Drug Development and Industrial Pharmacy, 34:726–734, 2008

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040801901868

informa
healthcare

Physicochemical Characterization of Interaction of Ibuprofen by Solid-State Milling with Aluminum Hydroxide

Subrata Mallick, Satyanarayan Pattnaik, and Kalpana Swain
Formulation Development and Drug Delivery Systems, Department of Pharmaceutics, College of Pharmaceutical Sciences, Mohuda, Berhampur, Orissa, India

Pintu K. De, Arindam Saha, Pushpen Mazumdar, and Gaurisankar Ghoshal
Seemanta Institute of Pharmaceutical Sciences, Jharpokharia, Mayurbhanj, Orissa, India

This present study is a preliminary exploration of the affinity between a carboxylic model drug ibuprofen and aluminum hydroxide. Ibuprofen was comilled with aluminum hydroxide in different weight ratios in the solid state and was characterized by scanning electron microscopy (SEM), X-ray powder diffractometry (XRD), Fourier transform infrared spectroscopy (FTIR), and in vitro dissolution studies. XRD and SEM studies indicated complete interaction of ibuprofen with aluminum hydroxide and complete amorphization of aluminum hydroxide–ibuprofen complexed salt as well, on comilling with aluminum hydroxide at 1:2 ratio. FTIR data showed the disappearance of acid carbonyl peak with the appearance and the corresponding increase in absorbance of new signal at 1,682 cm^{-1} in the 1:1 and 1:2 ibuprofen–aluminum hydroxide-comilled powder. The accompanied increase in the absorbance of carboxylate peak in the ibuprofen–aluminum hydroxide physical mixture, and 1:0.1, 1:0.5, 1:1, and 1:2 (IBA_{pm}, and $IB_1A_{0.1}$, $IB_1A_{0.5}$, IB_1A_1, and IB_1A_2, respectively) comilled powder indicated an acid–base reaction between ibuprofen and aluminum hydroxide. On storage at 40°C and 75% relative humidity (RH) for 10 weeks, XRD study showed the absence of reversion to the crystalline state and FTIR data revealed continued increase of new signal at 1,682 cm^{-1} relative to carboxylic acid peak and no reappearance of carboxylic acid peak. In vitro dissolution studies revealed that the percent release of ibuprofen from the aluminum hydroxide-comilled powder is in the following order: IB_1A_2 < IB_1A_1 < ibuprofen crystal < ibuprofen milled alone < $IB_1A_{0.1}$ < $IB_1A_{0.5}$. Aluminum metal cation might have interacted to form a complex through the carboxyl and carbonyl groups of ibuprofen. Improved dissolution of drug associated with $IB_1A_{0.1}$ and $IB_1A_{0.5}$ is because of the absence of a new signal at 1,682 cm^{-1} and improved amorphization of the drug to some extent. Dissolution of drug affected in IB_1A_2 and IB_1A_1 may be because of the insoluble stable complex formation.

Keywords solid state; interaction; x-ray powder diffractometry; FTIR; dissolution rate

Address correspondence to Subrata Mallick, Formulation Development and Drug Delivery Systems, Department of Pharmaceutics, College of Pharmaceutical Sciences, Mohuda, Berhampur 760002, Orissa, India. E-mail: smallickin@yahoo.co.in

INTRODUCTION

Ibuprofen is an arylacetic acid analogue with anti-inflammatory, antipyretic, and analgesic properties. It is also used in the treatment of rheumatoid arthritis and osteoarthritis. Biopharmaceutical classification system of the drug is characterized by high membrane permeability and slow dissolution rate because of low aqueous solubility and high per oral dose (Rinaki, Valsami, & Macheras, 2003). The solubility and dissolution-related bioavailability of poorly water-soluble drugs can be improved by improving the amorphization using solvent evaporation, melt extrusion, melt quenching, spray drying, milling, and so on (Leuner & Dressman, 2000; Mallick, Pattnaik, Swain, & De, 2007; Mallick, Sahoo, & Mitra, 2003). Amorphization of drug by comilling (Mallick, 2004) with adsorbents in the solid state for improvement of dissolution is one of the most explored fields in pharmaceutical technology and utilized for the drugs such as carbamazepine (Barzegar-Jalali et al., 2006), celecoxib (Nagarsenker & Joshi, 2005), naproxen (Mura et al., 2005a, 2005b; Zerrouk, Mennini, Maestrelli, Chemtob, & Mura, 2004), triamterene (Mukne & Nagarsenker, 2004), ibuproxam (Cirri et al., 2004), and dehydroepiandrosterone (Mora et al., 2003). Comilling is economically and environmentally desirable; unlike other techniques, it does not require toxic solvents (Sarkari et al., 2002) and sophisticated equipments (Moneghini, Kikic, Voinovich, Perissutti, & Filipovic-Grcic, 2001). In a recent study, each of the four drugs (ketoprofen, indomethacin, naproxen, and progesterone) was milled with Neusilin (amorphous magnesium aluminosilicate) to effect amorphization (Gupta, Goldman, Bogner, & Tseng, 2003).

