

Effects of Water Vapor Absorption on the Physical and Chemical Stability of Amorphous Sodium Indomethacin

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ABSTRACT

This study reports on the effects that water absorbed into amorphous sodium indomethacin (NaIMC) can have on simultaneous tendencies to crystallize to its trihydrate form and to undergo base-catalyzed hydrolysis because of the plasticizing effects of water on molecular mobility. Measurement of water vapor absorption at 30°C and powder x-ray diffraction patterns as a function of relative humidity (*RH*) reveal that upon exposure to 21% *RH*, NaIMC does not crystallize over a 2-month period. Measurements of the glass transition temperature as a function of such exposure reveals a change in T_g from 121°C, dry, to 53°C at 21% *RH*, such that T_g at 21% *RH* is ~13°C above the highest storage temperature of 40°C used in the study. At 56% *RH* and higher, however, crystallization to the trihydrate occurs rapidly; although over the 2-month period, crystallization was never complete. Assessment of chemical degradation by high-performance liquid chromatography analysis revealed significant instability at 21% *RH*; whereas at higher *RH*, the extent of chemical degradation was reduced, reflecting the greater crystallization to the more chemically stable crystalline form. It is concluded that when amorphous forms of salts occur in solid dosage forms, the simultaneous effects of enhanced water vapor sorption on crystallization and chemical degradation must be considered, particularly when assessing solid-state chemical degradation at higher temperatures and *RH* (eg, 40°C 75% *RH*).

KEYWORDS: water vapor sorption, amorphous, sodium indomethacin, chemical degradation, crystallization

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INTRODUCTION

An important aspect of early drug product development is the choice of the solid form of a drug that can provide optimal stability and bioavailability when formulated as a solid dosage form. A particularly challenging problem is the development of relatively hydrophobic drugs that often will not dissolve rapidly enough to be sufficiently absorbed upon administration. When the drug exhibits appropriate acid-base properties, the formation of crystalline salt forms, with enhanced water solubility, is a desirable strategy to accomplish this objective.

In some cases, however, the processing of crystalline salts (eg, lyophilization, milling, wet granulation, polymer film coating) can lead to partially or fully amorphous material.^{1,2} This result may be achieved purposefully, as in the lyophilization as a reconstitutable product of chemically unstable drugs intended for injection,^{3,4} or inadvertently, as when crystalline materials are milled, producing unexpected and often undetectable amorphous regions on the solid surface.^{5,6} Since amorphous forms of a drug are most often more chemically unstable than their corresponding crystalline forms,^{3,4} and since the amorphous form is thermodynamically metastable relative to the crystal,² the chances for physical (crystallization) and chemical instability are greatly enhanced under such circumstances. Furthermore, the exposure of such materials to elevated *RH* and temperatures would be expected to enhance crystallization and/or chemical degradation because of the well-recognized ability of water to act as a plasticizer in lowering the glass transition temperature, T_g , and increasing the molecular mobility that controls the rate of such diffusion-limited processes.^{7,8}

In this study, sodium indomethacin (NaIMC) has been used as a model of a hydrophobic molecule (indomethacin, IMC) with greatly increased solubility in water as the salt. Previous studies from this laboratory with amorphous NaIMC have characterized such parameters as T_g , molecular mobility, fragility, and molecular dispersions of the sodium salt, with its free acid form.^{9,10} In this study, the water vapor sorption by amorphous NaIMC is examined, with particular attention to the simultaneous effects of water on crystallization and chemical degradation, 2 forms of instability that

would be expected to offset any advantages of using salts, such as enhanced aqueous solubility and improved oral bioavailability.

MATERIALS AND METHODS

Materials

Crystalline NaIMC (sodium 1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetate) trihydrate was obtained as a gift from Merck & Co (Whitehouse Station, NJ) and used as received. The presence of 3 waters per mole of NaIMC was confirmed by Karl Fisher titration and thermogravimetric analysis. Anhydrous NaIMC was prepared by recrystallizing oven-dried NaIMC trihydrate from isopropyl alcohol, as well as by heating the trihydrate above 75°C to remove all of the water. The melting temperature of this crystalline anhydrous material was found to be 210°C. The amorphous form of NaIMC was prepared by freeze drying of an aqueous solution as described in detail elsewhere.⁹ The glass transition temperature of 121°C for the dry sample was in excellent agreement with previous results.⁹ The hydrolytic degradation product of NaIMC, 5-methoxy-2-methyl-3-indoleacetic acid (MMIA, Aldrich Chem Co, Milwaukee, WI), was used as an external standard for high-performance liquid chromatography (HPLC) analysis. It was recrystallized in 2 parts of a mixed solvent consisting of water:ethanol (1:1 vol/vol). Organic solvents used in HPLC analysis included acetonitrile, HPLC grade (EM Scientific, Gibbstown, NJ), and trifluoroacetic acid (99+%, spectrophotometric grade). Water used in this study was purified by a SYBRON/Barnstead pressure cartridge system (PCS) (Boston, MA).

