AAPS PharmSciTech, Vol. 10, No. 2, June 2009 (© 2009)
DOI: 10.1208/s12249-009-9221-6

Research Article

Preparation and Characterization of Co-Grinded Mixtures of Aceclofenac and Neusilin US_2 for Dissolution Enhancement of Aceclofenac

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Received 6 October 2008; accepted 13 February 2009; published online 15 May 2009

Abstract. The present study was carried out with a view to enhance the dissolution of poorly water-soluble BCS-class II drug aceclofenac by co-grinding with novel porous carrier Neusilin US_2 (amorphous microporous granules of magnesium aluminosilicate, Fuji Chemical Industry, Toyama, Japan). Neusilin US_2 has been used as an important pharmaceutical excipient for solubility enhancement. Co-grinding of aceclofenac with Neusilin US_2 in a ratio of 1:5 was carried out by ball milling for 20 h. Samples of co-ground mixtures were withdrawn at the end of every 5 h. and characterized for X-ray powder diffraction, differential scanning calorimetry, and Fourier-transform infrared spectroscopy. The analysis revealed the conversion of crystalline aceclofenac to its amorphous form upon milling with Neusilin US_2. Further, *in vitro* dissolution rate of aceclofenac from co-ground mixture was significantly higher compared to pure aceclofenac. The accelerated stability study of co-ground mixture was carried out at 40°C/75%RH for 4 weeks, and it showed that there was no reversion from amorphous to crystalline form. Thus, it is advantageous to use a porous carrier like Neusilin US_2 in improvement of dissolution of poorly soluble drugs.

KEY WORDS: aceclofenac; co-grinding; dissolution; Neusilin US_2; porous carrier.

INTRODUCTION

The drug must dissolve in the gastrointestinal fluid before it can permeate across the gastrointestinal barriers. Thus, dissolution of poorly water-soluble drugs becomes the rate-limiting step in their absorption. Enhancement of the rate of dissolution of such poorly water-soluble drug can facilitate formulation design of immediate release dosage forms. Dissolution enhancement can result in improved bioavailability, a critical determinant in the success of new chemical entity (1).

Several physical approaches which have been employed to improve drug dissolution include size reduction, melt adsorption, melt quenching, solvent deposition, spray drying, and freeze drying. These techniques often lead to the formation of amorphous solids which have higher dissolution rates and therefore higher bioavailability (2). Hancock and Parks reported two to four times higher solubilities of amorphous solids compared to crystalline solids (3). Gupta *et al.* reported enhancement of drug dissolution rate upon storage with three component granules (4,5) and by co-grinding ketoprofen, indomethacin, progesterone, and naproxen with Neusilin (6). Watanabe reported higher solubility of indomethacin due to amorphization by co-grinding with silica, (7,8) with cross povidone (9) and with PVP (10). Otsuka *et al.* proposed that "non-crystalline" form of indomethacin has 60% higher solubility than γ-polymorphs (11). The importance of humidity and ratio of indomethacin to neusilin in amorphization of crystalline drug was reported by Bogner *et al.* (2). Ali *et al.* used a vibration mill to prepare amorphous co-ground mixtures of flufenamic acid with amorphous calcium silicate and silicon dioxide (12). Volatile compounds such as naphthalene, *d*-camphor, and *p*-cresol amorphized and reportedly lost their volatility when co-ground with microcrystalline cellulose (MCC) (13). Amobarbital amorphized in the presence of variety of excipients such as carbon black, ethyl cellulose, precipitated silica, and activated charcoal (14). Poorly water-soluble drug TAS-301 was melt adsorbed onto calcium silicate to prepare amorphous state of the drug, which was physically stable with improvement of solubility and oral bioavailability (15). Roland *et al.* has studied the effect of co-grinding of poorly soluble drug nifedipine with various hydrophilic carrier such as partially hydrolyzed gelatin (PHG), polyvinylpyrrolidone (PVP), sodium dodecyl sulfate (SDS), hydroxypropyl methylcellulose (HPMC), polyethylene glycol (PEG), urea or Pluronic F108 and reported the enhancement of dissolution rate. PHG-ground mixtures resulted in the fastest dissolution rate followed by PVP, SDS, HPMC, pluronic, urea, and PEG (16).

Neusilin consist of amorphous microporous granules of magnesium aluminosilicate with a high specific surface area (~300 m^2 g). Neusilin has silanol groups on its surface, which

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make it a potential proton donor as well as acceptor. The hydrogen bonding potential of silanol in the local environment on silica surfaces is well documented (17–19).

Aceclofenac (AC) 2-[[2-[2-[(2,6 dichlorophenyl) amino) phenyl)acetyl)oxy)acetic acid is a nonsteroidal analgesic, antipyretic, anti-inflammatory drug. It possesses free carboxylic acid in the structure (20,21). The molecular weight of aceclofenac is 354.2. It belongs to a category of poorly water-soluble BCS class II drug, which exhibits poor solubility and dissolution (as shown in Fig. 1).

Milling is frequently used in the pharmaceutical industry to reduce the particle size of drugs. Other than the reduction in the particle size of a drug on milling, concurrent changes in the crystal structure of the drug have also been reported (22–24). A combination of impact and attrition during ball milling can bring about changes in the polymorphs and hydrates of a drug and can induce amorphization as well (10).