Literature survey revealed that metallic adsorbents such as Neusilin (magnesium aluminosilicate) and talcum (hydrous magnesium silicate, sometimes containing a small proportion of aluminum silicate) were effectively utilized for amorphization of drugs (Gupta et al., 2003; Kinoshita, Baba, Nagayasu, Yamabe, & Shimooka, 2002; Sharma, Sher, Badve, & Pawar,

2005; Smirnova, Suttiruengwong, Seiier, & Arlt, 2004; Watanabe, Ohno, Wakiyama, Kusai, & Senna, 2002).

Kaolin, a native hydrated aluminum silicate used as a good adsorbent, consists of microporous particles with a high specific surface area. Amorphization and improvement of dissolution of drug upon comilling with kaolin have already been reported in our previous publication (Mallick et al., 2008). Aluminum hydroxide interacts with the carboxyl and carbonyl groups of quinolones irreversibly and reduces bioavailability of the drug significantly (Lober et al., 1999; Mallick et al., 2007; Teng, Dogolo, Willavize, Friedman, & Vincent, 1997). No comprehensive work on the solid-state interaction of poorly water-soluble drug with aluminum hydroxide and its impact on dissolution of the drug, if any, have yet been reported.

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 defects in the crystal structure of the drug (Buckton, Choularton, Beezer, & Chatham, 1988; Kitamura, Miyamac, Koda, & Morimoto, 1989; Otsuka, Ofusa, & Matsuda, 1999). 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. 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 (Otsuka, Matsumoto, & Kareniwa, 1986).

In this study, we explored the feasibility of using a ball mill to facilitate any physical or chemical interaction between the adsorbent like aluminum hydroxide and ibuprofen in the solid state and examined its effect on dissolution. Ibuprofen was ball-milled with dried aluminum hydroxide gel in different ratios for 1 h. The resulting amorphous state of the drug was monitored by X-ray powder diffraction (XRD) and scanning electron microscopy (SEM). Fourier transform infrared spectroscopy (FTIR) was used to investigate the presence of any interaction between the drug and aluminum hydroxide. The free carboxyl acid, the carboxylate peak, and the new signal, if any, in the FTIR spectrum were monitored to identify the mechanism of interaction of ibuprofen (carboxylic acid-containing drug) with aluminum hydroxide. XRD and SEM methods were used to examine the crystallinity of the drug in the comilled powder. Physical or chemical stability of the resulting interaction of the drug was monitored by XRD and FTIR on storage of the comilled powders at 40°C and 75% relative humidity (RH) for 10 weeks. Finally, in vitro dissolution pattern of the drug, in different comilled powders was studied to investigate the impact of interaction on dissolution.

MATERIALS AND METHODS

Materials

Ibuprofen (crystalline powder) was purchased from Yucca Enterprises (Maharashtra, Mumbai, India). SD Fine Chemicals (Mumbai, India) supplied the dried aluminum hydroxide gel. It is a white light powder largely containing amorphous hydrated aluminum oxide together with varying quantities of basic aluminum carbonate and bicarbonate (minimum assay: 47% of Al_2O_3; maximum limits of impurities: chloride 0.5%, sulfate 0.25%, and arsenic 0.0005%). Moisture content is 8–10% and pH of the solution is not more than 10. It is insoluble in water and in ethanol (95%). It dissolves in dilute mineral acids and in excess of caustic alkali solutions, and it is used as antacid.

Solid-State Milling

Ibuprofen and aluminum hydroxide were mixed in a mortar with weight ratios as tabulated in Table 1 to obtain a physical mixture. The physical mixture (~5.5 g) was placed into a cylindrical vessel of outer diameter 14.3 cm and inner diameter 13.3 cm (inside capacity 1,000 mL). Stainless steel balls were used to perform the ball milling. The ball mill was manufactured by Swastik Electric and Scientific Work (Ambala Cantonment,

TABLE 1
Formulation Code of Powdered Samples of Ibuprofen

Powder Code	Ibuprofen (g)	Aluminum Hydroxide (g)	Drug–Aluminum Hydroxide Ratio	Status
IBC	Crystalline	–	–	Unmilled
IBM	Crystalline	–	–	Milled alone
$IB_1A_{0.1}$	5.0	0.5	10:1	Comilled
$IB_1A_{0.5}$	3.6	1.8	2:1	Comilled
IB_1A_1	2.7	2.7	1:1	Comilled
IB_1A_2	1.8	3.6	1:2	Comilled
IBA_{pm}[a]	1.0	1.0	1:1	Unmilled

Milling was performed for 1 h at room temperature (~25°C).

[a]Physical mixture prepared by blending crystalline drug and aluminum hydroxide in a mortar with spatula immediately before use.

India). For milling purposes, 100 balls (each ball having 1.27 cm diameter) were taken. Before milling, the vessel and the balls were washed and cleaned properly and dried. The ball mill was operated at 100 rpm. The ball charge in the vessel 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 passed through mesh 44 (opening ~350 μm) and used for further analysis. Separately, crystalline ibuprofen was also milled under the same milling condition. The extent of amorphization was estimated by evaluating them for drug crystallinity (using SEM and XRD). The interaction of the drug with aluminum hydroxide was confirmed by FTIR studies.

