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Research paper

Formation of physically stable amorphous phase of ibuprofen by solid state milling with kaolin

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Abstract

Ibuprofen was milled in the solid state with kaolin (hydrated aluminium silicate) in different ratio to examine the extent of transformation from crystalline to amorphous state. The physical stability of the resultant drug was also investigated. X-ray powder diffractometry (XRD) and birefringence by Scanning Electron Microscopy (SEM) studies indicated almost complete amorphization of the drug on ball milling with kaolin at 1:2 ratio. Fourier transform infrared spectroscopy (FTIR) data showed a reduction in the absorbance of the free and the hydrogen-bonded acid carbonyl peak of carboxylic acid group accompanied by a corresponding increase in the absorbance of the carboxylate peak, indicating an acid–base reaction between the carboxylic acid containing ibuprofen and kaolin on milling. The extent of amorphization and reduction in the carbonyl peak and increase in carboxylate peak was a function of kaolin concentration in the milled powder. On storage of milled powder (at 40 °C and 75% RH for 10 weeks), XRD and birefringence of SEM study showed the absence of reversion to the crystalline state and FTIR data revealed continued reduction of carbonyl peak, whereas, ibuprofen converted from its crystalline acid form to amorphous salt form on milling with kaolin. Kaolin-bound state of ibuprofen was physically stable during storage. In-vitro dissolution studies revealed that percent release of ibuprofen from the kaolin co-milled powder is in the order: 1:2 > 1:1 > 1:0.5 > 1:0.1> milled alone ibuprofen > crystalline ibuprofen.

Keywords: Amorphization; Solid state milling; XRD; SEM; FTIR; Kaolin; Ibuprofen; In-vitro dissolution

1. Introduction

The amorphous form of poorly water-soluble drug dissolves more rapidly than the corresponding crystalline form(s). Significant differences in the bioavailability are supposed to be exhibited by the amorphous and crystalline form of drugs that show dissolution rate limited bioavailability [1]. Amorphization of poorly water-soluble drugs is thus desirable as the main expertise of formulation development for significant improvement of bioavailability. Reversion from higher energy amorphous state to the lower energy crystalline state has been a major limitation associated with the successful commercialization of solid dosage forms of poorly water-soluble drugs [2–4]. Three component solid dispersion granules containing a poorly water-soluble drug, a solid dispersion carrier (Gelucire 50/13), and an adsorbent (Neusilin US2) have been reported for dissolution enhancement [5,6]. Neusilin consists of microporous granules of magnesium aluminosilicate with silanol groups on its surface, which make it a proton donor as well as an acceptor. Kaolin is a native hydrated aluminium silicate used as a good adsorbent, consisting of microporous particles with a high specific surface area. It has too on its surface silanol groups, the potential proton donor and acceptor. The present study explored the feasibility of using a ball mill to facilitate the hydrogen

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bonding between kaolin and ibuprofen. Milling is a mechanical process, regularly used in the pharmaceutical industry for the reduction of particle size of drugs. Sufficient strain is generated in the solid particles by the high levels of mechanical energy so as to cause particle fracture and concurrent changes in the crystal structure of the drug [7–9]. During ball milling, a combination of impact and attrition can bring about changes in the polymorphs and hydrates of a drug and can induce amorphization as well [10]. The resulting higher energy amorphous state of indomethacin using impact milling and melt quenching reverted to the lower energy crystalline state during storage at 30 °C and 0% RH [11]. The rate of reversion was higher for the impact-melted drug than the melt-quenched drug.

In a recent study, amorphization of a poorly soluble drug, TAS-301 was proposed to be associated with hydrogen bonding between the carbonyl group of the drug and the silanol groups on calcium silicate using melt adsorption technique [12]. Absorption experiments, through everted rat intestine, showed that PVP-nimesulide system (co-grinding) increased nimesulide bioavailability [13]. In the present study, commercially available crystalline ibuprofen was ball milled in the solid state with kaolin. Formation of amorphous phase was characterized by X-ray powder diffraction (XRD), Scanning Electron Microscopy (SEM). FTIR spectroscopy was used to investigate the presence of any interaction between ibuprofen and kaolin. The free carboxyl acid, hydrogen-bonded acid dimer peaks, and carboxylate peaks in FTIR spectrum were monitored to identify the mechanism of interaction of the carboxylic acid containing ibuprofen with kaolin. The physical stability of the resulting amorphous state of ibuprofen was also monitored by examining XRD and FTIR data, after storing the ball milled powder at 75% RH at 40 °C. Furthermore, the influence of drug/kaolin ratio of the milled powder on drug release was investigated.