Solid drugs may exist as crystalline substances or amorphous particles without identifiable structure. The amorphous or crystalline character substance can affect the stability and activity of the drug within the formulation. The amorphous form often presents greater solubility, dissolution velocity, and bioavailability than the crystalline structure, being that, in the amorphous state, the necessary energy for molecule separation is less than that of the crystalline form (25).

The amorphous state is characterized by the absence of the long-range, three-dimensional molecular order characteristic of the crystalline state. Practically, an amorphous material can be obtained in two ways: (1) by cooling the molten liquid until the molecular mobility is "frozen in," thus producing the glass (vitrification) and (2) by gradually inducing defects in the crystal until the amorphous form is attained (amorphization) (26).

Some of the useful properties of amorphous material are higher solubility, higher dissolution rate, and sometimes better compressibility. From thermodynamic point, it possesses higher energy, entropy, and free energy than corresponding crystals (27).

The problem associated with amorphous states generated by milling are prone to relax toward more stable state and can recrystallize more or less rapidly upon storage, which leads to less stable polymorphic form than nonmilled form. Sometimes,

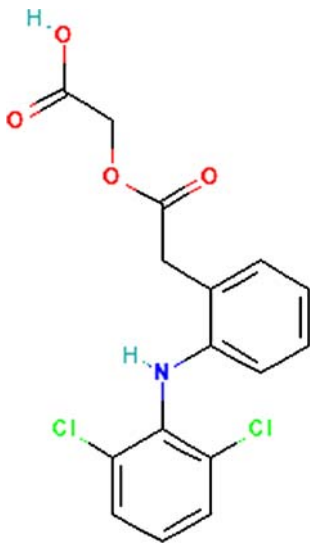

Fig. 1. Schematic diagram of Aceclofenac

milling processes induces nonequilibrium transformation which can result in critical stability issues (28). However it is not possible to predict the nature of transformation induced by milling, but it seems the two physical parameters that mainly drive the transformations are milling intensity (29,30) and milling temperature (31,33).

Increasing milling intensity has been found to drive some drug toward increasingly metastable states, e.g., indomethacin and cimetidine. Concerning milling temperature, it seems that amorphization mainly occurs when milling is performed well below the glass transition temperature (T_g) of the corresponding liquid, while polymorphic transformation mainly occurs when the milling is performed above T_g.

Aceclofenac exhibits very slight solubility in water, and as a consequence, it exhibits low bioavailability after oral administration (34,35). Therefore, the improvement of aceclofenac dissolution from its oral solid dosage forms is an important issue for enhancing its bioavailability and therapeutic efficacy.

Different approaches were used to enhance the dissolution of aceclofenac that include preparation of solid dispersion by using mixed surfactant system of SLS and alkyl polyglucosides (Patel *et al.* (36)), preparation of co-crystals of chitosan with aceclofenac (Mautik *et al.* (37)), preparation of spherical agglomerates of aceclofenac with HPMC (Usha *et al.* (38)), and preparation of inclusion complex with HP beta cycodextrin (Pathak and Dahiya (39)). Milling with porous carrier like Neusilin has been reported to enhance the dissolution of several drugs. But the same approach was not applied for aceclofenac till date. So, present study aims to enhance the dissolution of poorly water-soluble drug aceclofenac by co-grinding it with Neusilin in ball mill. The conversion of crystalline aceclofenac to amorphous form as well as the physical stability of the resulting amorphous state of the drug was monitored by X-ray powder diffraction (XRD) and differential scanning calorimetry (DSC). Fourier-transform infrared (FTIR) spectroscopy was used to investigate the presence of any interaction between drug and Neusilin. The product obtained by ball milling was subjected to dissolution rate and stability studies.

There have been contradictory reports in the literature regarding the physical stabilization of amorphous solids using silicates. Kinoshita *et al.*, showed that melt adsorption of a drug on Florite (amorphous calcium silicate) led to the formation of its amorphous state which was stable for 3 days at 60°C/80% RH and at least 2 years at ambient temperature and humidity (1). Watanabe *et al.*, however, reported the reversion of amorphous indomethacin co-ground with silica at 30-C/11% RH in 10 days (7) (2). Gupta *et al.* found that the amorphous drugs formed by co-grinding with Neusilin US$_2$ (magnesium aluminometasilicate) were physically stable for at least 4 weeks at 40°C/75% RH (6). Konno *et al.* have reported spontaneous amorphization of crystalline drugs stored (as a physical mixture) with silica (40). Since the amorphous form of the drug is associated with higher energy than its crystalline counterpart, spontaneous amorphization is an intriguing phenomenon. Attempts have been made to correlate the amorphization of the drugs by co-grinding, simple mixing, and fusion with the porous nature of the excipients (41,42). Kim *et al.* used porous and nonporous silicas to make amorphous solids by physical mixing and fusion. They suggested that amorphization and the subsequent stabilization of the amorphous state is dependent upon the porosity of the silicate (41). However, the silicates used in their study differed from

each other with respect to pH and surface area as well as porosity. However, in this article, stability study is carried out as time and condition suggested by Gupta *et al.* (6).