Methods

Thermal Analysis

The T_g of the amorphous samples at various states of hydration was measured using a Seiko 220C differential scanning calorimeter (DSC) (Seiko Instruments, Horsham, PA) and a Seiko DSC 5200 Data Station as described in detail elsewhere.⁹ T_g was reported as the onset temperature of the glass transition.

X-Ray Powder Diffraction

Powder diffraction patterns of solid samples were obtained using a scanning x-ray powder diffractometer (XRPD) (Scintag Inc, Santa Clara, CA). The radiation was generated with $\text{CuK}\alpha$ at 40 A and 35 kV. Data acquisition and analysis were performed on a PC with the Scintag software (Tektronix Inc, Wilsonville, OR). The quartz sample holder used

in this study had an etched area of 0.5 cm × 2 cm and a depth of 0.1 mm (provided by Daiichi Pharmaceutical Co, Tokyo, Japan). The solid samples were packed into the etched area, gently pressed using a glass slide to smooth the surface, and scanned over a range of 2θ° from 3° to 40°, at 2.5°/min.

Water Vapor Sorption Isotherms

The water vapor sorption of various samples of NaIMC at 30°C was measured using 2 methods, a microelectronic balance assembly and desiccators containing various saturated salt solutions. Samples of ~10 mg were measured using a model MB-300G VTI microelectronic balance system (VTI Corp, Hialeah, FL), which was associated with a vacuum pressure system including a diffusion pump (TV203, Edwards High Vacuum International, West Sussex, UK), and a mechanical pump. The sample was loaded onto the quartz sample pan and dried under vacuum at 60°C until the weight change was below the equilibrium criterion chosen for this study (ie, 5 μg in 5 minutes). The dried sample was cooled to the experimental temperature of 30°C and then exposed sequentially to different RH ranging from 0% to 90% in 5% steps. The same weight change criterion as that of the drying was chosen for establishing sorption equilibrium.

Water vapor sorption isotherms for relatively large sample sizes (>50 mg) were determined gravimetrically at discrete RH in desiccators containing various salt solutions. Bulk samples in loosely capped scintillation vials were dried overnight in the presence of P₂O₅ in a vacuum oven at 60°C. The desired amount of sample was then weighed into a tared scintillation vial in a glove box. The vial was then placed into a desiccator of desired RH that had been preequilibrated at the experimental temperature, and its weight was checked at different time intervals.

Chemical Instability Studies

Previous studies on the solid-state chemical degradation of crystalline, amorphous, and molten IMC at temperatures of 145°C to 185°C indicated significant thermal degradation of these dry samples.¹¹ Hydrolysis of IMC in alkaline aqueous solution has been shown to produce 4-chlorobenzoic acid (CBA) and MMIA as degradation products.¹² In this study, therefore, samples of amorphous NaIMC were stored in the dark at 4°C, 30°C, and 40°C under RH of 21%, 56%, and 83% and measured for hydrolytic degradation as a function of time. The different RHs were provided by desiccators containing the various salt solutions.

A Thermoseparation Products HPLC system (Spectra-Physics Analytical, Fremont, CA) was used to determine quantitatively the contents of NaIMC and its hydrolytic deg-

radation products when the amorphous form was stored at different temperatures and *RH*. The HPLC system consisted of a Spectra System P1000 pump, a Spectra System UV1000 detector, and a ChemJet integrator (Spectra-Physics Analytical, Fremont, CA). The column used was an Altex Ultrasphere-ODS reverse phase column (4.6 mm inner diameter [ID] × 25 cm, Alltech, Deerfield, IL) with an ODS guard column cartridge (2.0 mm ID × 1 cm, Upchurch Scientific, Oak Harbor, WA). The mobile phase consisted of acetonitrile:water:trifluoroacetic acid (50:50:0.1, vol/vol). The flow rate was 1.0 mL/min, and the detection wavelength was 220 nm. A solvent similar to the mobile phase but without trifluoroacetic acid was used to dissolve the sample for injection. A typical HPLC chromatogram for a degraded sample using the system mentioned above shows 3 peaks at 3.44 minutes (MMIA), 4.04 minutes (CBA), and 6.45 minutes (IMC).