Physicochemical Characterization

Fourier Transform Infrared Spectroscopy

The KBr disk sample preparation technique was used to obtain the FTIR spectra. FTIR spectroscopy was used to investigate the presence of any interaction between ibuprofen and aluminum hydroxide. An average of at least 50 scans of each sample was collected at a scanning speed 2 unit/s over a wave number region 4,000–600 cm^{-1} (Model: JASCO FTIR 410, Nicolet Instrument, Madison).

X-Ray Powder Diffraction

X-ray diffraction patterns of all the samples of ibuprofen in its pure crystalline state and on comilling with aluminum hydroxide were assessed for crystallinity using an automatic powder diffractometer (Model: C-3000, Seifert, Ahrensburg, Germany) using nickel–filtered Cu Kα radiation (λ = 1.54 A). 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 of 0.05 and 0.25 s per step.

Scanning Electron Microscopy

Surface topography of the powdered samples was assessed for crystallinity using SEM. SEM was done by Jeol Scanning Electron Microscope (Model: JSM 5200, Tokyo, Japan). The samples were mounted on an aluminum 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 A). During the 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 using Asia Pentax (Tokyo, Japan) camera with a 35-mm film.

Storage of Samples

The comilled powdered mixture, IB_1A_2 was stored at 40°C and 75% RH for 10 weeks. The initial and stored comilled mixture was compared to examine the interaction of the drugs, if any, with dried aluminum hydroxide gel using FTIR spectra. Any changes in drug crystallinity were compared in the initial and stored samples using XRD spectra.

Dissolution Rate Studies

Dissolution tests of ibuprofen crystal (10 mg) and comilled powders (equivalent to 10 mg ibuprofen) were performed using USP XXIV type II dissolution apparatus (Thermonic, Campbell Electronics, Mumbai, India) with a rotation speed of 100 rpm and temperature 37ºC. The dissolution study was first attempted in distilled water. These powder samples did not wet easily and stuck to the wall of the vessel and to the paddle because of their strong hydrophobic nature. Addition of 2 mg of sodium lauryl sulfate (SLS) per milliliter of distilled water produced such a rapid dissolution of the drug that it was impossible to observe any difference in the dissolution profiles of the ibuprofen crystal and milled and comilled powders with aluminum hydroxide. After addition of a small amount of 1 mg/mL of SLS, the wettability of the drug was sufficient to avoid these undesirable facts and to observe differences among the dissolution profiles of the crystal and milled and comilled powder formulations. The drug content in the withdrawn aliquots was analyzed spectrophotometrically at 220 nm (UV–VIS Spectrophotometer-108, Systronics, Ahmedabad, India).

RESULTS

Ibuprofen was ball-milled in the solid state alone and in the mixture with aluminum hydroxide. No significant change in drug crystallinity was found after milling for 1 h without aluminum hydroxide. Complete amorphization of indomethacin was reported by milling in an agate centrifugal ball mill at 4°C for 4 h (Otsuka et al., 1986) and a cryogenic impact mill for 1 h (Crowley & Zografi, 2002), immersing the milling vessel in liquid nitrogen (–196°C and ~0% RH condition). No changes in the crystallinity of ketoprofen, naproxen, indomethacin, and progesterone were reported after milling for 48 h (25°C and 40% RH) without Neusilin (Gupta, Vanwert, & Bogner, 2003). The differences in milling temperature and conditions accounted for the difference in the extent of amorphization of pure drugs. Ball milling was investigated here at laboratory ambient temperature (~25°C) because if the comilling of the drug with aluminum hydroxide were effective, the process would be simple and scalable. Indeed, amorphization was possible in the present comilling conditions in the presence of aluminum hydroxide. The physicochemical interaction of ibuprofen, upon comilling and after storage at 40°C and 75% RH for up to 10 weeks, was studied using FTIR, XRD, and SEM and is detailed below.

Changes in Crystallinity Because of Comilling

Ibuprofen was comilled with aluminum hydroxide in weight ratios of 10:1, 2:1, 1:1, and 1:2 ($IB_1A_{0.1}$, $IB_1A_{0.5}$, IB_1A_1, and

IB_1A_2, respectively) for 1-h period. Samples were withdrawn from the ball mill to determine the extent of amorphization of ibuprofen. SEM showed distinctive needle-like morphological views of geometric shape because of the crystalline nature in the initial sample of ibuprofen (Figure 1). Upon comilling ibuprofen–aluminum hydroxide, ibuprofen was identified as the reduced particles in the domain of irregular particles of aluminum hydroxide. Also, the geometric shape has gradually disappeared as a function of drug–aluminum hydroxide ratio. With the decreased drug–aluminum hydroxide ratios, increased amorphization of ibuprofen was observed significantly. Ibuprofen crystals were rarely found in the comilled samples of $IB_1A_{0.1}$ and $IB_1A_{0.5}$. The comilled samples of IB_1A_1 and IB_1A_2 produced moist agglomerate particles, wherein no ibuprofen crystal was identified. That indicated almost complete disappearance of crystal surface (loss of geometric shape of crystal). SEM of a physical mixture of drug and aluminum hydroxide 1:1 (IBA_{pm}) shows the presence of ibuprofen crystal geometry very clearly with slightly damaged surface.

