (81%) than MG-CEL (73%), therefore as compared to amorphization, melt granulation with Gelucire was dominating in improvement of dissolution, which might be attributed to the highly hydrophilic environment provided by Gelucire.[11)]

The dissolution profiles of the ACEL and stability samples are shown in Fig. 6. The dissolution of ACEL has improved to 42%. This limited dissolution of amorphous form might be due to the formation of small agglomerates of the spray-dried powder due to static charges. On storage, dissolution of ACEL has decreased but was always higher than crystalline form indicating that there was incomplete transformation of amorphous to crystalline form. XRPD and DSC data has supported this incomplete transformation of ACEL to crystalline form. On storage, the dissolution of CEL-PVP SD showed insignificant change in dissolution profile (Fig. 8), whereas decrease in dissolution profiles of MG-ACEL was observed on storage for 3-months (Fig. 7). This indicated that the amorphous form of the CEL was unstable in MG-ACEL. These results are contrast to our previous report where ET-PVP SD has shown decreased dissolution on storage and there was insignificant change in MG-AET dissolution on storage.

ACEL showed wide spectral differences from crystalline CEL (Fig. 9). The sharp doublet for N–H stretching vibration band (3338, 3232 cm^{-1}) in crystalline CEL was found to shift at higher wavenumber (3367, 3264 cm^{-1}) as broader hump in ACEL. Stretching vibration band for S=O was shifted at lower wavenumber from 1347 cm^{-1} in crystalline CEL to 1339 cm^{-1} in ACEL. Slight shift in C–F stretching vibration band was observed towards higher wavenumber in ACEL. The shift in vibration frequencies and broadness indicates stronger H-bonding in the ACEL, which was further explained by molecular modeling.

The interaction between the drug and the carrier often leads to identifiable changes in the IR profile of SDs. IR spectra of SDs, PMs and MGs were compared with the spectrum of the drug (Figs. 9, 10). The presence and absence of characteristic peaks associated with specific structural characteristics of the molecule was noted. 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. In case of CEL-PVP SD, downward shift of C=O stretching vibration band implies the strong ability of C=O group, in competition with S=O group, to H-bond with –N–H group of CEL. Gupta *et*

al. have studied role of molecular interaction in stability of CEL and PVP amorphous system. FT-IR and molecular modeling was used to explain this interaction and shown that CEL interacted with PVP through strong H-bonding. The molecular interactions between CEL and PVP supported the stabilizing action of PVP for amorphous CEL.[15] Surprisingly, there was no interaction between the –O–H group of Gelucire and –S=O group of ACEL. In case of MG-ACEL, it was assumed that ACEL would also form the H-bond with Gelucire. ACEL itself forms inter molecular hydrogen bonding during spray drying. During the amorphization CEL itself forms the intermolecular H-bonding between hydrogen of N–H and oxygen of S=O.[16] Therefore proton accepting sites of CEL are unavailable to form H-bonding with O–H group of Gelucire. The summary of the drug–drug, drug–excipient interaction is presented in Table 1. So whatever short-term stability observed in MG-ACEL was due to immobilization of the drug in the lipid matrix system rather than H-bonding.

For comparison the DRIFT data of ET, AET, PMs and SDs has been studied in the present study (Fig. 9). The DRIFT spectra of neat ET showed characteristic peaks at 1596.9 cm^{-1} (C–N stretching vibration); 1342 cm^{-1} (S=O stretching vibrations); and 840.9 cm^{-1} (C–Cl stretching vibration), respectively. In AET there was no significant difference in the spectra, due to lack of possibility of H-bonding, which was studied with molecular modeling (Fig. 11). The spectra of physical mixtures were equivalent to the spectra obtained by the addition of carriers and crystalline drug spectrum indicating absence of any interaction between drug and carrier during mixing. The DRIFT spectrum of MG-AET showed significant broadening O–H stretching vibrations as the peak characteristic. This indicated strong possibility of hydrogen bonding between the S=O group of ET and OH of Gelucire (Fig. 10). In case of ET-PVP SD there was no additional peak in comparison with PM, as both ET and PVP bears proton accepting groups (Fig. 9). Molecular modeling output of this interaction was already studied in our previous report.[9] From this study it was clear that ACEL did not form H-bond with Gelucire, and hence Gelucire is unable to stabilize amorphous celecoxib. Thus H-bonding has been confirmed as the mechanism for stabilization.

In the previous report, molecular modeling study confirmed lack of hydrogen bonding between the PVP and ET and possibility of hydrogen bonding between Gelucire and ET. The studies also showed no intra or intermolecular hydrogen bonding in ET. In contrast, CEL molecule showed intermolecular hydrogen bonding.[16] The possible sites for hydrogen bonding were hydrogen of $–NH_2$ and oxygen of $–SO_2$ group of another CEL molecule (Fig. 11), other sites also showed interaction but it was of no interest for this study. As

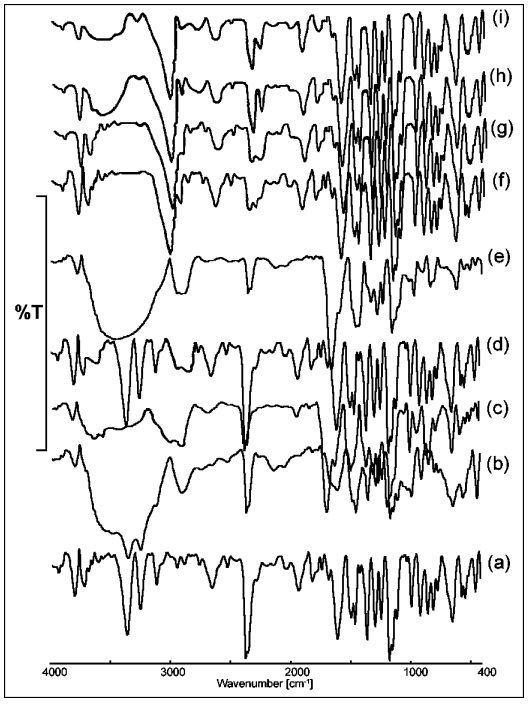

Fig. 9. Infrared Spectra during Initial Characterization of Different Formulations of CEL and ET with PVP

Key: CEL (a); ACEL (b); PVP (c); CEL-PVP PM (d); CEL-PVP SD (e); ET (f); AET (g); ET-PVP PM (h); ET-PVP SD (i).

