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Comparison of the Ability of Various Pharmaceutical Silicates to Amorphize and Enhance Dissolution of Indomethacin Upon Co-grinding

Deepak Bahl
School of Pharmacy, University of Connecticut, Storrs, Connecticut, USA

John Hudak
School of Pharmacy, University of Connecticut, Storrs, Connecticut, USA

Robin H. Bogner
School of Pharmacy, Institute of Material Science, University of Connecticut, Storrs, Connecticut, USA

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The physical stability, dissolution rate, and solubility enhancement of indomethacin amorphized by co-grinding with 6 pharmaceutical silicates were investigated. Mixtures of indomethacin and silicates were co-ground to amorphous states at room temperature and 75% relative humidity (RH) in a rolling jar mill. The fraction of indomethacin amorphized was higher than would be expected for monolayer coverage on the silicate, suggesting additional stabilization of the amorphous drug in the mesopores of the silicate. The co-ground amorphous indomethacin was physically stable for 3 to 6 months at 40°C/75% RH. The physicochemical properties (surface area, crystallinity, presence and absence of metal ions such as Mg^{2+}, Al^{3+}, Ca^{2+}) of the silicates affect the amorphization time, chemical stability, dissolution, and solubility.

Keywords amorphization, co-grinding, indomethacin, solubility, silicate

INTRODUCTION

Improvement in the oral bioavailability of poorly water-soluble compounds is often desired, particularly for highly permeable but poorly water-soluble (BCS class II) compounds. Improved bioavailability can often be achieved by an enhancement in the solubility and/or dissolution rate of the poorly water-soluble compound.[1,2] Many methods such as micronization, spray-drying,[3,4] salt formation, freeze-drying,[5,6] use of surfactants, melt quenching,[5] solvent deposition,[7,8] melt adsorption,[9] and formation of prodrugs have been employed to improve dissolution rate and/or solubility of poorly water-soluble drugs. An amorphous form of a compound is at a higher thermodynamic energy state in comparison with any of its crystalline states.[10] The amorphous form, therefore, should provide an advantage in terms of dissolution rate, solubility, and bioavailability. Increases of 2 to 24 times in the experimental "solubilities" or peak concentrations of amorphous solids as compared with their corresponding crystalline counterparts have been reported.[11]

Amorphous solids tend to revert to their lower energy, thermodynamically favorable crystalline states. Therefore physical stabilization of amorphous solids, although desirable, is often challenging. Watanabe et al reported greater stability of indomethacin amorphized by co-grinding with silica for 180 min as compared with neat melt-quenched amorphous indomethacin at 30°C/11% relative humidity (RH). However, recrystallization was observed in both samples within 10 days.[12] On the other hand, Gupta et al reported that amorphous drugs formed by co-grinding with Neusilin US2 (amorphous magnesium aluminometasilicate) were physically stable for at least 1 month at 40°C/75% RH.[13] Kinoshita et al also reported physical stability of TAS-301 (amorphized by melt adsorption on porous calcium silicate) for at least 2 years at ambient temperature and humidity.[1] Our previous study reported physical

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Address correspondence to Robin H. Bogner, 69 North Eagleville Road, U3092, School of Pharmacy, University of Connecticut, Storrs, CT 06269, USA; E-mail: robin.bogner@uconn.edu

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stability of amorphous indomethacin formed by co-grinding with Neusilin US2 for at least 3 months at 40°C/75% RH.[14] Neusilin US2 has a high specific surface (300 m^2/g).[15] The presence of silanols on its surface makes it a potential proton donor as well as a proton acceptor. The hydrogen bonding potential of silanols[12,16,17] is well documented. Hydrogen bonding between silanols and drug as well as interaction between the drug and metal ions on the surface of Neusilin US2 were suggested stabilizing mechanisms of indomethacin in its amorphous state.[14] The stabilization of amorphous drugs in mesopores of silicas has also been suggested by Kim et al.[9] However, their explanation may not be unique because the silicates differed not only in porosity but also in pH and surface area.[9]

Co-grinding with silica has been reported to both increase and decrease dissolution depending on the drug. Yang et al showed a slower dissolution rate of prednisone compared with its crystalline form.[7] In contrast, an improvement in the dissolution rate and bioavailability of indomethacin by interaction with silica was reported by Watanabe et al.[18] A vibration mill was used to co-grind indomethacin with silica for 30 and 180 min. Faster dissolution of indomethacin co-ground for 180 min as compared with 30 min co-ground indomethacin was attributed to the presence of microcrystalline indomethacin (although X-ray amorphous) in the latter sample. In a separate experiment, indomethacin was melt quenched in the presence and absence of silica. Dissolution of melt-quenched indomethacin (in the absence of silica) was slower than any of the other samples investigated. Interestingly, indomethacin melt quenched in the presence of silica showed a much faster initial dissolution rate compared with the sample co-ground for 180 min. However, at the end of 1 hour in the dissolution medium, the dissolved concentrations of indomethacin co-ground with silica for 180 min and of melt-quenched indomethacin (with silica) were essentially superimposable. The initial lower rate of dissolution for indomethacin co-ground with silica for 180 min (compared with indomethacin melt quenched with silica) was attributed to the presence of a stronger chemical interaction (ie, formation of a Si-O-C bond) in the former. However, the formation of a chemical bond is inconsistent with dissolution enhancement of co-ground indomethacin. Nevertheless a 1- to 1.3-fold improvement in bioavailability was reported in rats for both these amorphous states of indomethacin (as compared with a physical mixture of indomethacin with silica).[18] Similarly, hydrogen bonding was proposed between the carbonyl group of a drug (TAS-301) and the silanols of Florite (amorphous calcium silicate) to explain the stabilization of the amorphous form prepared by melt adsorption.[1,19] The melt-adsorbed drug showed an increased solubility of 1.7-fold, and a dissolution rate and bioavailability of 2.7-fold, compared with its crystalline form.[1]

Our previous study reported a dramatically higher dissolution rate and dissolved concentration of indomethacin amorphized by co-grinding with Neusilin US2 as compared with the dissolution rate and solubility of the γ-polymorph.[20] Here we evaluate the generality of amorphization and solubility enhancement of indomethacin by co-grinding with a range of pharmaceutical silicates (Florite-F, Veegum-F, kaolin, calcium silicate, and Aerosil-200). The effect of crystallinity, surface area, pH, and chemical nature of the silicate was evaluated on amorphization time, dissolution rate, and solubility of co-ground amorphous indomethacin.

MATERIALS AND METHODS

Materials

Indomethacin USP was purchased from Spectrum Chemicals (New Brunswick, New Jersey). Pharmaceutical silicates used in this study include Neusilin US2, Veegum-F, Florite-F, calcium silicate, kaolin, and Aerosil-200. Neusilin US2 (magnesium aluminometasilicate) and Veegum-F (magnesium aluminosilicate) were obtained as gift samples from Fuji Chemicals (Englewood, New Jersey) and RT Vanderbilt Company, Inc (Norwalk, Connecticut), respectively. Kaolin USP (aluminum silicate) was purchased from Fisher Scientific (Pittsburgh, Pennsylvania). Two types of calcium silicates, crystalline calcium silicate and Florite-F (amorphous calcium silicate) were supplied by JM Huber Corporation (Havre de Grace, Maryland) and Tokuyama Corporation (Tokyo, Japan), respectively. Aerosil-200 (colloidal silicon dioxide) was provided by Degussa Corporation (Piscataway, New Jersey). Concentrated hydrochloric acid was purchased from JT Baker (Philipsburg, New Jersey). A Barnstead/Thermolyne NANOpure deionization system (Dubuque, Iowa) was used as a source of purified water for preparation of dissolution media. Ammonium molybdate reagent was prepared using ammonium hydroxide solution (Acros Organics, Morris Plains, New Jersey) and ammonium molybdate tetrahydrate (Fischer Scientific, Rochester, New York).

Evaluation of Pharmaceutical Silicates

The surface area of each silicate was determined by a single-point BET analysis method (Flosorb II 2300, Micromeretics, Norcross, Georgia) using 30% nitrogen in helium. The samples (approximately 50–100 mg) were purged with nitrogen gas for 12 h at room temperature to remove any residual moisture. Prior to measurements the BET tube was weighed to obtain the sample mass.