The X-ray diffraction pattern (Figure 2) of ibuprofen showed high-intensity reflections to the interplanar distances—14.5, 7.2, 5.3, 4.7, and 4.0 Å at 6.1°, 12.2°, 16.6°, 19.0°, and 22.3° (2θ), respectively. The spectrum of aluminum hydroxide revealed intensity reflection corresponding to 6.5 and 4.8 Å at 13.7° and 18.5° (2θ), respectively. X-ray diffraction pattern of the physical mixture (IBA_{pm}, 1:1) was slightly poor in reflections in the angle range 5–40° (2θ). Compared to crystalline ibuprofen, the pattern of milled ibuprofen alone revealed no significant difference (14.5, 7.2, 5.3, 4.7, 4.4, and 4.0 Å at 6.1°, 12.2°, 16.6°, 19.0°, 20.2°, and 22.3° (2θ), respectively). The pattern of IB_1A_2 showed very poor diffraction peaks at 13.7° and 18.5° (2θ) of 6.5 and 4.8 Å, respectively. IB_1A_1 and $IB_1A_{0.5}$ showed major intensity reflections to the interplanar distances—6.1 and 4.7 Å at 14.4° and 18.5° (2θ) and 6.3 and 5.8 Å at 14.0° and 16.6° (2θ), respectively. $IB_1A_{0.1}$ showed intensity reflections to the interplanar distances—14.5, 7.2, 6.3, 6.0, 5.3, 5.0, 4.7, 4.5, 4.4, and 4.0 Å at 6.1°, 12.2°, 14.0°, 14.7°, 16.6°, 17.7°, 18.9°, 19.5°, 20.2°, and 22.3° (2θ), respectively. Therefore, XRD results indicated the reduced ordering of the crystal lattice.

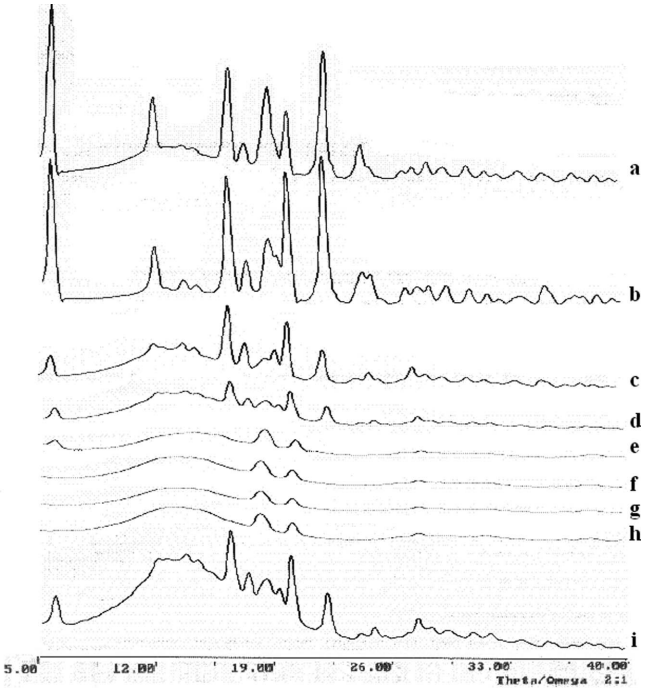

FIGURE 2. X-ray powder diffraction pattern of samples of ibuprofen crystal, milled alone, and comilled for 1 h with aluminum hydroxide: (a) IBC, (b) IBM, (c) $IB_1A_{0.1}$, (d) $IB_1A_{0.5}$, (e) IB_1A_1, (f) IB_1A_2, (g) IB_1A_2 stored at 40°C and 75% RH for 10 weeks, (h) aluminum hydroxide, unmilled, and (i) IBA_{pm}.

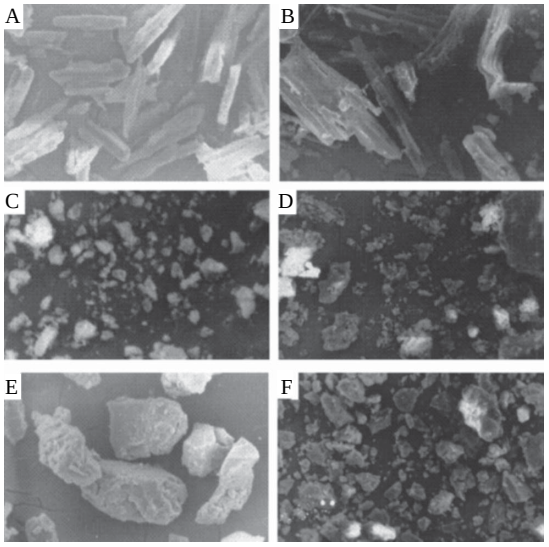

FIGURE 1. Scanning electron micrographs of samples of ibuprofen crystals, physical mixture, and powders comilled for 1 h with aluminum hydroxide at different ratios. (A) IBC (ibuprofen crystalline powder) (distinctive birefringence); (B) IBA_{pm} (birefringence is not affected); (C) $IB_1A_{0.1}$ (birefringence is slightly affected); (D) $IB_1A_{0.5}$ (agglomeration of particles, birefringence moderately affected); (E) IB_1A_1 (agglomeration of particles, birefringence greatly affected); and (F) IB_1A_2 (agglomeration of particles, almost disappearance of birefringence) Magnification ×350.