MATERIALS AND METHODS

Materials

Neusilin US_2 (Fuji Chemical Industry, Toyama, Japan) was obtained as a gift sample from Gangwal Chemicals, Mumbai. Aceclofenac was obtained as a gift sample from Alembic, Vadodara. All other chemicals and solvents were of analytical grade.

Methods

Preparation of Co-Ground Mixture of Aceclofenac and Neusilin US_2

A powder mixture comprising of aceclofenac and neusilin in a ratio of 1:5 by weight was milled at 25°C using a modified ball mill for a period of 20 h (6). A jar rolling mill with a plastic jar (outer diameter=5.5 in.) and glass balls (outer diameter= 1.2 in.) was used to perform the ball milling operation. The speed of the cylindrical jar was maintained at 80 rpm, which allows for significant attrition with some impact. Physical mixture of (6 g) of aceclofenac and neusilin was milled up to 20 h. (Gupta *et al.*) to effect conversion to amorphous states of the drug. Milling was performed at room temperature of 25°C, and no increase in the temperature of the milled material was detected at the end of the process. The milled material was sieved through mesh no. 30 (600 μm opening) and stored in glass vials at room temperature until used for further analysis.

Characterization of Co-Ground Mixtures of Aceclofenac and Neusilin US_2

The co-ground mixture was characterized with respect to the following methods (43,44):

1. FTIR studies
2. Differential scanning calorimetry studies
3. X-ray diffraction studies
4. *In vitro* drug dissolution studies
5. Stability studies

FTIR Studies

IR spectra of aceclofenac, Neusilin US_2, and co-grinded mixture of aceclofenac–Neusilin US_2 collected at different time intervals was taken on a FTIR (Perkin Elmer, Spectrum GX- FTIR, USA). The pellets were prepared using KBr press (Spectra Lab, Mumbai, India) using a mixture of sample and KBr in ~1:10 ratio. The spectra were recorded over the wave number range of 4,000 to 400 cm^{-1}.

Differential Scanning Calorimetry Studies

Samples of aceclofenac, Neusilin US_2, and co-grinded mixture of aceclofenac–Neusilin US_2 collected at 0 and 20 h time intervals, respectively, were separately weighed and hermetically sealed in the aluminum pans. A Thermal Analysis System instrument (Perkin Elmer DSC-pyris -1, USA) with intracooler, a refrigerated cooling system, was used. Indium standard was used to calibrate the DSC temperature and enthalpy scale. The system was purged with nitrogen gas at a flow rate of 80 mL/min. Initially, the samples were held at 50°C for 1 min and after that heating was performed from 50°C to 320°C at a scan rate of 10°C/min.

X-Ray Diffraction Studies

X-ray diffraction (XRD) pattern of the sample of the Neusilin US_2 and co-ground samples were studied by placing a thin layer of the powder in conventional cavity mounts of an X-ray diffractometer (PHILLIPS, X'Pert, Holland).

The sample scan was started at 5.0175° angle at 2Ø ° to 100.00250° end angle with step size at 2Ø° of 0.0550°. The source was X-ray tube with Cu target operated at 2 kW X-ray power that generated K-Alpha 1 X-ray radiation and detector was Xe-filled counteract or proportional detector.

In vitro Drug Dissolution Studies

The dissolution studies of pure aceclofenac (100 mg), co-ground mixture collected at the end of 5 h and at the end of 20 h (equivalent to 100 mg drug), respectively, were performed using USP XXIV type II dissolution apparatus (Veego Make, India) for 8 h. The dissolution medium used was 500 ml of distilled water maintained at 37°C±0.5°C. The paddle speed was 100 rpm. Five-milliliter samples were collected at 15, 30, 45, 60, 80, 100, 120, 150, 180, 240, 300, 360, 420, and 480 min and replaced with equal quantity of dissolution medium. After filtration through Whatman filter paper 42 (Whatman, Middlesex, UK), samples were analyzed using double beam UV spectrophotometer at 275.5 nm.

Stability Studies of Co-Ground Mixture of Aceclofenac and Neusilin US_2

The milled powders were stored at 40°C and 75% RH for 4 weeks. FTIR spectra of the fresh sample and stored samples were compared to examine the interaction of the aceclofenac with Neusilin US_2, if any. XRD and DSC data of the fresh and stored samples were compared to evaluate any changes in drug crystallinity.

RESULT AND DISCUSSION

FTIR Studies

The FTIR study was carried out to find out the interaction taking place between the Neusilin US_2 and aceclofenac at a structural level during co-grinding. The Fig. 2 shows the FTIR spectra of the six different samples taken at different time intervals.