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The tube was then connected to the BET instrument and immersed in liquid nitrogen for adsorption of nitrogen to proceed. Upon completion of adsorption, the liquid nitrogen was removed and the tube was then immersed in a beaker containing water at 37°C for desorption of the nitrogen adsorbed by the sample. The volume of gas adsorbed was used to calculate the specific surface of the sample in m^2/g. All measurements were made in triplicate.

The pH of suspensions of each silicate was determined at room temperature without separating the supernatant. A 4% w/v suspension of each silicate was prepared (in triplicate) by adding 2 g of silicate to 50 mL of deionized water. The suspension was stirred for 30 min followed by determination of pH, which was found to be constant for at least 1 min.

The buffering capacity of 4% w/v suspensions of silicates was determined (in triplicate) by titration of the suspensions first with 1N HCl to a pH of about 1, followed by titration with 1N NaOH to a pH of about 10, and finally titration with 1N HCl to the starting pH. In a separate set of experiments, suspensions were titrated (in triplicate) in reverse starting with addition of 1N NaOH to a pH of about 10, followed by addition of 1N HCl to a pH of about 1 and finally addition of 1N NaOH to the starting pH. Buffering capacity was calculated.[21]

The crystallinity of each silicate was evaluated using a diffractometer (Model D5005, Bruker AXS Inc, Madison, Wisconsin) using Cu$K\alpha$ radiation, a voltage of 40 kV, and a current of 40 mA. The powder samples were scanned at a rate of 2°/min over a 2 θ range of 10° to 40°, with a sampling interval of 0.02°.

General Description of the Co-grinding Process

A rolling jar mill (Model #202421, Paul O Abbe Inc, Little Falls, New Jersey) with a cylindrical porcelain jar (outer diameter = 5.25″; internal volume = 1000 mL) and zirconia balls (diameter = 0.25″) were used for co-grinding process. The grinding process was performed as described previously[14] and all batches were prepared in triplicate unless otherwise noted. A saturated NaCl solution was used to equilibrate indomethacin, silicate, the porcelain jar and zirconia balls at room temperature and 75% RH in a glove box for 36 h prior to co-grinding. A hygrometer (Model LAM 880D, Mannix, Lynbrook, New York) was used to monitor humidity inside the glove box.

Description of the Cryo-grinding Process

A freezer mill (Model 6750, Spex Certiprep Inc, Metuchen, New Jersey) was used to affect conversion of indomethacin-silicate mixtures when the duration of amorphization by co-grinding using the jar mill was greater than 20 days. The freezer mill consisted of a reservoir to which liquid nitrogen was poured. The grinding chamber consisted of a polycarbonate cylindrical tube, a steel impactor, and 2 steel end plugs. In each experiment, 2.5 g of powder (drug-silicate mixture) was added to the grinding chamber along with the impactor. The sealed grinding chamber was immersed in liquid nitrogen and precooled for 15 min prior to grinding. Each grinding cycle consisted of 2 min of grinding followed by a cooling period of 2 min. The impactor speed was 20 impacts per second. The number of 2 min grinding cycles was increased to achieve longer grinding times. The grinding times in the text refer to the total time of grinding and exclude the cooling periods.

Storage Conditions

Indomethacin co-ground with the various silicates was stored in open glass vials in sealed jars maintained at 40°C for 3 months. A saturated NaCl solution was used to maintain 75% RH in the jars. Samples were taken at monthly intervals.

Evaluation of Crystallinity of Powders Ground with Silicates

Fourier Transform Infrared (FTIR) scans of indomethacin in the neat crystalline state and after co-grinding or cryo-grinding with silicates were collected on an IR spectrophotometer (Model Magna IR 560, Nicolet Instruments Technologies Inc, Westbury, Wisconsin) with golden gate attenuated total reflectance (ATR) assembly equipped with diamond-ZnSe crystal using OMNIC® software. Data acquisition parameters and the PLS analysis of percent crystallinity were previously reported.[14] In addition, powder X-ray diffraction (PXRD) scans of indomethacin in the neat crystalline state and upon co-grinding or cryo-grinding with silicates were collected as described above for neat silicates.

Evaluation of Surface Area, Pore Volume and Pore Diameters of Indomethacin Co-ground with Neusilin US2

The surface area of indomethacin co-ground with Neusilin US2 in the ratio 1:5 w/w (at 0 and 3 months of storage at 40°C/75% RH) was analyzed by BET nitrogen adsorption method as described above for neat silicates. The mesopore volume and mesopore diameter were calculated based on the Barrett, Joyner, and Halenda (BJH)

method.[22] The model assumes cylindrical pore geometry and is based on the "Gurvitsch rule," which states that the volume of liquid condensed in the pores from a condensable gas near its saturation vapor pressure is equivalent to the total volume of the pores.[23] The micropore volume and micropore diameter were calculated based on the Horvath-Kawazoe method[24] assuming cylindrical pores.

Chemical Stability

Initial and stored co-ground indomethacin samples were assayed by gradient reverse phase HPLC using a 3.9 × 150 mm, 5-micron C8 column (SymmetryShield RP, Waters Corporation, Milford, Massachusetts). The mobile phase consisted of 0.1% TFA in acetonitrile. A diode array detector at 210 nm was used for quantification. The degradation of indomethacin in the samples was calculated based on percent peak area of degradants expressed as percent area relative to total area of all peaks in the chromatogram.

Solubility and Dissolution Rate Studies

A USP type II (paddle) dissolution apparatus (Vanderkamp 600, Vankel Industries, Chatham, New Jersey) was used to evaluate the dissolution rate and solubility of powders (n = 3). As with a previous study,[20] a paddle height adjusted to 0.7″ from bottom of the vessel and high rotation speed (250 rpm) were employed to prevent heap formation at the bottom of the vessel. Either crystalline indomethacin or co-ground amorphous indomethacin was dissolved in 900 mL of 0.1N HCl at 37°C. Each sample consisted of an amount equivalent to 100 mg of indomethacin. Aliquots were withdrawn through a 0.22 μ acetate filter and analyzed by absorbance at 318 nm. The pH at the end of dissolution was monitored and compared with the initial pH. At the end of each dissolution study, the remaining suspension was filtered through a 0.22 μ filter. The nature of the recovered solids (partially wet) was assessed by PXRD using scanning parameters as described above.

RESULTS AND DISCUSSION

Characterization of Pharmaceutical Silicates

A wide range of pH (4.5–9.7) is observed for 4% w/v suspensions of different silicates (Table 1). Aerosil-200 is the most acidic in nature while kaolin is only slightly acidic. Both types of calcium silicates (crystalline calcium silicate and Florite-F) are basic. A pH of 7.4 for Neusilin US2 (amorphous magnesium aluminometasilicate) showed it to be more neutral. Interestingly, its crystalline counterpart, Veegum-F (crystalline magnesium aluminosilicate) is basic (pH 9.7).

Table 1
Surface area and pH of different pharmaceutical silicates

Pharamaceutical Silicate	Surface Area (m^2/g)†	Normalized Weight (g)*	pH**
Neusilin US2	300 (3.9)	1.0 (0.01)	7.4 (0.2)
Florite-F	130 (1.9)	2.3 (0.01)	9.1 (0.2)
Veegum-F	53 (1.3)	5.6 (0.00)	9.7 (0.1)
Aerosil-200	200 (4.5)	1.5 (0.02)	4.5 (0.1)
Calcium silicate	12 (2.1)	24.0 (0.01)	9.6 (0.1)
Kaolin	13 (0.1)	23.1 (0.00)	6.2 (0.2)

Standard deviation of 3 samples is in parentheses.
†Surface area as determined by BET nitrogen adsorption method.
*Weight (in grams) of silicate required to have same surface area as 1 m^2/g of Neusilin US2.
**pH of 4% w/v suspension.

The surface area of the silicates ranged from 13 to 300 m^2/g (Table1). In order to compare the effect of (a) the different cations, Al^{3+}, Ca^{2+}, Mg^{2+}, and (b) crystallinity of silicates on amorphization time, we co-ground using the same drug weight–to-silicate surface area ratio. Thus normalized weight, which is the weight of silicate (in grams) required to have the same surface area as 1 g of Neusilin US2, our standard, was calculated (Table 1). The wide range of surface area of the different silicates restricted selection of some silicates for co-grinding, when normalization of surface area of silicates was required. For example, 23 g of kaolin would be required to be equivalent to 1 g of Neusilin US2 in terms of surface area. Thus kaolin and calcium silicate were not selected for co-grinding experiments involving surface-normalized amounts of silicates as discussed later in the next section (Co-grinding Indomethacin With Pharmaceutical Silicates).