Thus complete amorphization of the aluminum hydroxide-bound ibuprofen was monitored from XRD spectrum of the comilled IB_1A_2 powder (Figure 2). SEM method supported the evidence for obtaining the amorphization from the complete disappearance of geometric shape of the crystal. In comparison to the intense peaks for ibuprofen alone in the crystal, IB_1A_2 does show two XRD peaks at 13.7° and 18.5° (2θ) only because of aluminum hydroxide (Figure 2).

Changes in Molecular Interaction Because of Comilling

As shown in Figure 3, the carboxylic acid peak of ibuprofen at 1,719 cm^{-1} gradually decreased in the ball-milled powder

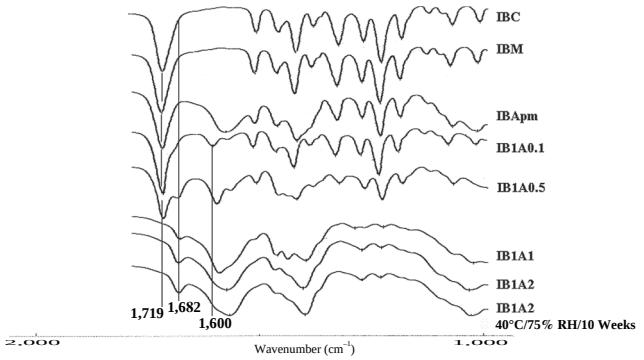

FIGURE 3. Fourier transform infrared spectroscopy (FTIR) spectra of samples of ibuprofen crystal milled alone and comilled for 1 h with aluminum hydroxide at different ratios to investigate the type of interaction. Spectrum of ibuprofen crystals (IBC, ibuprofen crystalline powder) showed free acid carboxyl peak at 1,719 cm^{-1} with high intensity. In IB_1A_1 and IB_1A_2 comilled powders, a new signal at 1,682 cm^1 appeared and the carboxylic acid at 1,719 cm^{-1} disappeared. The formation of carboxylate peak in the range 1,600–1,572 cm^{-1} gradually increased in $IB_1A_{0.1}$ through IB_1A_2. The stored IB_1A_2 comilled powder (40°C and 75% RH for 10 weeks) did not show any sort of reversion. A shoulder appeared at the carboxylate range (1,572 cm^{-1}) in the physical mixture (IBA_{pm}, 1:1).

$IB_1A_{0.1}$ and $IB_1A_{0.5}$ and disappeared completely in IB_1A_1 and IB_1A_2. The powder samples of ibuprofen obtained during milling, similar to other reported carboxylic acid-containing drugs such as ketoprofen, indomethacin, and naproxen (Gupta et al., 2003), did not show the peaks for the acid dimer and the free acid carbonyl in the FTIR spectra in IB_1A_1 and IB_1A_2. Rather, in IB_1A_1- and IB_1A_2-comilled powders, a new signal appeared at ~1,682 cm^{-1}, which could be associated with the new "chemical entity." Considering the acidic nature of the carboxylic acid group of ibuprofen, the possibility of an acid–base interaction between the drug and aluminum hydroxide was investigated. An acid–base reaction between the carboxylic acid-containing drug and aluminum hydroxide does explain the changes in the FTIR spectra of milled powders. As expected, in an acid–base reaction, the acid carboxyl peak for the carboxylate ion appeared.

The carboxylate peak in the range 1,600–1,573 cm^{-1} gradually increased in the comilled powder $IB_1A_{0.1}$ through IB_1A_2. The presence of a carboxylate ion shows a strong peak at 1,593–1,573 cm^{-1} in the FTIR spectra of IB_1A_1 and IB_1A_2, respectively. In the FTIR spectra, the aforementioned change was observed as a function of the drug–aluminum hydroxide ratio. Weak appearance of the peak of carboxylate ion (~1,576 cm^{-1}) was also observed even in the physical mixture (IBA_{pm}, 1:1) with aluminum hydroxide. Ibuprofen crystals milled alone did not show any significant change in peak characteristic of ibuprofen compared with unmilled crystal.

However, XRD and SEM make the study more sensitive than FTIR regarding amorphization. The FTIR study rather revealed the interaction between ibuprofen and aluminum hydroxide.