2. Materials and methods

2.1. Materials

Ibuprofen, carboxylic acid containing drug (crystalline powder), was purchased from Yucca Enterprises, Maharastra, India. Light kaolin is a native hydrated aluminium silicate. It is soft, white or yellowish white powder and characteristic earthy or clay like taste and when moistened with water becomes darker and develops pronounced clay like odour. It is insoluble in water, cold diluted acids or solutions of alkali hydroxides. It was obtained from Scientific Traders, Balasore, India.

2.2. Solid state milling

A ball mill with a cylindrical jar (outer diameter = 14.3 cm, inner diameter = 13.3 cm, and internal volume = 1000 ml) and stainless steel balls were used to perform the ball milling. The ball mill was manufactured by Swastik Electric and Scientific Work, Ambala Cantt, India. For milling purposes 100 balls (each ball having 1.27 cm diameter) were taken. Before milling ball mill and balls were washed and cleaned properly and dried. The speed of rotation of the cylindrical jar was maintained at 100 rpm. The ball charge in the jar allows smooth cascading motion during milling. The rotation of the mill along with the balls allows significant attrition and impact. Milling was performed for 1 h at room temperature (~25 °C) and no significant increase in temperature of the milled material was detected at the end of the process. The milled material was sieved through mesh # 44 and used for further analysis. Powder mixtures of ibuprofen/kaolin in the ratio by weight were milled as tabulated in Table 1. In addition, pure crystalline ibuprofen powder was also milled alone. The extent of amorphization was estimated by evaluating them for drug crystallinity using Scanning Electron Microscopy and XRD. The interaction of the drug with kaolin was confirmed by FTIR studies.

2.3. Drug–kaolin interaction studies

FTIR spectra of pure crystalline as well as milled powders were measured for comparison. KBr pellets of ibuprofen as well as milled powders were prepared. An average of at least 50 scans of each sample was collected at a scanning speed 2 U/s over a wave number region 4000–600 cm^{-1} (Model: JASCO FTIR 410, Nicolet Instrument).

2.4. Evaluation of crystallinity

Samples of ibuprofen in its pure crystalline state and on milling with kaolin were assessed for crystallinity using a X-ray diffractometer (Model: SEIFERT, C-3000, Germany) using Nickel-filtered CuKα radiation ($\lambda = 1.54$ Å). The voltage and current were 35 kV and 30 mA, respectively, and smoothed 95. Measurements were carried out in the angular range from 5° to 40° (2θ) using step size 0.05 and 0.25 s per step.

In addition, samples of drug in its pure crystalline state and on milling with kaolin were assessed for crystallinity using SEM. SEM was done by Jeol Scanning Electron Microscope (Model: JSM 5200, Japan). The samples were

Table 1
Formulation code of powdered samples of ibuprofen crystalline and milled with kaolin[a]

Powder code	Ibuprofen (g)	Kaolin (g)	Drug/kaolin ratio
Ibc	Crystalline (unmilled)	None	–
Ibm	Milled	None	–
$Ib_1K_{0.1}$	5.0	0.5	10:1
$Ib_1K_{0.5}$	3.6	1.8	2:1
Ib_1K_1	2.7	2.7	1:1
Ib_1K_2	1.8	3.6	1:2
IbK_{pm}[b]	Crystalline: 1.0	1.0	1:1

[a] Milling was performed for 1 h at room temperature (~25 °C).
[b] Physical mixtures prepared by blending crystalline drug and kaolin in a mortar with spatula immediately before use and not milled.

mounted on an aluminium stab by using a double-sided adhesive tape. Then it was placed in an ion coater unit (Model: IB-2, Hitachi, Tokyo, Japan) for gold coating (200 Å). During gold coating process the samples were exposed to vacuum of 10^{-50} mm. Afterwards, an accelerating voltage of 25 kV was applied and the image was photographed by Asia Pentex Camera of 35 mm film.