IR spectrum of pure aceclofenac shows characteristic peaks at 965.21 cm^{-1} (O–H bending out of plane), 3,319.73 cm^{-1} (secondary amine N–H stretching or O–H stretching), 1,771.89 cm^{-1} (–C=O stretching) 1,577.9 cm^{-1},

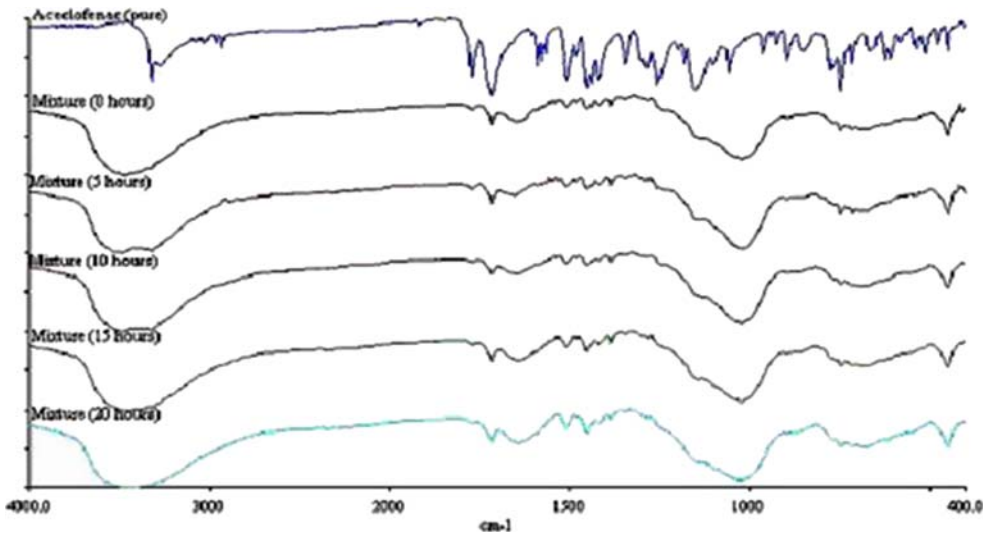

Fig. 2. FTIR analysis of *a* Aceclofenac, *b* Neusilin, c Mixture at 0 h, and *d* Mixture at 20 h

1,508.07 cm^{-1} (–C=C stretching of aromatic), and some prominent bands such as 1,344.6–1,256.58 cm^{-1} (–C–O stretching). Characteristic peaks of drug are also present in IR spectrum of mixture of the aceclofenac–neusilin at different time intervals with some broadening and reduction in intensity. The mixture of aceclofenac–neusilin gives peak near 3,469.63 cm^{-1} indicating formation of H-bond between OH of –COOH and Si of SiO_2. This leads to formation Si–O–C bridging bond formation. Further, there is reduction in the intensity of the peaks 1,771.89 and 1,717 cm^{-1} indicating interaction but not disappearance of the drug peak. Hence, it is confirmed that neusilin binds with the aceclofenac by forming H-bond and converts from its crystalline form to its amorphous form.

Formation of H-bond was previously reported by Gupta *et al.* on co-grinding carboxylic acid containing drugs such as indomethacin, ketoprofen, naproxen, and progesterone with Neusilin US_2 (6). Aceclofenac is a carboxylic acid-containing drug, so it has an acidic nature; thus, there is a possibility of an acid–base interaction between the drug and Neusilin US_2. Watanable *et al.* reported that pK_a values of SiO_2 and indomethacin are so close that a silanol group may become amphoteric, functioning as a Bronsted acid and as a Bronsted base (45). Further, Neusilin US_2 is amorphous and practically insoluble in water. The pH of the 4% *w*/*v* slurry of Neusilin US_2 in water is 7.4 indicating its neutral nature (19).

The acid–base reaction taking place can also be explained from the FTIR spectra of the milled powder. As expected in an acid–base reaction, free acid carbonyl peak and the drug dimer or oligomer peaks disappeared, and the peak for the carboxylate ion appeared in the region of 1,540–1,650 cm^{-1} (in this case, the peak appeared at 1,652 cm^{-1}) in the FTIR spectrum (46). Also, the free acid carbonyl peak becomes weaker in the amorphous neusilin-bound states of the carboxylic acid-containing drug. The changes in the FTIR spectra indicate an acid–base interaction between the carboxylic acid-containing drugs and neusilin to form their salts.

It was suggested that water mediates the acid–base reaction between the crystalline states of MgO and aceclofenac to result in crystalline magnesium salt of aceclofenac. FTIR data showed a peak of carbonyl at 1,717 cm^{-1} in the spectrum of aceclofenac. This carbonyl peak becomes significantly weaker and is accompanied by the appearance of a new carboxylate peak at 1,652 cm^{-1}. Disappearance of the carbonyl peak and the appearance of the carboxylate peak in the FTIR spectra of aceclofenac milled with amorphous neusilin suggest amorphous salt formation in the present study. While FTIR provides the evidence of salt formation, XRD and DSC data suggest that the salt is amorphous.

Electrostatic forces between COO^- group present in aceclofenac and counterions, such as Mg^{2+} and Al^{3+} present in neusilin, are responsible for causing amorphous salt formation of drug through hydrogen bonding. These interactions seem to drive or are responsible for amorphization of the drug in the present study.

Differential Scanning Calorimetry Studies

DSC patterns of four different samples are shown in the Fig. 3, and the following parameters were observed. Aceclofenac shows peak at 153.683°C with a peak height of 19.3266 mW, and Neusilin US_2 shows peak at 221.406 °C with a peak height of 0.6928 mW.