Drugs generally have a higher enthalpy in the amorphous state compared with the crystalline state. Sorption of moisture into an amorphous region would increase molecular mobility and subsequently decrease glass transition temperature. Hence, to evaluate any further changes in drug–aluminum hydroxide interaction and drug crystallinity, the IB_1A_2 powder was stored at 40°C and 75% for 10 weeks. The amorphous nature of aluminum hydroxide-bound state appears to be stable. As shown in Figure 3, the acid carbonyl peak (1,719 cm^{-1}) in the crystalline ibuprofen did not reappear on storage of powder IB_1A_2. Instead, the absorbance of the new signal at 1,682 cm^{-1} associated with the new "chemical entity" increased, relative to the carboxylate peak at 1,572 cm^{-1} slightly. Also, the XRD did not show any significant changes in the stored sample, indicating the absence of any reversion to the crystalline state of the drug (Figure 2). In contrast to the results using 1:2 ibuprofen to aluminum hydroxide ratio (IB_1A_2), when ibuprofen is comilled with aluminum hydroxide in 10:1, 2:1, and 1:1 weight ratios ($IB_1A_{0.1}$, $IB_1A_{0.5}$, and IB_1A_1) for 1 h, the absorbance of the new signal (1,682 cm^{-1}) is still increasing, indicating incomplete interaction with aluminum hydroxide (Figure 3). However, the acid carboxyl peak (1,719 cm^{-1}) was already being consumed in the IB_1A_1-comilled powder. Supporting evidence for incomplete amorphization was obtained from the presence of peaks in the XRD spectrum of the $IB_1A_{0.1}$-, $IB_1A_{0.5}$-, and IB_1A_1-comilled powders (Figure 2). However, on storage at 40°C and 75% RH for 10 weeks, the IB_1A_2-comilled powder did not show any sort of reversion either amorphous form to crystalline form or chemically interacted form to free form of the drug. This indicates an irreversible interaction.

Changes in Dissolution of Drug

The dissolution profiles of unmilled crystalline ibuprofen and milled powders have been evaluated for 120 min and depicted in Figure 4. Because of its poor aqueous solubility, ibuprofen crystalline powder (IBC) exhibited a slow rate of dissolution even in the medium containing 1 mg of SLS per milliliter with 63.4 ± 1.9% (n = 4) being released at the end of a 120-min period. A slightly increased percentage of dissolution was found from Ibuprofen crystals milled alone (IBM) (69.4 ± 2.1%, n = 4). The $IB_1A_{0.5}$-comilled powder exhibited the greatest percentage of dissolution of ibuprofen (81.0 ± 1.5%, n = 4). The $IB_1A_{0.1}$-comilled powder showed decreased dissolution (72.8 ± 2.8, n = 4) than $IB_1A_{0.5}$. A decreased dissolution of ibuprofen has been observed when the ibuprofen–aluminum hydroxide ratio by weight was decreased to 1:1 (IB_1A_1) and 1:2 (IB_1A_2) (60.9 ± 1.8 and 53.4 ± 1.9, respectively). Thus, the percent release of ibuprofen from crystalline, milled alone, and comilled with aluminum hydroxide samples can be placed in the increasing following order: $IB_1A_2 < IB_1A_1 < IBC < IBM < IB_1A_{0.1} < IB_1A_{0.1}$.

DISCUSSION

Moist agglomerate particles produced after comilling samples of IB_1A_1 and IB_1A_2 may be because of the interaction of

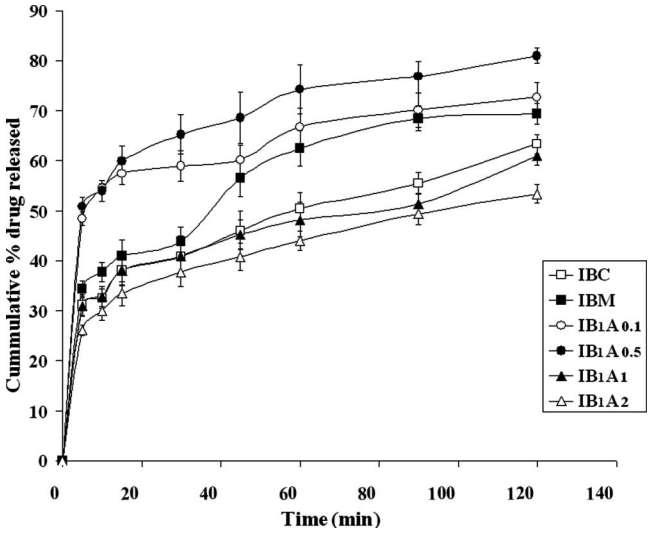

FIGURE 4. Cumulative percentage of ibuprofen released in in vitro dissolution studies from samples of ibuprofen crystal, milled alone, and powders comilled for 1 h with aluminum hydroxide at different ratios. Each point represents mean ± *SD*, $n = 4$. Dissolution studies revealed that the percentage release of ibuprofen was mostly affected in the IB_1A_2 and IB_1A_1 than in the $IB_1A_{0.1}$ and $IB_1A_{0.5}$ comilled powders Total status can be expressed in the following order: $IB_1A_2 < IB_1A_1 < IBC < IBM < IB_1A_{0.1} < IB_1A_{0.5}$.