2.5. Storage of samples

The milled powder, Ib_1K_2, was stored at 40 °C and 75% RH. FTIR spectra of the initial and stored (for 10 weeks) milled powder were compared to examine the interaction of the drug, if any, with kaolin. XRD spectra of the initial and stored (for 10 weeks) milled powder were compared to evaluate any changes in drug crystallinity.

2.6. Dissolution rate studies

Samples of ibuprofen crystal (10 mg) and milled powders equivalent to 10 mg ibuprofen were tested for dissolution rate studies in 900 ml distilled water (USP paddle method: Thermonic, Campbell Electronics, Mumbai, India, at 100 rpm and 37 °C). The drug content in the withdrawn aliquots was analyzed spectrophotometrically at 220 nm (UV–VIS spectrophotometer-108, Systronics, Ahmedabad, India).

3. Results

Ibuprofen was ball milled in the solid state in the absence and presence of kaolin. No change in drug crystallinity was found after milling for 1 h without kaolin. No changes of crystallinity of ketoprofen, naproxen, indomethacin, and progesterone were reported after milling for 48 h (25 °C and 40% RH) without Neusilin [14]. Although complete amorphization of indomethacin was reported by milling in an agate centrifugal ball mill at 4 °C in 4 h [10] and cryogenic impact milling in 1 h [11], immersing the milling vessel in liquid nitrogen (−196° and ~0% RH condition). Ball milling was investigated here at laboratory ambient temperature (~25 °C) because if amorphization of drug by ball milling with kaolin were possible, the process would be simple and scalable. Indeed, amorphization was possible in the present ball milling conditions in the presence of adsorbent. The physical properties of amorphous states of ibuprofen upon milling and after storage at 40 °C and 75% RH for up to 10 weeks were studied using FTIR, XRD, and SEM and are detailed below.

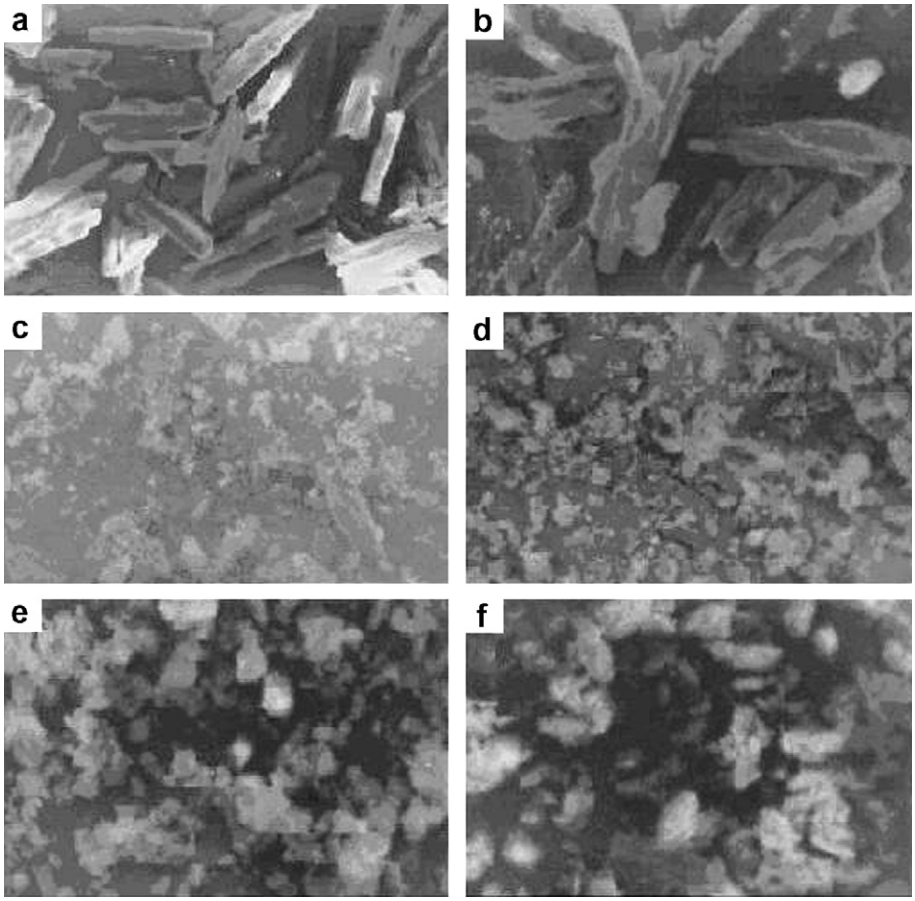

Fig. 1. Scanning electron micrographs of samples of ibuprofen crystals, physical mixture and powders milled for 1 h with kaolin at different proportions. (a) Ibc (distinctive birefringence); (b) IbK_{pm} (birefringence is not affected); (c) $Ib_1K_{0.1}$ (birefringence is slightly affected); (d) $Ib_1K_{0.5}$ (birefringence is moderately affected); (e) Ib_1K_1 (birefringence is greatly affected); (f) Ib_1K_2 (almost disappearance of birefringence). Magnification 350×.