While observing the DSC pattern of mixture at 0 h, it was observed that the peak of the aceclofenac appears at 152.370 °C, which is near to the original peak, but peak height reduces significantly to 1.6275 mW. Further, the peak of the Neusilin US_2 also shifts toward a higher melting point 251.03°C, but there is reduction in the peak height.

The DSC pattern of Mixture collected at the end of 20 h shows disappearance of the drug melting point peak from 153.683°C indicating complete amorphization of aceclofenac at the end of 20 h. As previously reported by Gupta *et al.*, the melting point is considered as important criteria for milling of the drug with carrier. Analogous to heat providing the energy to disrupt the crystal lattice during melting, mechanical energy leads to amorphization during ball milling. So, the drug with higher melting point would require longer time for amorphization on milling. The melting point of aceclofenac is 153°C; hence, it was ball milled for 20 h to achieve complete amorphization (6).

It was shown by Tong *et al.* that stronger electrostatic interactions between the carboxylate group of indomethacin and counterions, such as sodium and potassium, can increase the

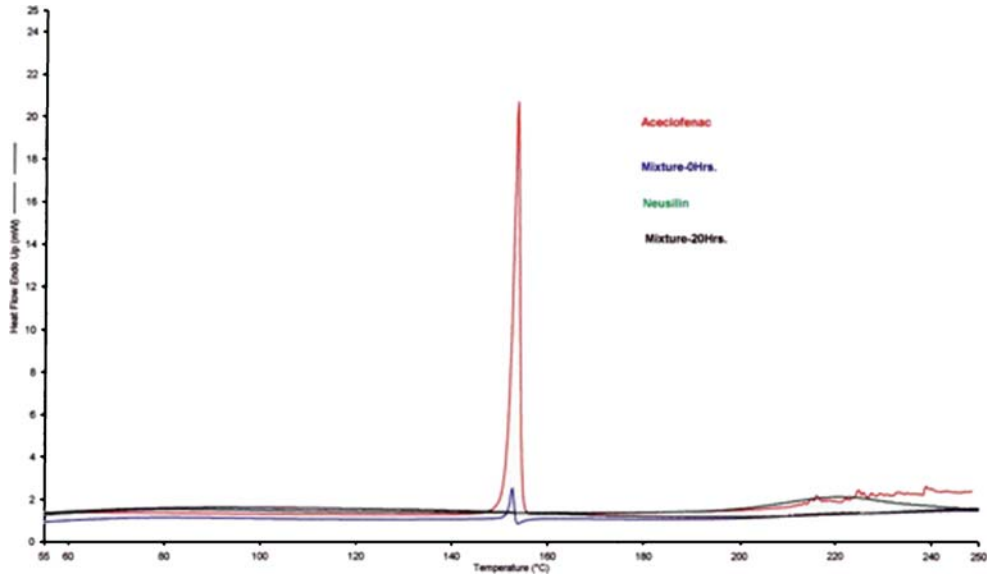

Fig. 3. DSC analysis of *a* Aceclofenac, *b* Neusilin, c Mixture at 0 h, and *d* Mixture at 20 h

glass transition temperature, T_g, of the amorphous salts, resulting in higher physical stability of the salt in comparison with the acid at a particular storage temperature. The T_g of the salt of indomethacin with monovalent lithium (139°C) (46) was much higher than that of the melt-quenched acid (44°C) (47), and it was suggested that the T_g might be even higher for salts with divalent magnesium (present in Neusilin), thereby improving the physical stability of the amorphous salt of indomethacin. Similarly for aceclofenac, it was not possible to determine the T_g of the amorphous neusilin-bound drugs by DSC, which may very well be higher than the melting point of the drugs.

Supporting evidence for amorphization of the aceclofenac on milling is obtained from the absence of any peaks in the XRD patterns.

X-Ray Diffraction Studies

The XRD analysis was carried out for the four different samples, and the plots are shown in Fig. 4 after overlapping on single scale to study the difference in crystallinity of aceclofenac. The XRD of pure aceclofenac is shown by black lines, and it shows characteristics peaks at 18.32°, 19.23.°, 22.07°, 24.30°, and 25.76° and 31.97° at (2 θ). The peak at 25.76° at (2 θ) was used to compare the XRD pattern of Neusilin US_2 and co-ground mixture of aceclofenac–neusilin collected at 0- and 20-h intervals.

The XRD represented by the green lines is that of Neusilin US_2, and it gives no peaks indicating its amorphous nature. The other two XRD patterns shown by blue line and