Figure 1A shows the results of titration of Neusilin US2 suspension starting with 1N HCl. There is a steep decline in pH from 7.2 to 3.5 followed by buffering at pH 3.5. Further addition of 1N HCl decreased the pH to 1. Upon addition of 1N NaOH to suspension, a steep increase in the pH to 3.5 was observed, followed by buffering at pH 4.1. Further addition of 1N NaOH increased the pH to 10. At pH 10, addition of 1N HCl steeply lowered the pH to 7.2. Comparison of results for forward and backward titration showed hysteresis, a pH-dependent change in the Neusilin surface. This change is consistent with the previously reported release of silicic acid and ions (Mg^{2+} and Al^{3+}) from Neusilin US2 in 0.1N HCl.[20] Titration of Neusilin US2

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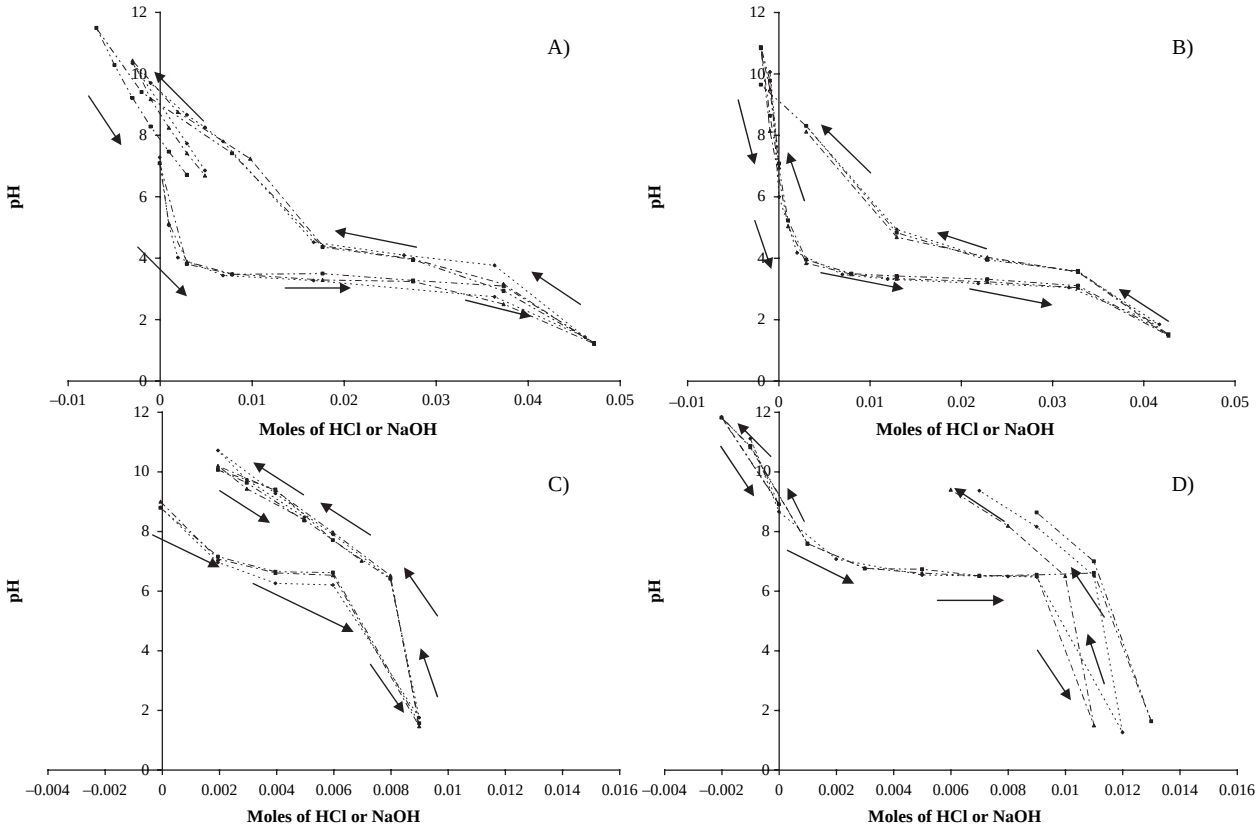

Figure 1. Titration of Neusilin US2 and Florite: (A) Neusilin—acid first followed by base; (B) Neusilin—base followed by acid; (C) Florite—acid first followed by base; (D) Florite—base followed by acid.

suspension starting with base is reported in Figure 1B. No hysteresis was observed when the starting pH was increased to 10, suggesting that the surface of Neusilin is unaffected at alkaline pH. However, as observed in Figure 1A, hysteresis (Figure 1B) in the acidic region again suggests the dissolution of Neusilin US2 in the acidic pH. The corresponding results for titration of Florite-F starting with 1N HCl and with 1N NaOH are shown in Figure 1C and 1D, respectively. The results suggested that alkaline conditions do not affect the surface of Florite-F. In addition, hysteresis on acid treatment seems to change the surface of Florite-F (similar to the observed change in the surface of Neusilin US2 on acid treatment). The buffering capacity of Neusilin US2 (0.09) is greater than that of Florite-F (0.06). The apparent pK_as of Neusilin US2 and Florite-F are 3.5 and 6.8, respectively. Kaolin, calcium silicate, Veegum-F, and Aerosil-200 showed minimal to no buffering capacity with no apparent pK_as (data not shown). The order of buffering capacities of different silicates is as follows: Neusilin US2 > Florite-F >> Aerosil-200 = Veegum-F = kaolin = calcium silicate.

Powder X-ray diffraction patterns of the silicates are shown in Figure 2. The crystallinity of kaolin and calcium silicate was confirmed by the presence of sharp peaks in their respective diffraction patterns. On the other hand, a broad halo at ~20° 2θ for Aerosil-200 and Neusilin US2 confirmed their amorphous nature. Florite-F (reportedly amorphous calcium silicate) showed 2 peaks at ~11° and ~21° 2θ

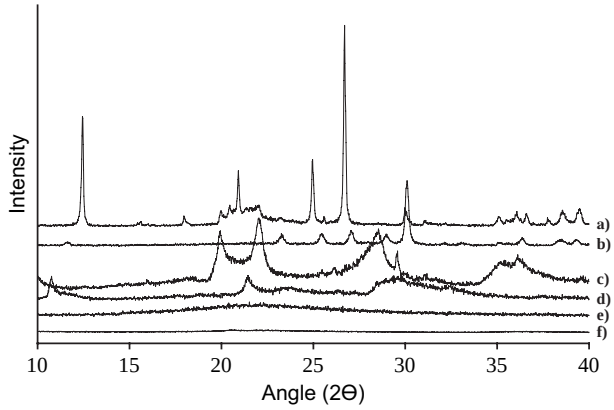

Figure 2. XRD scans of pharmaceutical silicates: (a) Kaolin, (b) calcium silicate, (c) Veegum-F, (d) Florite-F, (e) Aerosil-200, (f) Neusilin US2.

and 2 broad amorphous halos at ~24° 2 θ and ~31° 2 θ. It should be noted that Florite-F and Veegum-F both appear to be partially disordered even though Veegum-F is widely considered to be crystalline.[25] A sample of Veegum-F showed birefringence when analyzed using polarized light microscopy, thereby confirming at least partial crystallinity.

Co-grinding Indomethacin with Pharmaceutical Silicates

Indomethacin was co-ground with Neusilin US2, Florite-F, Veegum-F, kaolin, calcium silicate, and Aerosil-200 (1:5 w/w) in a jar mill. ATR-FTIR was previously established as a far more sensitive technique than PXRD for detecting crystallinity of indomethacin in the presence of Neusilin US2.[14] Thus indomethacin-silicate powders were co-ground until no change in their respective FTIR spectra was observed upon further grinding. The absence of significant polymorphic transformation of indomethacin after grinding with each silicate was confirmed by PXRD.