3.1. Ibuprofen milled with kaolin

Ibuprofen was ball milled with kaolin in weight ratios of 10:1, 2:1, 1:1, and 1:2 ($Ib_1K_{0.1}$, $Ib_1K_{0.5}$, Ib_1K_1, and Ib_1K_2, respectively) for 1 h period. Samples were withdrawn from the ball mill to determine the extent of amorphization of ibuprofen. Scanning electron microscopy showed birefringence (distinctive needle like morphological views) due to the crystalline nature of ibuprofen in the initial samples (Fig. 1). On milling with kaolin, the particle size of ibuprofen was reduced. Also, birefringence (using SEM) decreased as a function of drug/kaolin ratio. With the decreased drug/kaolin ratios significantly increased amorphization of ibuprofen was observed. Crystals were not completely disappeared in the milled samples of $Ib_1K_{0.1}$ and $Ib_1K_{0.5}$. Ibuprofen crystals are not at all identified in the milled samples of Ib_1K_1 and Ib_1K_2 indicating almost disappearance of crystal (loss of geometric shape of crystal). SEM of physical mixture of drug and kaolin 1:1 (IbK_{pm}) shows the presence of ibuprofen crystal geometry very clearly with slightly damaged surface.

FTIR spectra revealed the presence of free acid carbonyl peak at 1719 cm^{-1} with high intensity in the ibuprofen crystal, but very weak in the milled ibuprofen–kaolin mixture (Fig. 2). Considering the acidic nature of the carboxylic acid group of ibuprofen, the possibility of an acid–base interaction between the drug and Al_2O_3 of kaolin (hydrated aluminium silicate, $Al_2O_3{\cdot}SiO_2{\cdot}nH_2O$) was investigated. An acid–base reaction between the carboxylic acid containing drug and kaolin does explain the changes in the FTIR spectra of milled powders. The presence of a carboxylate ion shows peak at ~1592 cm^{-1} in the FTIR spectrum. In the FTIR spectra, the aforementioned change was observed as a function of the drug/kaolin ratio. A reduction in absorbance of the free and hydrogen bound acid carbonyl peak accompanied by a corresponding increase in the absorbance of carboxylate peak was noted. The peak of carboxylate ion also appeared, but very weak in the physical mixture (IbK_{pm}, 1:1) with kaolin. Whereas, ibuprofen milled alone (Ibm) did not show any significant change in peak characteristics when compared with ibuprofen unmilled crystal (Ibc).

X-ray diffraction pattern (Fig. 3) of ibuprofen (Ibc) revealed high intensity reflections and they corresponded to the following interplanar distances: 14.5, 7.2, 5.3, 4.7, and 4.0 Å with characteristic peaks at 6.1°, 12.2°, 16.6°, 19.0°, and 22.3° (2θ), respectively. The pattern of milled ibuprofen alone (Ibm) did not present any significant difference compared to crystalline ibuprofen. The spectrum of kaolin showed two reflections of higher intensity. The interplanar distances corresponding to the high intensity reflections were 7.2 and 3.6 Å with peaks at 12.3° and 24.9° (2θ), respectively. The X-ray pattern of the physical mixture of ibuprofen and kaolin (IbK_{pm}, 1:1) showed the peaks characteristic of both ibuprofen and kaolin and was slightly poor in reflections in the angle range of 5–40° (2θ). The XRD pattern of Ib_1K_2 did not show up very well in reflections (7.2 and 3.6 Å with peaks at 12.3° and 24.9° (2θ), respectively) compared to $Ib_1K_{0.1}$, $Ib_1K_{0.5}$, and Ib_1K_1. The two peaks shown by the milled sample, Ib_1K_2, argue against amorphous nature of kaolin only. Therefore, XRD results testified the reduced ordering of the crystal lattice as the following: Ibc > Ibm > IbK_{pm} > $Ib_1K_{0.1}$ > $Ib_1K_{0.5}$ > Ib_1K_1 > Ib_1K_2.