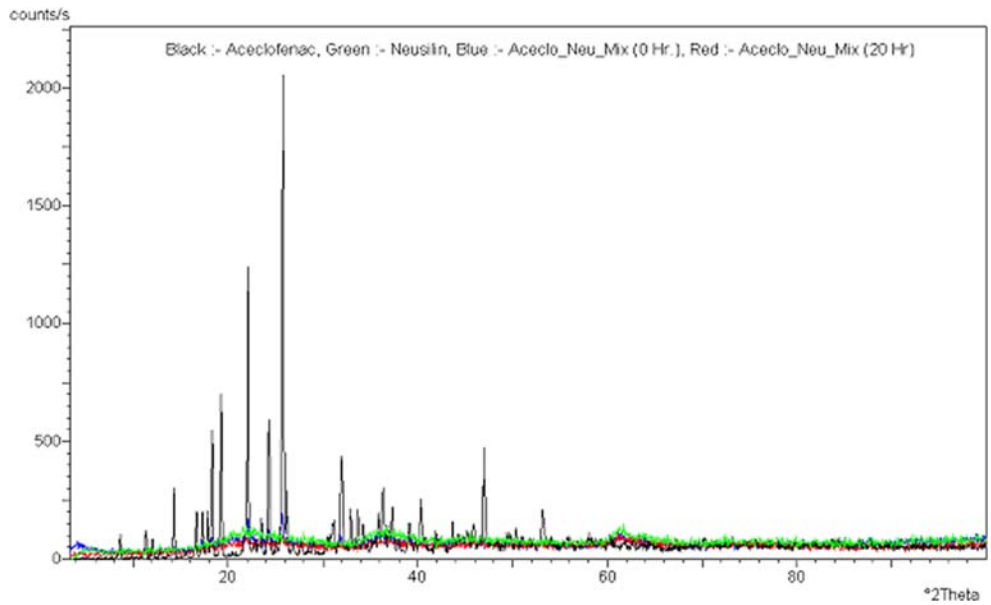

Fig. 4. XRD patterns of *a* Aceclofenac, *b* Neusilin, *c* Mixture at 0 h, and *d* Mixture at 20 h

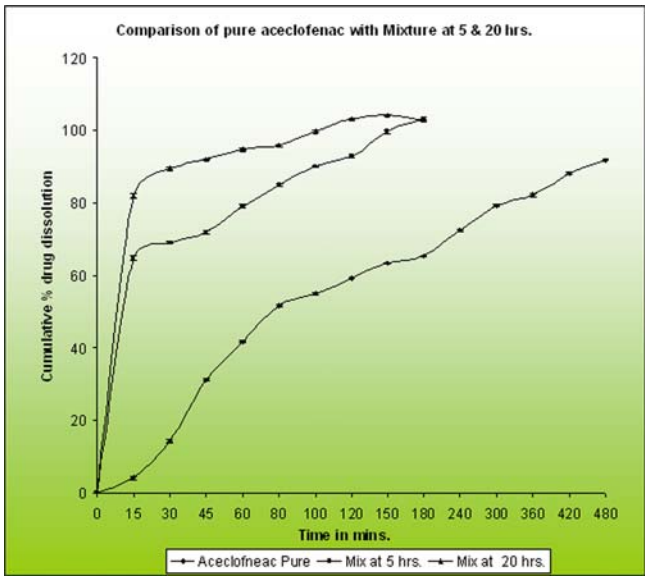

Fig. 5. Comparison of dissolution profile of pure drug and mixture collected at 5 and 20 h interval

red line are of co-ground mixtures of aceclofenac–neusilin at 0 h and aceclofenac–neusilin at 20-h intervals, respectively. It is observed that the intensity of the peak reduces in case of blue lines (mixture at 0 h interval) indicating that Neusilin US_2 interferes with the aceclofenac probably by forming hydrogen bond and thus reduces the crystallinity of the drug.

Further, the XRD pattern of the mixture collected at 20-h interval, indicated by red lines, indicates complete amorphization of the drug because XRD pattern of red lines does not show any peaks. Hence, XRD data reveals conversion of aceclofenac from crystalline form to its amorphous form.

Aceclofenac was ball milled alone to check the effect of ball milling on the drug properties, and the results show that there is no change in XRD, FTIR, and DSC spectra compared to spectra of pure drug without milling. The only difference observed is reduction in particle size from volume mean diameter (VMD) 144 to 18.2 μm. So, it is confirmed that only ball milling does not produce amorphous form of aceclofenac, but it is neusilin which is playing a significant role to achieve conversion of drug from crystalline to amorphous via formation of hydrogen bonding.

In vitro Drug Dissolution Studies

In vitro drug dissolution studies were carried out for 8 h on three different powder samples, i.e., aceclofenac alone (pure drug), mixture of Neusilin US_2, and aceclofenac collected at the end of 5 h ($Mix_{5\ h}$) and mixture of Neusilin US_2 and aceclofenac collected at the end of 20 h ($Mix_{20\ h}$).

The dissolution study was carried out to obtain the cumulative percent drug dissolution for 8 h. Figure 5 shows the graph of percent dissolution *versus* time.

The results of *in vitro* dissolution studies carried out of aceclofenac pure, a mixture of neusilin and aceclofenac collected at 5-h interval and at the end of 20 h co-grinding are shown in the Fig. 5.

From the graph, it is evident that pure aceclofenac shows the cumulative percent drug dissolution of 92% at the end of 8 h. While co-ground mixture of Neusilin US_2 and aceclofenac, collected at the end of 5-h interval and at the end of 20 h interval, show 103% drug dissolution within 3 h. Hence co-ground mixtures give faster dissolution rates compared to crystalline aceclofenac (pure drug), which can be due to dual effect produced during milling, i.e., conversion of crystalline form of aceclofenac to amorphous form during co-grinding as well as particles size reduction of aceclofenac during co-grinding, as reduction in particles size will provide larger surface area for the drug to dissolve in dissolution media.