Co-grinding indomethacin with calcium silicate led to the formation of large (6.3–6.5 mm diameter) spherical aggregates of powder. No amorphization of indomethacin was affected after grinding with calcium silicate for 14 days. So, calcium silicate was not explored further. Indomethacin co-ground with Aerosil-200 took 31 days to amorphize using the jar mill. In addition, the powder turned grayish black. In order to shorten the grinding time, a cryo-mill was used to amorphize indomethacin with Aerosil-200 (1:5 w/w). Cryo-grinding for 30 min was sufficient to completely amorphize indomethacin in the presence of Aerosil-200. No grayish-black color of the powder was observed even after cryo-grinding for 30 min (for a total of 1 h grinding time).

The amorphization times for indomethacin co-ground in a 1:5 w/w ratio with Neusilin US2, Florite-F, Veegum-F, and kaolin were 5, 8, 7, and 14 days, respectively. The amorphization times did not correlate with suspension pH of the silicate. However, there was an inverse rank-order correlation of amorphization times with the surface area of the silicate. No conclusions could be drawn regarding a correlation of the amorphization times with crystallinity of the silicate since surface area depends strongly on crystallinity.

The effect of normalizing surface area of various silicates on amorphization times of indomethacin was investigated by grinding the drug with Neusilin US2 (1:1), Florite-F (1:2.3), Veegum-F (1:5.6), and Aerosil-200 (1:1.5), where the ratios are expressed by weight. The amorphization times were 8, 11, and 7 days for indomethacin co-ground with Neusilin US2, Florite-F, and Veegum-F, respectively, and 60 minutes for indomethacin cryo-ground with Aerosil-200 in the ratio 1:1.5 w/w. Comparison of these amorphization times of indomethacin (using surface area normalized amounts of silicates) with the corresponding amorphization times of indomethacin ground in the ratio 1:5 w/w suggests faster amorphization when higher ratios of silicates are used. However, normalizing for surface area did not equalize the amorphization times, so amorphization is a function of more than surface area alone. Neither suspension pH nor crystallinity of the silicate correlated with amorphization time (using surface area–normalized silicates). The metal-ion containing silicates (Mg^{2+}, Al^{3+}, or Ca^{2+}) resulted in faster amorphization times than Aerosil-200 (silicon dioxide), which does not contain any metal ions. In addition, faster amorphization was observed with silicates containing both Mg^{2+} and Al^{3+} (Neusilin US2 and Veegum-F) as compared with Florite-F, which contains Ca^{2+}.

As reported previously, the FTIR spectra for crystalline γ-indomethacin and melt-quenched indomethacin displayed characteristic dimer peaks at 1710 cm^{-1} and 1704 cm^{-1}, respectively. Melt-quenched indomethacin also showed a monomer peak at 1735 cm^{-1}. The disappearance of the dimer peak of indomethacin amorphized by co-grinding with Neusilin US2 has been reported elsewhere.[14] Ion-dipole interactions between the metal ions (Mg^{2+} and/or Al^{3+}) on the surface of Neusilin US2 and carboxyl group of indomethacin and/or hydrogen bonding between silanols and carbonyl group of indomethacin had been used to explain the disappearance of the dimer peak.[14] Indomethacin amorphized by co-grinding with Florite-F, Veegum-F, and kaolin (1:5 w/w) showed a similar disappearance of the indomethacin dimer peak (Figure 3). However, indomethacin co-ground with Aerosil-200 showed a shift in the dimer peak at 1704 cm^{-1} and a broad monomer peak at ~1735 cm^{-1} more characteristic of the melt-quenched sample (Figure 3). The disappearance of the dimer peak is more associated with the Mg^{2+}, Al^{3+}, or Ca^{2+} ion-containing silicates presumably due to ion-dipole interactions.

Chemical degradation of 0.5% to 4.5% of indomethacin co-ground with the different silicates in the ratio 1:5 was determined by a stability-indicating HPLC assay (Table 2). The chemical composition of the silicate dictates the extent of observed chemical degradation of indomethacin co-ground with different silicates. Kinoshita et al reported 0.5% to 5.6% degradation of TAS melt adsorbed on Florite-F.[19] In the present study, the observed degradation (Table 2) of indomethacin co-ground with Florite-F was highest compared with the degradation with other silicates. The chemical degradation of indomethacin cryo-ground with Aerosil-200 for 30 and 60 min was 0.8% and 2.4%, respectively.

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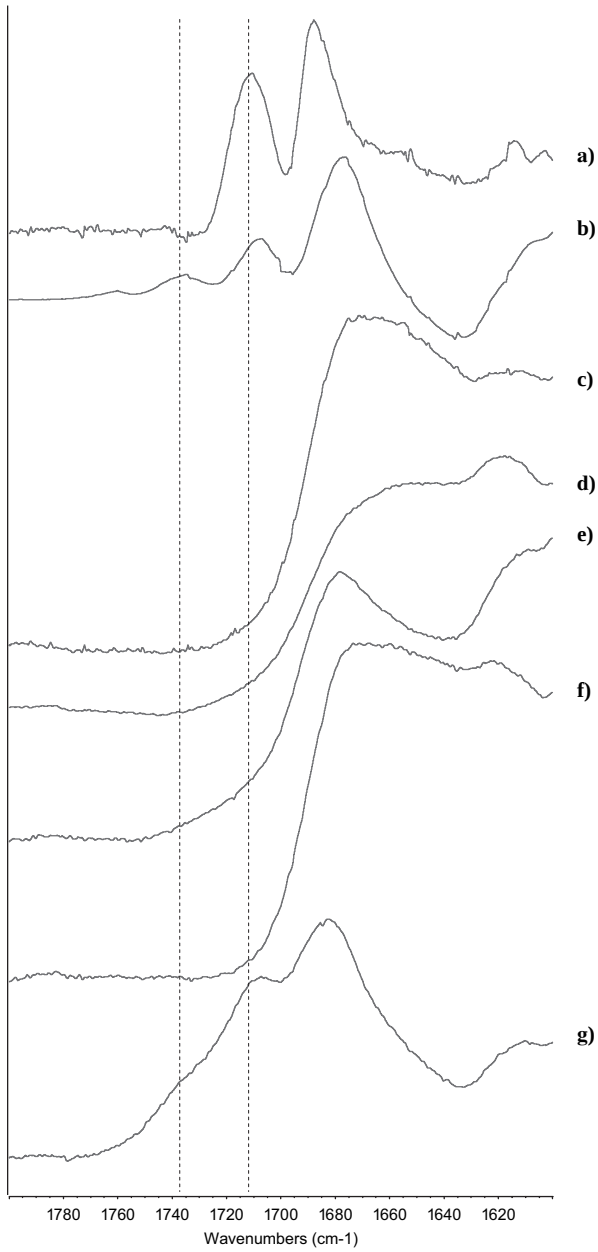

Figure 3. ATR-FTIR scans of: (a) crystalline indomethacin; (b) melt-quenched indomethacin; (c) indomethacin co-ground with Neusilin US2 (1:5 w/w); (d) indomethacin co-ground with Veegum-F (1:5 w/w); (e) indomethacin co-ground with Kaolin (1:5 w/w); (f) indomethacin co-ground with Florite-F (1:5 w/w); (g) indomethacin cryo-ground with Aerosil-200 (1:5 w/w).

Physical Stability of Co-ground Indomethacin

Indomethacin co-ground with Neusilin US2 (1:4 and 1:5) at 75% RH was physically stable for 3 months stored at 40°C/75% RH.[14] The co-ground samples when stored for 6 months were amorphous as confirmed by absence of birefringence under polarized light (Figure 4a and 4b). However, the ATR-FTIR method detected ~30% crystallinity in the samples stored for 6 months (n = 3). Careful comparison of the IR scans of samples stored for 6 months with initial samples showed changes in the peaks at 1356 to 1367 cm^{-1} (corresponding to C–H bond stretching at $C_9H_{34,35}$) and at 1479 to 1492 cm^{-1} (due to C–H stretching at C_{13}, C_{14}, C_{16}, and C_{17}) region (Figure 5). On the other hand, the IR scans of the 6-months-stored sample did not change with respect to the peaks for dimer (1700–1727 cm^{-1}) and for C_{12} to C_{17} deformation (shoulder at 1471 cm^{-1}) occurring due to interaction between benzoyl group of indomethacin and silanols of Neusilin US2. Without all of the corresponding IR changes associated with an amorphous to crystalline transition occurring consistently, we find the ATR-FTIR quantification method to be unreliable at 6 months of storage. Polarized light microscopy (Figure 4c) of a sample corresponding to 5% crystallinity (prepared by mixing γ-indomethacin with Neusilin US2 in the ratio 1:5 w/w) revealed birefringence comparable with the amorphized sample stored for 6 months (Figure 4a and 4b), suggesting that the level of crystallinity in co-ground amorphous samples stored for 6 months at 40°C/75% RH is about 5%, perhaps less.