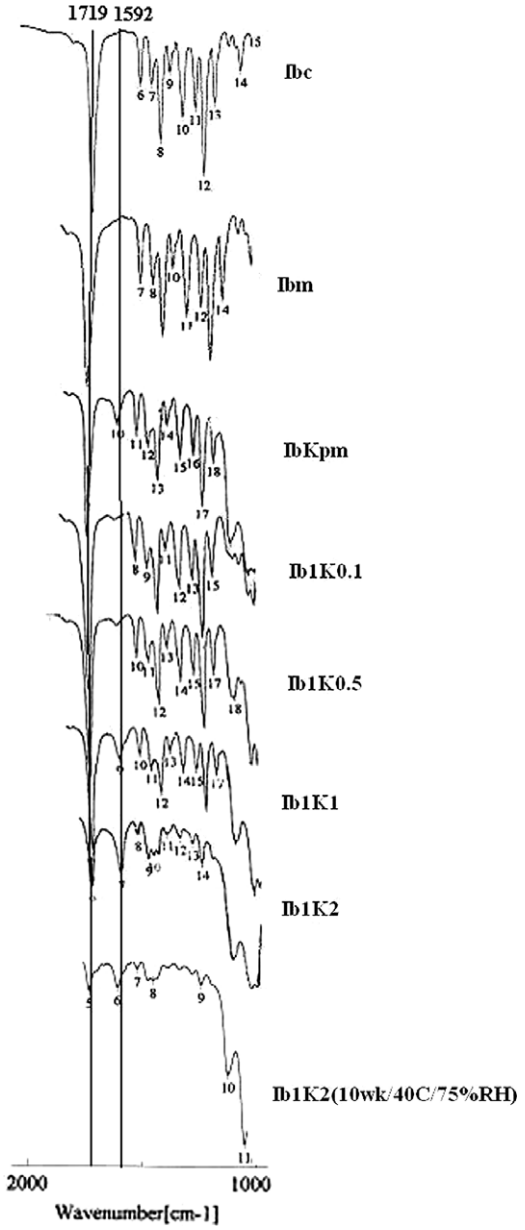

Fig. 2. FTIR spectra of samples of ibuprofen crystal and powders milled for 1 h without and with kaolin at different proportions to investigate the type of interaction. Spectrum of ibuprofen crystals (Ibc) shows free acid carbonyl peak at 1719 cm^{-1} with high intensity. The presence of carboxylate ion shows peak at ~1592 cm^{-1} in the spectra of milled powder containing kaolin and also in the physical mixture (IbK_{pm}, 1:1).

After storage of the Ib_1K_2 powder at 40 °C and 75% RH for 10 weeks, it was evaluated for any changes in ibuprofen–kaolin interaction and drug crystallinity. The amorphous kaolin-bound state of ibuprofen appears to be physically stable. As shown in figure, the free acid carbonyl peak (1719 cm^{-1}) in the crystalline ibuprofen did not reappear

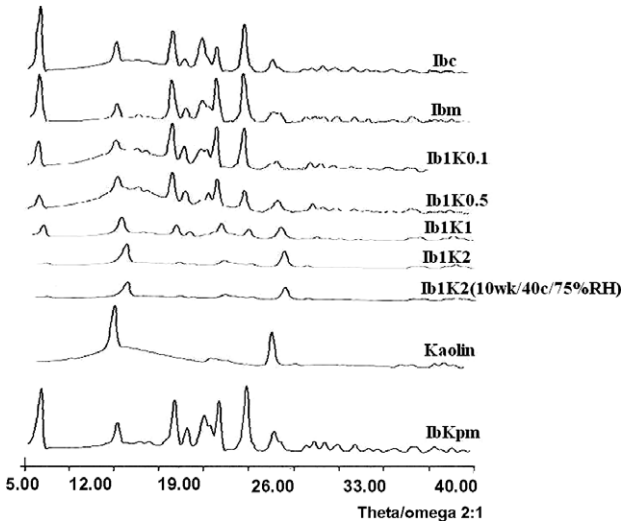

Fig. 3. X-ray powder diffraction patterns of samples of ibuprofen crystal and powders milled for 1 h with kaolin at different proportions.

on storage of the powder Ib_1K_2. Moreover, the presence of carboxylate peak of the same powder did not disappear after storing but shifted slightly from 1592 to 1595 cm^{-1}.