aluminum hydroxide and ibuprofen with squeezing out of inherently bound water associated with aluminum hydroxide. This suggested that the interaction force between ibuprofen–aluminum hydroxide systems is stronger than the water held in aluminum hydroxide. Formation of the amorphous state of aluminum hydroxide-bound ibuprofen is possible by ball milling with aluminum hydroxide, whereas amorphization does not occur on milling the drug alone. Ibuprofen that has the proton-donating group showed amorphization on comilling with aluminum hydroxide. Considering the acidic nature of the carboxylic acid-containing drug, ibuprofen, the possibility of an acid–base interaction between the drug and aluminum hydroxide was investigated. This acid–base reaction does explain some of the changes in the FTIR spectra of comilled powders. As expected in an acid–base reaction, the free acid carboxyl peak disappeared and the peak for the carboxylate ion appeared. The presence of a carboxylate ion shows a strong peak in the region 1,540–1,650 cm^{-1} in the FTIR spectrum (Gupta et al., 2003; Mallick et al., 2008; Tong, Taylor, & Zografi, 2002). As observed in Figure 3, a decrease in acid carbonyl peak (1,719 cm^{-1} in the crystalline state) was accompanied by an increase in the absorbance of the carboxylate ion peak (1,572–1,600 cm^{-1}). The aforementioned change was observed as a function of the drug–aluminum hydroxide ratio and did not disappear after storage of comilled powder. The changes in the FTIR spectra indicate an acid–base interaction between the carboxylic acid-containing ibuprofen and aluminum hydroxide to form their salt. Additionally, a new signal appeared at 1,682 cm^{-1} in $IB_1A_{0.5}$ and gradually became strong in IB_1A_1 and IB_1A_2 and further absorbance increased in the stored (40°C, 75% RH, 10 weeks) IB_1A_2-comilled powder. This confirmed the formation of a chemical bond and these interactions may ultimately affect the release profile of the drug in the biological systems. Pignatello, Spadaro, Vandelli, Forri, and Puglisi (2004) in their study described that the chemical interaction of ibuprofen and Eudragit RL100 (coevaporates is because of the anionic nature of the carboxylic drug and the presence of positively charged quaternary ammonium group in Eudragit RL100.(During formulation development work involved in ibuprofen, a solid-state interaction between MgO and ibuprofen was observed (Kararli, Needham, Suel, & Finnegan, 1989). 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 (Kararli et al., 1989). It was suggested that 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 carboxyl peak at 1,700 cm^{-1} in the spectrum of ibuprofen. This carboxyl peak was significantly weaker and was accompanied by the appearance of a new carboxylate peak at 1,590 cm^{-1} in the ibuprofen salt $NaHCO_3$; $K_2CO_3.1.5H_2O$, CaO, and $Mg(OH)_2$ also showed solid-state reactions with ibuprofen (Kararli et al., 1989). Disappearance of the carbonyl peak and reappearance of the carboxylate peak in the FTIR spectra of ibuprofen comilled with aluminum hydroxide suggest amorphous salt formation in this study. Although FTIR provides evidence for salt formation, XRD and SEM data suggest that the salt is amorphous.

Aluminum hydroxide has an isoelectric pH of 11.4 (Rinella, White, & Hem, 1998; Shirodkar, Hutchinson, Perry, White, & Hem, 1990). As such, inherently bound water associated with aluminum hydroxide will have an alkaline pH not more than 10 and the surface of the aluminum hydroxide will be positively charged. Thus ibuprofen, being a weak acid, is electrostatically attracted to aluminum hydroxide. Investigation of adsorption from the molecular standpoint will help clarify not only the chemical interaction with other substances but also the mode of action of a compound in question.

The metal cation of aluminum hydroxide might have interacted to form a complex through the carbonyl and carboxyl groups of ibuprofen (Lober et al., 1999). It was shown by Tong et al. (2002) 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 amorphous salts, resulting in higher physical stability of the salt in comparison with the acid at a particular storage temperature.

In addition to the changes in drug–aluminum hydroxide interaction and drug crystallinity on comilling, these changes were observed during storage of the milled powder as well. Absorbance of a new signal at ~1,682 cm^{-1} increased relative to the carboxylate peak at ~1,572 cm^{-1} on storage (10 weeks, 40°C, and 75% RH). As shown in Figure 3, the ratio of the absorbance of new signal at ~1,682 cm^{-1} relative to the carboxylate

formation in the initial IB_1A_2-comilled powder (0.35) was some what more than that of the IB_1A_1-comilled powder (0.29). The same ratio increased on storage (0.46) (10 weeks, 40°C, and 75% RH). A corresponding decrease in the drug crystallinity (from XRD study) and drug dimer content (FTIR study) were observed on storage of the three component granules (drug, Gelucire, and Neusilin) (Gupta et al., 2001). Gelucire served as the vehicle for mobility of drug to reach the surface and interact with Neusilin. In this study, we observed the changes in carboxylic acid group and drug crystallinity in ibuprofen–aluminum hydroxide-comilled powder. The moisture present in aluminum hydroxide (8–10%) brought about the molecular mobility.

The decrease in the carboxylic acid group seems to correspond to an increase in the carboxylate ion of ibuprofen, supporting the conversion from the acid to a salt on comilling. XRD provided the evidence supporting amorphization as a function of drug–aluminum hydroxide ratio, with a significant reduction in the peaks at 6.1° and 12.2°, 16.6°, 18.9°, and 22.3° (2θ) angle of the comilled material of $IB_1A_{0.1}$ and a further reduction in the peak at 16.6° (2θ) angle only of $IB_1A_{0.5}$ abolishing other peaks. The comilled material IB_1A_1 and IB_1A_2 showed almost complete disappearance of the characteristic peaks supporting almost complete amorphization. The fragment of the pattern corresponding to the other angle range of very smaller intensities revealed the characteristics of the peaks of comilled powder, which indicated the formation of new crystal lattice or crystal defect. These observations suggest that moisture present in aluminum plays the role of a medium in the conversion of the drug from the crystalline state to the amorphous state on milling and during storage.