Table 2
Chemical stability of indomethacin co-ground with different pharmaceutical silicates at initial and 3 months storage, determined using a stability-indicating HPLC method

Sample	Condition	Potency*
IND:Neusilin US2 (1:5)	Initial	97.4
	3M/40°C/75% RH	89.8
IND:Florite-F (1:5)	Initial	95.5
	3M/40°C/75% RH	84.8
IND:Veegum-F (1:5)	Initial	99.5
	1M/40°C/75% RH	97.4
	3M/40°C/75% RH	95.2
IND:Kaolin (1:5)	Initial	98.8
	3M/40°C/75% RH	96.5
IND:Aerosil-200 (1:5)	30 mins cryoground	99.2
	1 hr cryoground	97.6

*Percent peak area.

The dimensions of a molecule of indomethacin (calculated using Hyperchem, Gainesville, Florida) approximated by a rectangle that contains the structure are 4.27 A° × 8.97 A° × 12.66 A° (Figure 6). Using these dimensions, the amount of indomethacin that would form a monolayer on the surface of Neusilin US2 (surface area 300 m^2/g) was calculated. Based on the lowest and highest surface area faces of the rectangle containing the indomethacin molecule, 0.16 to 0.47 g of indomethacin would provide monolayer coverage on one gram of Neusilin

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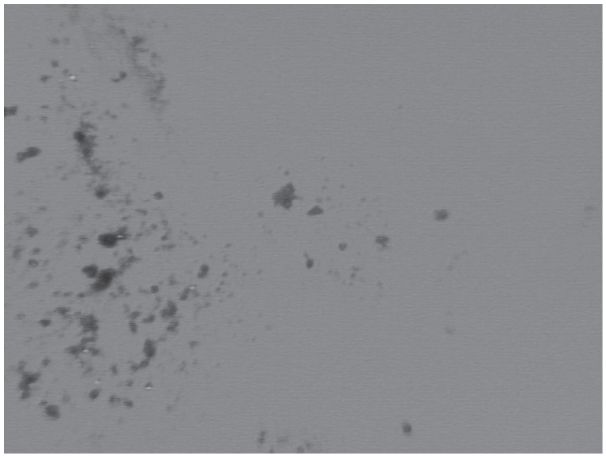

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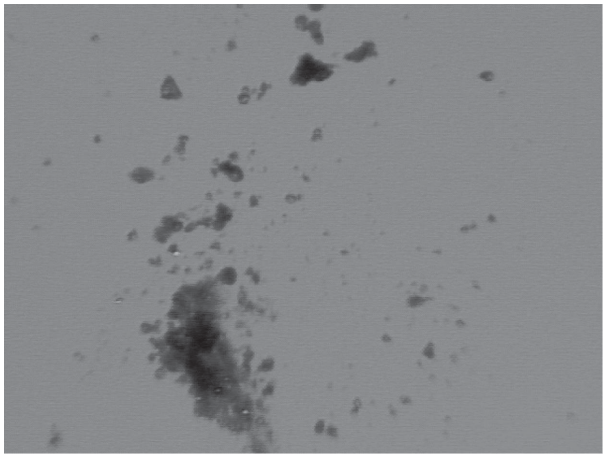

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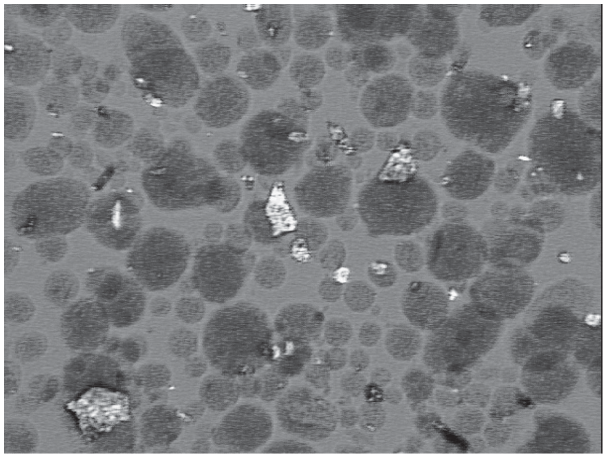

Figure 4. Polarizing light micrographs of indomethacin co-ground with Neusilin and stored at 40°C/75% RH for 6 months: (A) 1:4, (B) 1:5, (C) 5% crystalline indomethacin (at initial time only).

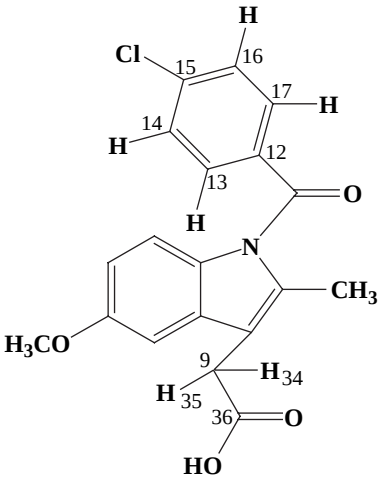

Figure 5. Structure of indomethacin.

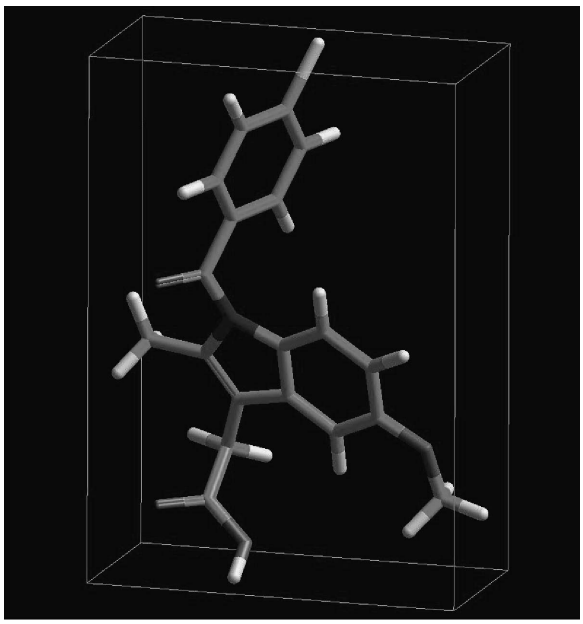

Figure 6. 3D structure and unit cell dimensions of indomethacin molecule.

US2. This corresponds to a ratio of indomethacin:Neusilin US2 of 1:2 to 1:6 w/w. Amorphization of indomethacin co-ground with Neusilin US2 was reported for the ratios 1:0.5 and 1:1,[14] which are well above monolayer coverage. The ratio (w/w) of indomethacin:silicate needed for monolayer coverage was similarly calculated to be 1:3-1:10, 1:5 to 1:14, 1:13 to 1:33, and 1:50 to 1:100 for Aerosil-200, Florite-F, Veegum-F, and kaolin, respectively. All of the silicates investigated in the present study amorphized indomethacin well above monolayer coverage.