Also, the XRD did not show any significant difference in the peaks of the stored sample, indicating the absence of any significant reversion to the crystalline state.

3.2. In-vitro release behaviour: dissolution studies

The results of in-vitro drug release profiles from ibuprofen crystalline, milled alone and milled with kaolin for 1 h at different ratios up to 120 min are depicted in Fig. 4. The formulation Ib_1K_2 exhibited the greatest percentage of drug release ($83.5 \pm 10.1\%$). Slightly increased values of percent drug release were found from ibuprofen crystalline than that from milled alone samples. Over and above percent release of ibuprofen increased gradually with the gradual increase in kaolin proportion in the milled powders.

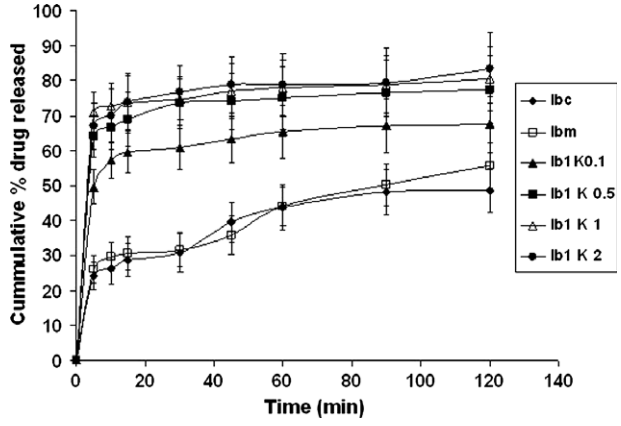

Fig. 4. Cumulative percentage of ibuprofen released in in-vitro dissolution studies from samples of ibuprofen crystal and powders milled for 1 h without and with kaolin at different proportions. Each point represents mean ± SD, $n = 3$. Ib_1K_2 and Ib_1K_1 exhibited significantly greater dissolution rate compared to Ibm and Ibc ($p < 0.05$).

Cumulative percent releases of ibuprofen from the samples are in the order as: $Ib_1K_2 > Ib_1K_1 > Ib_1K_{0.5} > Ib_1K_{0.1} >$ Ibm > Ibc.

4. Discussion

Formation of the amorphous state of ibuprofen is feasible by ball milling with kaolin, whereas amorphization does not occur on milling the drug alone. The carboxylic acid containing drug, ibuprofen, showed almost complete amorphization on milling with kaolin (Ib_1K_2). The resulting amorphous state of the drug appears to be physically stable during storage at 40 °C and 75% RH for up to 10 weeks.

This acid–base reaction does explain some of the changes in the FTIR spectra of milled powders. As expected in an acid–base reaction the free acid carboxyl peak and the drug dimer or oligomeric peaks disappeared and the peak for the carboxylate ion appeared. The presence of a carboxylate ion shows a strong peak in the region 1540–1650 cm^{-1} in the FTIR spectrum [14,15]. As observed (Fig. 2), a decrease in drug dimer peak (1719 cm^{-1} in the crystalline state) was accompanied by an increase in the absorbance of the carboxylate ion peak (1592 cm^{-1}) and the change was observed as a function of the drug/kaolin ratio and also on storage of milled powder. The changes in the FTIR spectra are supposed to indicate an acid–base interaction between the carboxylic acid containing ibuprofen and Al_2O_3 of kaolin to form its salt.

Additionally, an acid–base reaction between MgO and ibuprofen was reported to result in the formation of the magnesium salt of ibuprofen in the solid state [16]. It was suggested water mediates the acid–base reaction between the crystalline states of MgO and ibuprofen to result in a crystalline magnesium salt of ibuprofen. FTIR data showed the presence of a carbonyl peak at 1700 cm^{-1} in the spectrum of ibuprofen. This carbonyl peak was significantly weaker and was accompanied by the appearance of a new carboxylate peak at 1590 cm^{-1} in the ibuprofen salt. Disappearance of the carbonyl peak and reappearance of the carboxylate peak in the FTIR spectra of ibuprofen milled with kaolin suggest amorphous salt formation in the present study. While FTIR provides evidence for salt formation, XRD and SEM data suggest that the drug is amorphous.