Further, when comparing the dissolution profile of both the mixtures, the mixture collected at 20-h interval showed initial drug dissolution slightly faster than the mixture collected

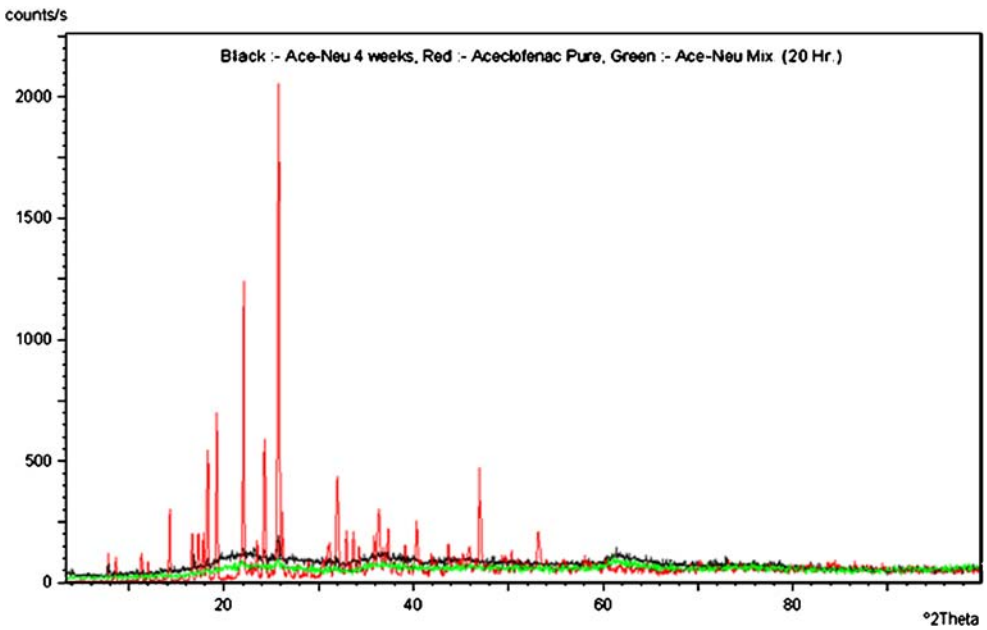

Fig. 6. XRD patterns of *a* Aceclofenac, *b* Neusilin, *c* Mixture at 20 h, and *d* Mixture after four weeks storage at 40°C and 75% RH

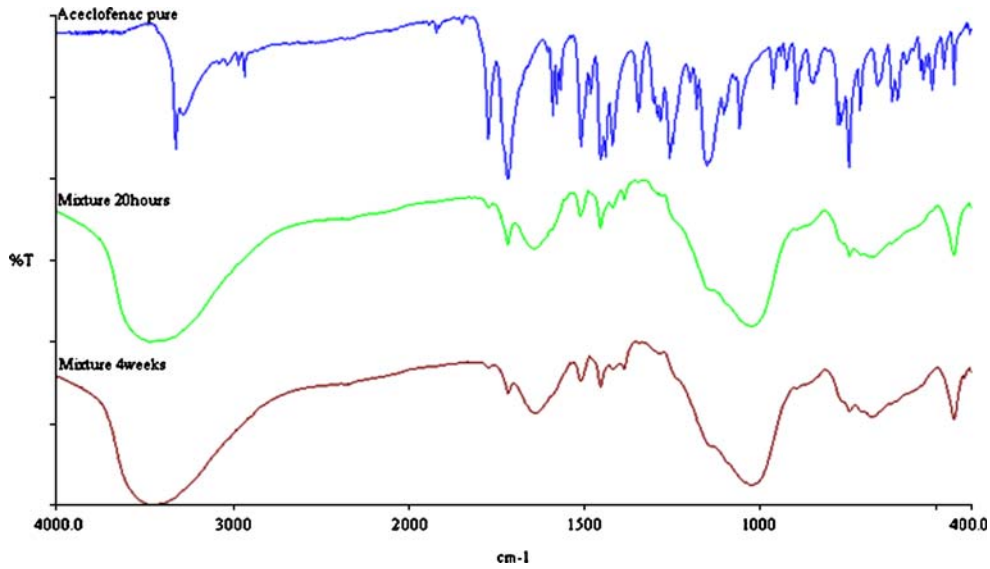

Fig. 7. FTIR spectra of *a* Aceclofenac, *b* Neusilin, *c* Mixture at 20 h, and *d* Mixture after four weeks storage at 40°C and 75% RH

at 5-h interval. So, it indicates that upon further co-grinding after 5 h, complete amorphization of aceclofenac occurs.

Stability Study of Co-Ground Mixture of Aceclofenac and Neusilin US_2

The physical stability of the resulting amorphous state of the drug after co-grinding with Neusilin was monitored by XRD and DSC. The FTIR was also taken to identify the mechanism of interaction. The samples were stored in vials at 40°C and 75% RH for 4 weeks. The data collected from the 4-week stability samples were compared with those of pure aceclofenac and co-ground mixture collected at 20-h interval.