The release of a drug from a delivery system involves factors of both dissolution and diffusion. The release rate of a drug like ibuprofen is only important where it is the rate-limiting step in the absorption process. As is evident from the profiles in Figure 4, the extent of dissolution varies according to the following order: IB_1A_2 < IB_1A_1 < ibuprofen crystalline < ibuprofen milled alone < $IB_1A_{0.1}$ < $IB_1A_{0.5}$. The higher dissolution rate of the drug milled alone relative to the crystalline drug is owing to the increase in effective surface area as a result of the reduction in crystal size. Because of chemical interaction, IB_1A_1- and IB_1A_2-comilled powders have shown poor release of drug. Timmers and Sternglanz (1978) reported that aluminum, in particular, forms a very stable complex with carboxyl and carbonyl groups containing quinolones that are not easily soluble. Similarly, in this work, aluminum might have produced a stable complex with the carboxyl group of ibuprofen, which is also not easily soluble and affected the release. The absorbance of the new signal at 1,682 cm^{-1} in IB_1A_2 is more than the IB_1A_1-comilled powder indicates that the chemical interaction is more prominent and the extent of drug release from IB_1A_2 may be due to the presence of carboxylate, even after complete amorphization (absence of XRD peaks of ibuprofen crystal). The IB_1A_1-comilled powder having less prominent new signal at 1,682 cm^{-1} exhibited better release of drug than the IB_1A_2-comilled sample. The most improved dissolution of drug associated with $IB_1A_{0.5}$-comilled powder is because of the absence of new signal at 1,682 cm^{-1} and improved amorphization to some extent from the crystalline drug. The new signal at 1,682 cm^{-1} is absent in the $IB_1A_{0.1}$-comilled powder, but dissolution of the drug is affected relative to the $IB_1A_{0.5}$-comilled powder because of less amorphization of the drug in $IB_1A_{0.1}$.

The positively charged quaternary ammonium groups of Eudragit RL100® and anionic carboxylic drug molecules (ibuprofen) can interact chemically and ultimately may affect the release profile of the drug in the biological media (Pignatello et al., 2004). Aluminum hydroxide detoxifies the endotoxin by adsorbing it in the vaccine and then not releasing it in the interstitial fluid upon administration (Norimatsu et al., 1995; Shi, Hogenesch, Regnier, & Hem, 2001; Sourek, Kevin, Trnka, & Zelenkova, 1991). The strong and extensive interaction of gatifloxacin by aluminum hydroxide because of irreversible binding with metal cations of aluminum hydroxide through the carboxyl and carbonyl groups of gatifloxacin reduces bioavailability of the drug (gatifloxacin) significantly (Lober et al., 1999; Mallick et al., 2007).

In addition to the changes in drug–aluminum hydroxide interaction and drug crystallinity on milling, these changes are observed during storage of the comilled powder as well. The absorbance of new signal at 1,682 cm^{-1} relative to ~1,572 cm^{-1} (carboxylate peak) in the FTIR spectrum of IB_1A_2-comilled powder increased on milling and increased further on storage (40°C, 75% RH, 10 weeks). XRD was sensitive enough to detect the changes in the crystallinity of the drug in IB_1A_2-comilled powder (Figure 2). In a previous publication, we have reported changes in FTIR and XRD from the ibuprofen–kaolin-comilled powder on storage at 40°C, 75% RH for 10 weeks (Mallick et al., 2008) and we reported that the moisture adsorbed by kaolin brought about the molecular mobility. In this study, the equilibrium moisture content of aluminum hydroxide mediated the drug interaction with aluminum hydroxide and conversion of the drug from crystalline state to amorphous aluminum hydroxide-bound state on comilling and during storage.

CONCLUSIONS

The appearance of a new signal at ~1,682 cm^{-1} by FTIR study in $IB_1A_{0.5}$-, IB_1A_1-, and IB_1A_2-comilled powder confirmed the formation of chemical bond that may ultimately affect the release of the drug in the biological system. FTIR spectroscopy further showed the disappearance of carboxylic acid peak and the appearance of carboxylate peak in the comilled powdered sample of ibuprofen and aluminum hydroxide, which suggested amorphous salt formation. The extent of amorphization was a function of aluminum hydroxide concentration in the comilled sample. On storage of comilled powder at 40°C and 75% RH for 10 weeks, XRD data revealed the

absence of reversion to the crystalline state. FTIR spectra revealed no reappearance of carboxylic acid or carboxylate peak. This proved that aluminum hydroxide interacted irreversibly with ibuprofen and the complexed amorphous salt produced was stable during storage and affected dissolution of ibuprofen significantly. Dissolution studies revealed that the percentage release of ibuprofen from comilled powder was also affected and can be expressed in the following order: $IB_1A_2 < IB_1A_1 < IBC < IBM < IB_1A_{0.1} < IB_1A_{0.5}$. This kind of work represents an important preformulative phase, ordinarily be undervalued, for the optimization of drug delivery systems. The overall biological behavior of the system can in fact also depend on the nature and strength of the possible interactions among its components. Further studies in this area are required to be carried out to improve the understanding of these complex systems. Studies related to interaction of other drugs containing carboxyl and carbonyl groups with aluminum hydroxide could be a potential area of research in the future.

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