Electrostatic forces (between COO^- and counter ion Al^{3+}) and hydrogen bonding interactions seem to drive the amorphization of the drug in the present study. It was shown by Tong et al. that stronger electrostatic interactions between the carboxylate group of indomethacin and counterions, such as sodium and potassium, resulted in higher physical stability of the salt in comparison with the acid at a particular storage temperature [15].

The dimer content of ibuprofen, indicating intermolecular hydrogen bonding associated with crystalline drug, in the milled powders did not disappear completely on milling but decreased further on storage (10 weeks, 40 °C and 75% RH). In another publication, changes in FTIR and XRD from three component granules (drug, Gelucire and Neusi-

lin) on storage [6] have been reported. Corresponding decrease in the drug crystallinity (from XRD study) and drug dimer content (FTIR study) was observed on storage. Gelucire served as the vehicle for mobility of drug to reach the surface and interact with Neusilin. Equilibrium moisture content of kaolin at 25 °C is 1% w/w at 15–65% RH and moreover, at 75% RH, kaolin absorbs water [17]. In the present study we observed further changes in drug dimer and drug crystallinity in ibuprofen–kaolin milled powder on storage at 75% RH/40 °C for 10 weeks and the moisture content of kaolin may be the reason for bringing about the molecular mobility.

As shown in Fig. 2, the ratio of the % T of dimer peak at 1719 cm^{-1} relative to the carboxylate peak at ~1591 cm^{-1} in the physical mixture 1:1 (IbK_{pm}:0.26) was some what less than that of the milled powder of $Ib_1K_{0.5}$ (0.29) and Ib_1K_1 (0.39). The same ratio increased in the powdered sample of Ib_1K_2 (0.91) and further increased even on storage at 75% RH for 10 weeks (0.98). This ratio increased in the following order: $Ib_1K_{0.1} < IbK_{pm} < Ib_1K_{0.5} < Ib_1K_1 < Ib_1K_2 < Ib_1K_2$ (75% RH/40 °C). Thus, the decrease in the acid dimer seems to correspond to an increase in the carboxylate ion of ibuprofen, supporting the conversion from the acid to a salt on milling and during storage. XRD provided the evidence supporting amorphization of drug, with significant reduction in the characteristic peaks of ibuprofen of the milled material on storage at 75% RH as well.

These observations suggest that moisture present in the powder plays the role of a medium in the conversion of the drug from the crystalline state to the amorphous kaolin-bound state on milling and during storage. Watanabe et al. [18] in his recent study attributed the physical stabilization of indomethacin to its restricted molecular mobility due to a mechanochemical reaction on milling with a mixture of $Mg(OH)_2$ and SiO_2 and the formation of bridging bonds. Ibuprofen milled alone exhibited slightly increased dissolution due to increased surface area of drug particle rather than the crystalline drug. Kaolin co-milled powders have shown greater dissolution because of amorphization of drug. Increase in dissolution extent could be attributed to the corresponding reduced ordering of crystal lattice. Gamma polymorphs of indomethacin have been transformed to amorphous state during milling and this amorphous state has shown 60% higher solubility than the crystalline state [10]. Although we can attribute the stabilization of the kaolin-bound amorphous state of the drug to the aforementioned mechanisms, further work needs to be performed to improve our understanding of these complex systems.

5. Conclusions

Amorphization of ibuprofen could be possible upon ball milling of the drug with kaolin in the solid state. Standard analytical techniques such as XRD and SEM birefringence studies indicated amorphization of the drug. FTIR spectroscopy showed the disappearance of carbonyl peak and reappearance of carboxylate peak in the powdered sample of ibuprofen milled with kaolin which suggested amorphous salt formation. The extent of amorphization was a function of kaolin concentration in the milled powder. On storage of milled powder at 40 °C and 75% RH for 10 weeks XRD and FTIR data revealed the absence of reversion to the crystalline state. This proved kaolin-bound state of ibuprofen was physically stable during storage. Dissolution studies revealed that the percent release of ibuprofen from milled powder is in the order: $Ib_1K_2 > Ib_1K_1 > Ib_1K_{0.5} > Ib_1K_{0.1} >$ Ibm > Ibc.

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