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The greater amounts of indomethacin amorphized by Neusilin US2 (than the amount suggested based on monolayer calculations) are consistent with capillary condensation of indomethacin in the pores of Neusilin US2 as previously suggested[14] for Neusilin US2 and shown[26] for activated carbon. The pore volume (0.059 cm^3/g) of Neusilin US2 co-ground (for 10 days) with indomethacin in the ratio 1:0.5 (indomethacin:Neusilin US2) is lower than that of neat Neusilin US2 (0.525 cm^3/g) ground for 10 days, also suggesting condensation of indomethacin in the pores. The melting point of partially crystalline co-ground indomethacin (~152°C-154°C) was lower and broader than the melting point of neat crystalline indomethacin (162°C), suggesting the presence of drug in the pores of Neusilin US2. Others have documented condensation of drugs in the mesopores of silicates[9,27] and depression of melting point of compounds present in the pores of silicates.[4,28] Indeed the depression of melting point in pores is used to calculate pore radii (assuming cylindrical pores).[29,30]

Physical stability of amorphous and partially amorphous indomethacin (co-ground with Neusilin US2 in weight ratio of 1:0.5) is shown in Table 3. Faster recrystallization was observed for partially amorphous samples as compared with that of completely amorphous samples. The remaining crystalline indomethacin (in partially amorphous samples) could serve as seeds for faster recrystallization. When physical stability of 3 different batches of completely amorphous indomethacin (co-ground with Neusilin US2 in the ratio 1:0.5) was followed for 3 months, one batch co-ground for only 13 days crystallized much faster while the other two co-ground for 16 days recrystallized more slowly (to only 40%) (Table 3) even though 10 days of grinding was shown to be sufficient to completely amorphize indomethacin with Neusilin US2 (1:0.5 w/w).[14] Watanabe et al also reported inhibition in recrystallization kinetics with increased time of grinding past complete amorphization.[12] The IR of indomethacin co-ground with Neusilin US2 for 10, 13, and 16 days, respectively, were identical to each other. Perhaps FTIR is not sensitive enough to capture any remaining crystalline regions serving as seeds for recrystallization. The presence of undetected crystalline indomethacin serving as seeds for recrystallization[12] could explain the observed reversion of indomethacin on storage although the silica employed in 2 studies differ from each other.

It should be noted that no recrystallization of indomethacin (co-ground with Neusilin US2 in the weight ratios of 1:1, 1:4, and 1:5) was observed when stored at 40°C/75% RH for 3 months.[14] Thus while a critical ratio of indomethacin:Neusilin US2 was reported for amorphization as 1:0.5 or lower,[14] the minimum ratio of 1:1 (or somewhere between 1:0.5 and 1:1) is required for physical stability of amorphous indomethacin. This is still greater than the ratio expected to form a monolayer, so some other mechanism, perhaps capillary condensation, is responsible for stabilization.

The physical stability of indomethacin co-ground with Florite-F, Veegum-F, and kaolin (1:5 w/w) was investigated. As reported earlier (Figure 3), the dimer peak of crystalline indomethacin was absent when indomethacin was co-ground with Florite-F, Veegum-F, and kaolin. FTIR spectra for the initial co-ground samples and those stored for 3 months did not change (data not shown) indicating the absence of significant reversion on storage. Thus co-ground amorphous indomethacin (with a variety of silicates) was physically stable for 3 months at 40°C/75% RH. Supporting evidence for absence of crystallinity during storage was obtained using PXRD (showing characteristic amorphous halos), absence of birefringence under polarized light and the absence of any melting peak (at 162°C) of indomethacin by DSC (data not shown).

The stability of indomethacin cryo-ground with Aerosil-200 was not investigated due to the limited amount of sample available. Others have reported that amorphous indomethacin prepared by spray-drying with Aerosil-200 (a process different than ours) and stored for 2 months at 40°C/75% RH was stable.[4] It should be noted that indomethacin co-ground with the amorphous silicates Florite-F and Neusilin US2 (in the ratio 1:5) is at or below

Table 3

Percent crystallinity of amorphous indomethacin and partially crystalline indomethacin co-ground with Neusilin (1:0.5 w/w) and stored at 40°C/75% RH

Initial State	Co-grinding time	Initial	1M/40°C/75% RH	2M/40°C/75% RH	3M/40°C/75% RH
Partially crystalline	7 days	24	64	62	93
	7 days	28	56	54	91
	7 days	23	54	57	92
Amorphous	13 days	0	66	65	72
	16 days	0	23	38	42
	16 days	1	22	38	40

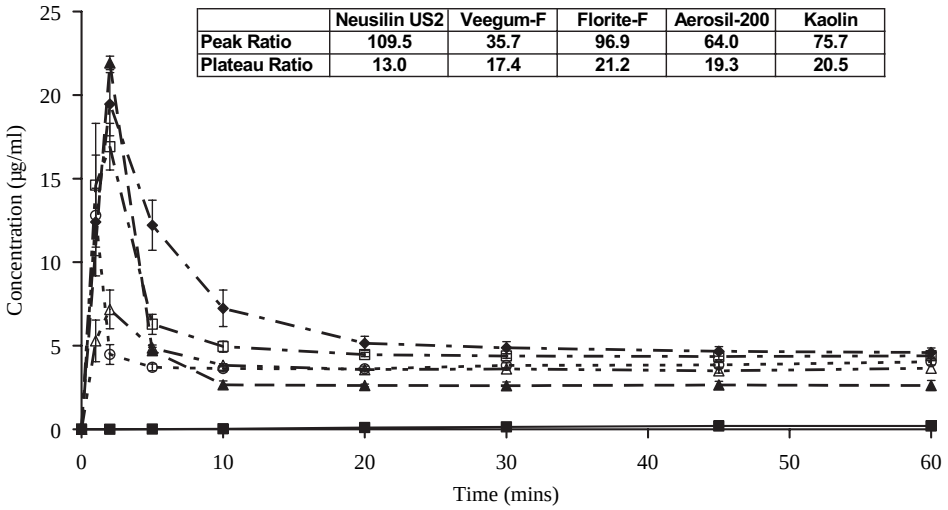
monolayer coverage. Interestingly, indomethacin co-ground with the crystalline silicates Veegum-F and kaolin in a 1:5 ratio is above monolayer coverage and yet remains physically stable. The reason is not obvious and needs investigation. Further, there seems to be no correlation between the pH of the silicate and observed physical stability of the co-ground amorphous indomethacin.

Dissolution and Solubility Studies

The solubility of γ-indomethacin in 0.1N HCl was determined to be 0.2 μg/mL (Figure 7). Indomethacin amorphized by co-grinding with different silicates showed a characteristic peak in concentration (or maximum transient concentration [MTC]) followed by a rapid decline in concentration to a plateau (or maximum sustained concentration [MSC]), due to crystallization of indomethacin. The pH of the medium at the end of the study was the same as the initial value. Detection of only the γ-polymorph of indomethacin by PXRD from the solids recovered at the end of the 60-minute dissolution confirmed the absence of any polymorphic transformation. Peak and plateau concentration ratios of indomethacin co-ground with different silicates (see the table in Figure 7) were calculated by dividing the MTC and the MSC, respectively, by the solubility of crystalline indomethacin. The MTCs for indomethacin amorphized by co-grinding with different silicates (in the ratio 1:5 w/w) were in the following order: Neusilin US2 (21.92 μg/mL) > Florite-F (19.38 μg/mL) > kaolin (16.83 μg/mL) > Aerosil-200 (12.79 μg/mL) > Veegum-F (7.14 μg/mL). The MSCs attained were in the order: Florite-F (4.24 μg/mL) > kaolin (4.09 μg/mL) > Aerosil-200 (3.85 μg/mL) > Veegum-F (3.48 μg/mL) > Neusilin US2 (2.42 μg/mL). It should be noted that the order of MTCs and MSCs could change with a change in the ratio of drug to silicate.[20]

The dissolution of indomethacin co-ground with surface area–normalized amounts of silicates was investigated. No MTCs (except in the case of Veegum-F) were observed during dissolution of indomethacin amorphized by co-grinding with various surface area–normalized silicates (Figure 8). The reason for the difference in the observed MTCs needs further investigation. At this time, it is hypothesized (consistent with monolayer adsorption and capillary condensation) that with the lower ratio of drug to silicate (ie, higher fraction of silicate) used for amorphization, a greater fraction of indomethacin is adsorbed on the surface rather than present in the pores. The higher fraction of drug adsorbed on the silicate surface results in a higher peak (apparently supersaturated) concentrations.

The MSCs (for indomethacin co-ground with silicates using surface area–normalized amounts) attained were in the following order: Veegum-F (3.48 μg/mL) > Aerosil-200 (2.75 μg/mL) > Neusilin US2 (2.27 μg/mL) > Florite-F (1.20 μg/mL). An increase in the MSC of co-ground amorphous drug has been shown to be due to presence of silicic acid and metal ions (Mg^{2+} and Al^{3+}) in the dissolution medium.[20] The type and amount of silicate affects the amount of silicic acid and/or ions released in to the dissolution medium and therefore the differences in experimentally observed MSCs of indomethacin co-ground with different (surface area–normalized) silicates.