The XRD pattern of pure aceclofenac gives the characteristics peaks at 18.32°, 19.23.°, 22.07°, 24.30° and 25.76° and 31.97° at 2 θ. The peak at 25.76° at 2 θ was used to compare the XRD pattern of fresh mixture collected at 20 h and mixture after 4 weeks of storage. The XRD patterns of both the mixtures shows no peaks indicating complete amorphization (Fig. 6). This indicates no reversion of drug form its amorphous state to its crystalline state during its storage at 40°C and 75% RH for 4 weeks

Further, FTIR data also confirms stability of H-bond formed between aceclofenac and neusilin formed during milling. From FTIR of the mixture stored for 4 weeks, it can be seen that broadening of peak 3,469.63 cm^{-1} still persists as shown in Fig. 7.

Further, supporting evidence for stability of amorphization state was obtained from DSC analysis of the mixture stored for 4 weeks (Fig. 8). No peak was observed at melting point peak of aceclofenac at 153.683°C in this sample.

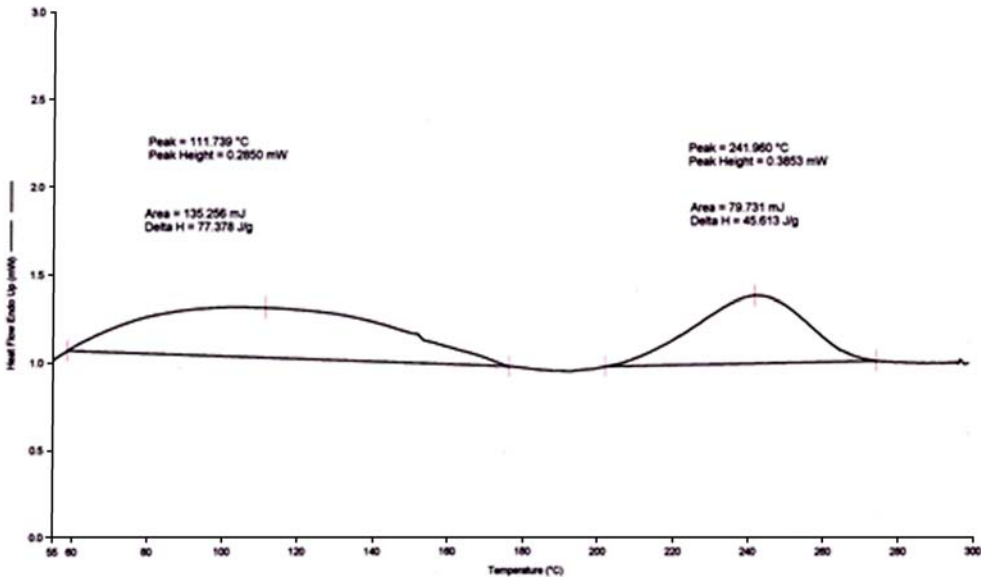

Fig. 8. DSC analysis of the mixture stored for 4 weeks at 40°C and 75% RH

So, from all the three analysis, it is confirmed that aceclofenac retains its amorphous state after 4 week stability period, and no reversion to its crystalline state occurs.

Formation of the amorphous state of aceclofenac is feasible by ball milling with Neusilin. The resulting amorphous states of the drug appear to be physically stable during storage at 40°C and 75% RH for up to 4 weeks.

It was shown by Tong *et al.* that stronger electrostatic interactions between the carboxylate group of indomethacin and counterions, such as sodium and potassium, can increase the glass transition temperature, T_g, of the amorphous salts, resulting in higher physical stability of the salt in comparison with the acid at a particular storage temperature. The T_g of the salt of indomethacin with monovalent lithium (139°C) (46) was much higher than that of the melt-quenched acid (44°C) (47), and it was suggested that the T_g might be even higher for salts with divalent magnesium (present in Neusilin), thereby improving the physical stability of the amorphous salt of indomethacin. A similar hypothesis can be applied for aceclofenac that the T_g of the amorphous neusilin-bound drug may very well be higher than the melting point of the drug thereby improving the physical stability of the co-ground mixture. The physical stabilization of aceclofenac co-ground mixture can also be attributed to its restricted molecular mobility due to mechanochemical reaction on milling with neusilin and formation of bridging bonds as suggested by Watanable *et al.* (48).

CONCLUSION

The present study shows the utility of a novel porous carrier such as neusilin to enhance the solubility and dissolution of poorly water-soluble drug aceclofenac. A simple method of co-grinding was adopted to convert crystalline form of drug to amorphous form. The results indicate that neusilin enhances the dissolution of aceclofenac and also provides physical stability by preventing reversion of drug from crystalline state to amorphous state after co-grinding. This approach can be further extended for dissolution enhancement of other BCS class II drugs.

ACKNOWLEDGEMENTS

The authors are thankful to Gangwal Chemical, Mumbai and Alembic Ltd. Vadodara for providing free gift samples of Neusilin US$_2$ and aceclofenac, respectively. The authors are also thankful to Mr. Vipul Vaghela for providing valuable suggestions during these studies and SICART for providing the analytical service for this work.

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