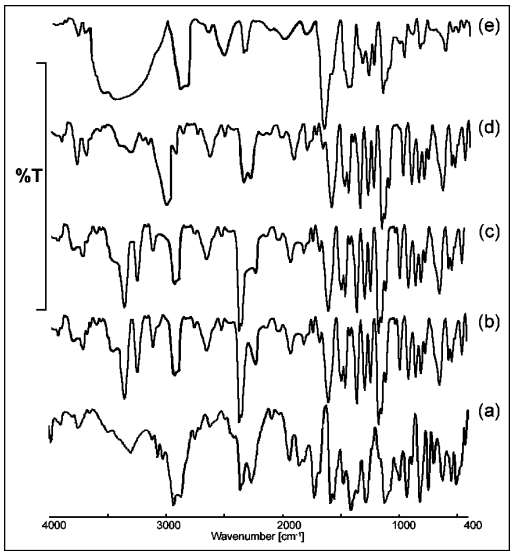

Fig. 10. Infrared Spectra during Initial Characterization of Different Formulations of CEL and ET with Gelucire

Key: Gelucire (a); CEL-Gelucire PM (b); MG-ACEL (c); ET-Gelucire PM (d); MG-AET (e).

Table 1. Molecular Interaction Possibility of Different Samples

Sample	Interaction possibility	Reason for interaction
AET	No molecular interaction	Only proton accepting group
ACEL	Intra- or inter-molecular interaction	Both proton donating and accepting group are present
ET-PVP SD	No molecular interaction	Both ET and PVP are proton acceptor
CEL-PVP SD	Molecular interaction	PVP is proton acceptor where as CEL is proton donor
MG-AET	Molecular interaction	Gelucire is proton donor and ET is proton acceptor
MG-ACEL	No molecular interaction	Hydrogen bonding sites of ACEL are blocked during amorphization

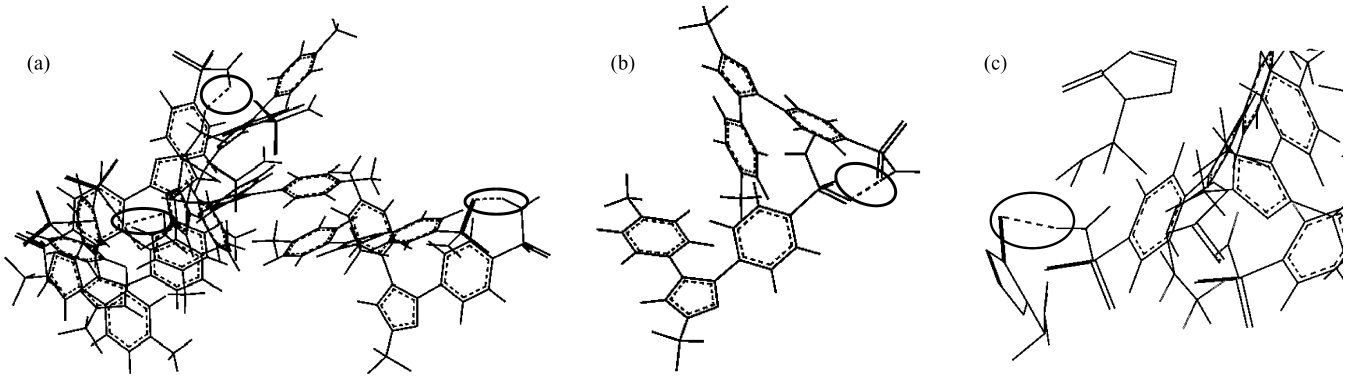

Fig. 11. Stereoview Showing the Intermolecular Hydrogen Bonding between the Celecoxib Molecules after Spray Drying (a), the Magnifying View of the Same (b) and Interaction between Celecoxib and PVP (c)

The dotted line (encircled) represents the hydrogen bonding between the $-SO_2$ group, $-NH_2$ group of celecoxib and =O group of PVP.

there was intermolecular hydrogen bonding, no site remained free to form hydrogen bond with Gelucire. Hence, Gelucire was unable to stabilize the ACEL. The dynamics for CEL and PVP showed interaction between carbonyl oxygen of PVP and amido hydrogen of CEL. Similar interaction study of CEL in CEL-PVP-meglumine amorphous ternary system has been carried out using FT-IR and molecular modeling study. Authors have shown that meglumine interacted extensively with CEL through H-bonding at lower proportion but there was no comment on interaction between CEL and PVP in ternary system.[17)]

Conclusion

Solid dispersions with PVP have shown success in stabilizing ACEL in contrast to our previous study on etoricoxib. Melt granulation of ACEL with Gelucire did not show stabilizing ability even though CEL has S=O group for the formation of H-bond with Gelucire. The reason for contrary conclusion to our previous report was intermolecular H-bonding in ACEL that was well explained by molecular modeling and IR studies. Out of two proposed mechanisms for amorphous drug stabilization by Gelucire, H-bonding is more dominant than immobilization of molecule in lipid matrix.

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