	Neusilin US2	Veegum-F	Florite-F	Aerosil-200	Kaolin
Peak Ratio	109.5	35.7	96.9	64.0	75.7
Plateau Ratio	13.0	17.4	21.2	19.3	20.5

Figure 7. Dissolution profiles (n = 3) of 100 mg indomethacin ground with different pharmaceutical silicates (1:5 w/w) in 0.1N HCl (900 mL): –▲– Neusilin US2, –Δ– Veegum-F, –♦– Florite-F, –□– Kaolin, –○– Aerosil-200, –■–crystalline indomethacin.

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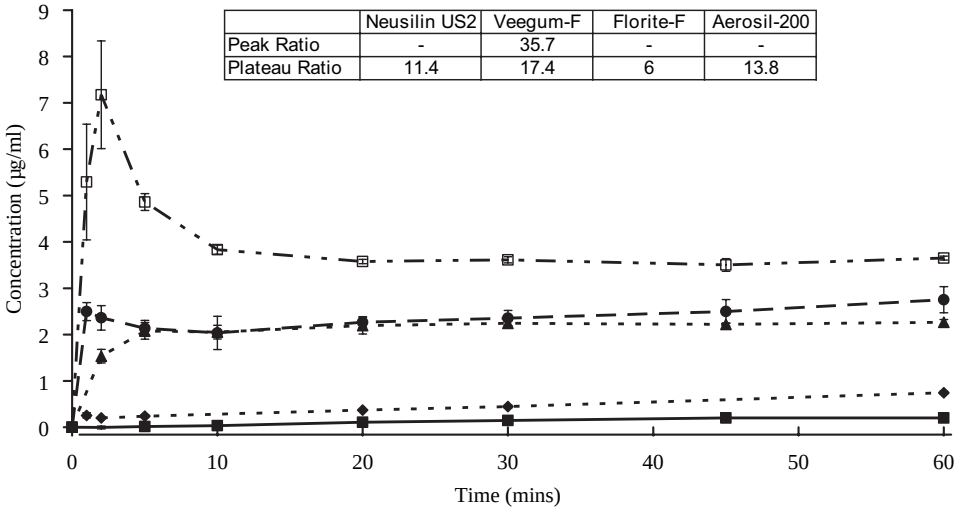

Figure 8. Dissolution profiles of 100 mg of indomethacin co-ground with different pharmaceutical silicates (surface area normalized) in 0.1N HCl (900 mL): -♦- Florite-F (1:2.3), -▲- Neusilin US2 (1:1), -●- Aerosil-200 (1:1), -□- Veegum-F (1:5), –■– crystalline indomethacin. Ratio of drug to silicate is in parentheses.

Effect of Storage on Dissolution and Solubility

The effect of storage on dissolution and solubility of indomethacin co-ground with silicates (1:5 w/w) was investigated. Figure 9 compares the dissolution profiles of indomethacin co-ground with Neusilin US2 initially and at 1 to 3 months of storage at 40°C/75% RH. The peak and plateau ratios at respective time points are reported in the inset table in Figure 9. An increase in the MTC from the initial sample (21.9 µg/mL) to the sample stored for 1 month (24.4 µg/mL) was observed ($P < .05$). Further storage for 2 months did not change the MTC. The MSC of indomethacin co-ground with Neusilin US2 (at initial time point) was 13 times higher than the solubility of crystalline indomethacin and increased with storage time. The dissolution profiles of indomethacin co-ground with Florite-F, Veegum-F, and kaolin (1:5 w/w) initially and after 3 months of storage are shown in Figures 10 to 12, respectively. Both MTCs and MSCs increased upon storage at 40°C/75% RH for indomethacin-Florite-F (Figure 10)

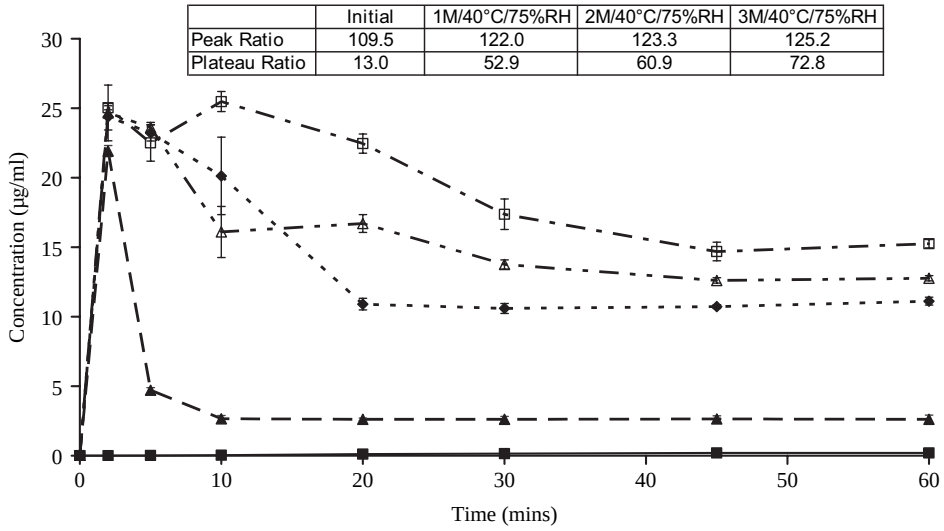

Figure 9. Dissolution profiles (n = 3) of indomethacin co-ground with Neusilin US2 (1:5 w/w) in 0.1N HCl (900 mL): –▲– initial, –♦– 1M/40°C/75% RH, –Δ– 2M/40°C/75% RH, –□– 3M/40°C/75% RH, –■– crystalline indomethacin.

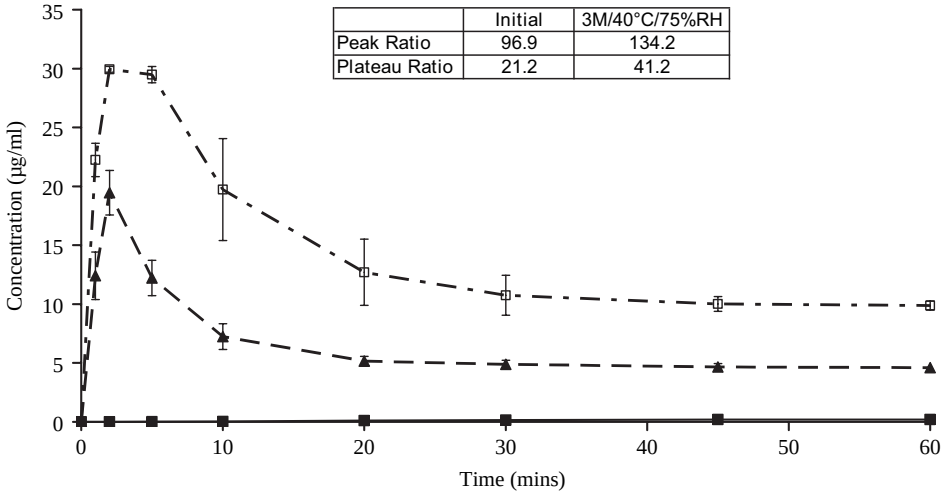

Figure 10. Dissolution profiles (n = 3) of indomethacin co-ground with Florite-F (1:5 w/w) in 0.1N HCl (900 mL): –▲– initial, –□– 3M/40°C/75% RH, –■– crystalline indomethacin.

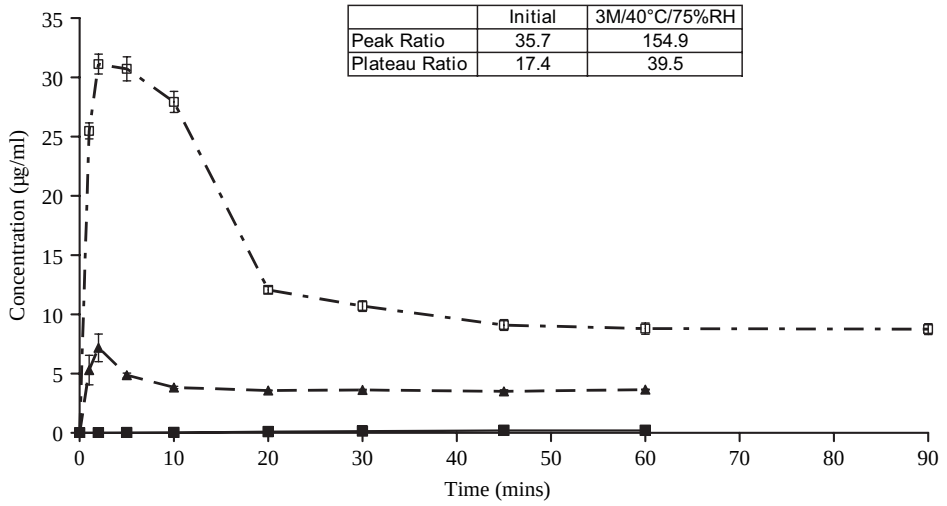

Figure 11. Dissolution profiles (n = 3) of indomethacin co-ground with Veegum-F (1:5 w/w) in 0.1N HCl (900 mL): –▲– initial, –□– 3M/40°C/75% RH, –■– crystalline indomethacin.

and indomethacin-Veegum F (Figure 11). There was no change in MTC, but a significant increase of MSC upon storage (Figure 12) for indomethacin co-ground with kaolin. Thus all 4 silicates presently investigated changed the dissolution of co-ground amorphous indomethacin upon storage.

Possible mechanisms for the observed increase in the dissolution of co-ground amorphous indomethacin upon storage were investigated. The chemical stability of indomethacin co-ground with different silicates initially and at 3 months of storage is reported in Table 2. A ~10% decline in potency on storage was observed for indomethacin co-ground with amorphous porous silicates (Neusilin US2 and Florite-F). A 2.3% and 4.3 % decline in potency of stored co-ground indomethacin was determined for samples co-ground with kaolin and Veegum-F, respectively (Table 2). It should be noted that with all 4 silicates, an increased MSC (2.3–5.6 times) was observed upon storage. We noted that higher degradation of indomethacin co-ground with amorphous silicates as compared with that of crystalline silicates also correlates with the surface area of the silicate. The pH of the silicate (Table 1) does not seem to correlate with the chemical stability (Table 2) of co-ground

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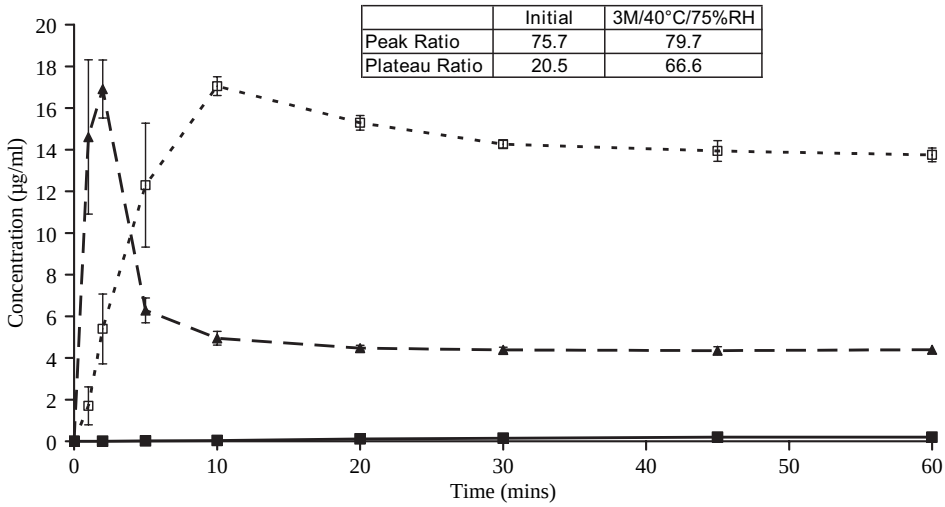

Figure 12. Dissolution profiles (n = 3) of indomethacin co-ground with Kaolin (1:5 w/w) in 0.1N HCl (900 mL): –▲– initial, –□– 3M/40°C/75% RH, –■– crystalline indomethacin.

indomethacin upon storage. However, in any case, there is not sufficient degradation to account for the large increases in MSC of co-ground amorphous indomethacin upon storage.

The co-ground amorphous indomethacin-Neusilin US2 system was further investigated. Table 4 compares surface area, meso- and micropore volumes, and meso- and micropore diameters of indomethacin co-ground with Neusilin US2 (1:5) initially and at 3 months of storage. A small decrease in surface area from 31 m^2/g (initial) to 25 m^2/g was observed at 1 month of storage, which remained constant for the next 2 months. Pore volumes and pore diameters for initial and stored samples were also similar. The absence of any significant change in the surface area, pore volume, and pore diameter of co-ground amorphous indomethacin upon storage suggests that it is unlikely that there is any further deposition or depletion of drug from the pores during storage. Thus neither surface area nor porosimetry could explain higher MTCs and/or MSCs of co-ground amorphous indomethacin on storage.

In a separate set of experiments, the dissolution of 600 mg of initial and stored samples of indomethacin co-ground with Neusilin US2 (1:5 w/w) were studied in 900 mL of 0.1N HCl at 37°C. The concentration of dissolved silicic acid at 60 min was determined using a silicomolybdate method.[20] The concentration of silicic acid increased from 324 µg/mL (initially) to 496 µg/mL (for the 3-months-stored sample). An increase in the MSC of indomethacin due to dissolved silicic acid and ions (Mg^{2+} and/or Al^{3+}) has been reported previously.[20] Thus, an increase in dissolved silicic acid may account for the increased MSC of indomethacin upon storage. However, the reaction that produces the increase in silicic acid upon storage is not obvious.

Table 4
Surface area, pore volume and pore diameter of powder (indomethacin co-ground with Neusilin in the ratio 1:5 for 5 days) at initial time point and storage at 40°C/75% RH

Condition	Surface Area (m^2/g)*	Pore Volume (cm^3/g)*	BJH Average Pore Diameter (A°)*	HK Pore Volume (cm^3/g)*	Median Pore Diameter (A°)*
Initial	30.6 (0.1)	0.122 (0.002)	161.9 (5.5)	0.039 (0.001)	52.7 (1.7)
1M/40°C/75% RH	24.8 (1.3)	0.126 (0.011)	195.0 (12.0)	0.030 (0.002)	52.7 (4.2)
2M/40°C/75% RH	24.9 (0.5)	0.106 (0.001)	165.3 (6.5)	0.030 (0.000)	51.8 (2.3)
3M/40°C/75% RH	23.9 (0.8)	0.118 (0.013)	175.3 (30.3)	0.031 (0.001)	55.0 (1.5)

*Standard deviation of 2 readings is in parentheses.

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CONCLUSIONS

Indomethacin was successfully amorphized by co-grinding with different silicates having various physicochemical properties such as surface area, pH, crystallinity, and metal ions. A shorter amorphization time of indomethacin was found when co-grinding with metal ion-containing silicates (as compared with co-grinding with silicon dioxide). In addition, higher surface area silicates lower the amorphization time. The co-ground amorphous indomethacin was physically stable by ATR-FTIR for 3 to 6 months at 40°C/75% RH. All of the silicates investigated in the present study amorphized indomethacin well above monolayer coverage. Porosimetry of co-ground samples suggested stabilization of amorphous indomethacin in the mesopores of Neusilin US2.

In addition to their ability to produce amorphous drug, Neusilin US2 and Florite-F act as buffers with the apparent pK_as of 3.5 and 6.8, respectively. The higher plateau concentrations of co-ground amorphous indomethacin seen on dissolution are highly dependent on (a) the amount of silicate and (b) the type of silicate used for co-grinding. Enhancement in solubility of co-ground amorphous indomethacin was found to be due to interaction of drug with silicic acid and ions (Mg^{2+}, Al^{3+}, and Ca^{2+}) released (from at least one of the silicates) into the dissolution medium. The amorphous indomethacin (prepared by co-grinding with Neusilin US2, Florite-F, Veegum-F, and kaolin) was physically stable with respect to PXRD and FTIR scans, yet showed further enhancement in the solubility (2.3 to 5.6 times) upon storage (compared with their initial plateau concentrations) at 3 months at 40°C/75% RH. An increase in the dissolved silicic acid (released from Neusilin US2) may account for the increased plateau concentration of indomethacin upon storage.

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