Quantitative analysis, following the amount of NaIMC and MMIA, was based on a response factor, *R*, which is the ratio of the molar extinction coefficient of MMIA to that of NaIMC. Calibration curves for both materials were constructed by plotting the corresponding peak height against molar concentration. In this study, since hydrolytic degradation of NaIMC in the solid state often occurred at a level far below 10%, the hydrated amorphous sample was diluted in 2 steps, the first to determine the peak height of MMIA and the second to determine the peak height of NaIMC. First a sample of ~5 mg was dissolved in 1 mL of solvent, and the MMIA peak height was measured. Then 0.5 mL of the above sample was further diluted to 10 mL in a volumetric flask, and the NaIMC peak height was measured. In the appropriate concentration range tested, the calibration curves for MMIA and NaIMC at λ220 nm are $Y = -1265.95 + 1.0794 \times 10^6 X$ ($r^2 = 0.9998$) and $Y = 698.3 + 4.12310^6 X$ ($r^2 = 0.9998$), respectively.

RESULTS AND DISCUSSION

Water Vapor Sorption Isotherms for Sodium Indomethacin

As expected, samples of the NaIMC trihydrate crystals exposed to *RH* of 56% or higher for 20 days revealed negligible adsorption of any additional water vapor.

In Figure 1, the typical water vapor uptake isotherm for freeze-dried amorphous NaIMC at 30°C is compared with that of crystalline anhydrous NaIMC. In contrast to the 1-step change over a narrow range of *RH* from the dehydrated NaIMC to the trihydrate form (14.2% wt/wt) in the crystalline state, the isotherm of amorphous NaIMC appears to consist of 4 stages. Below 30% *RH*, the water uptake increases in a linear manner. From 30% to 50% *RH*, there appears to be a major step-wise increase of vapor uptake,

which results in a water content higher than that expected stoichiometrically in the NaIMC trihydrate (14.2%). The 40% to 60% and 70% to 100% *RH* regions show a similar pattern of linear increase of water uptake with an increase of *RH*, with about a 2% step-wise weight increase between the 2 regions. Long-term storage of amorphous NaIMC in desiccators at 21%, 56%, and 83% *RH* for 20 days led to the same results, indicating that these data represent equilibrium values. Such step-wise water absorption would appear to be related to crystallization of NaIMC as *RH* increases (to be discussed below).

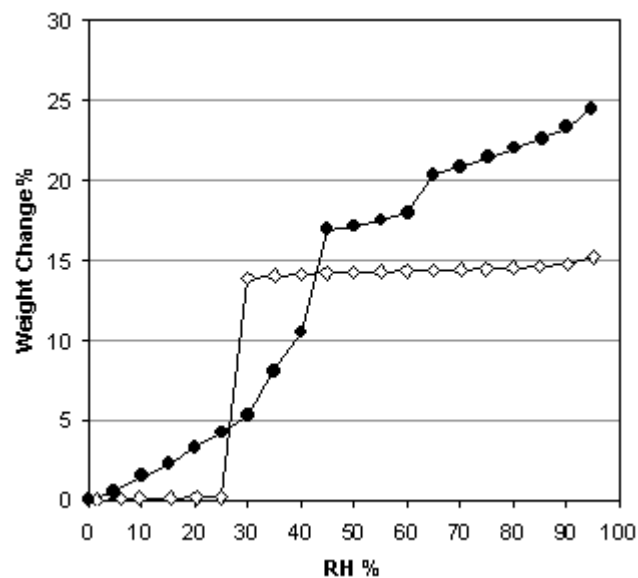


Figure 1. Water vapor sorption isotherms at 30°C for crystalline anhydrous NaIMC (◇) and amorphous NaIMC (●).

Crystallization From the Amorphous State

The powder x-ray diffraction (XRPD) patterns for NaIMC trihydrate, NaIMC anhydrous, and amorphous NaIMC are depicted in Figure 2. Here, it can be seen that the amorphous form gives the typical “halo” pattern generally observed for amorphous materials. Comparison of the crystalline anhydrous and trihydrate samples reveals that the anhydrous crystal exhibits a diffraction pattern that is somewhat similar to that of the trihydrate. A peak at 13.3° 2θ is unique to the anhydrous form, whereas peaks at 10.8° and 12.5° 2θ are also characteristic of the trihydrate. This finding suggests, but does not prove, that water in the trihydrate may exist in some type of “channel” or “tunnel” in the crystal lattice.¹³ However, attempts to obtain crystal structures of the anhydrous and trihydrate forms, to date, have been unsuccessful.

Also included in Figure 2 is the XRPD pattern of crystalline NaIMC trihydrate, which was ground in a stainless steel Wig-L-Bug (Crescent Dental Mfg Co, Lyons, IL) for 60

minutes. This partially crystalline NaIMC was purposely made to mimic the low degree of recrystallization of amorphous NaIMC to form the trihydrate. It can be seen that, at low crystallinity, some of the prominent peaks are absent from the diffractograms because of preferred crystal orientation.

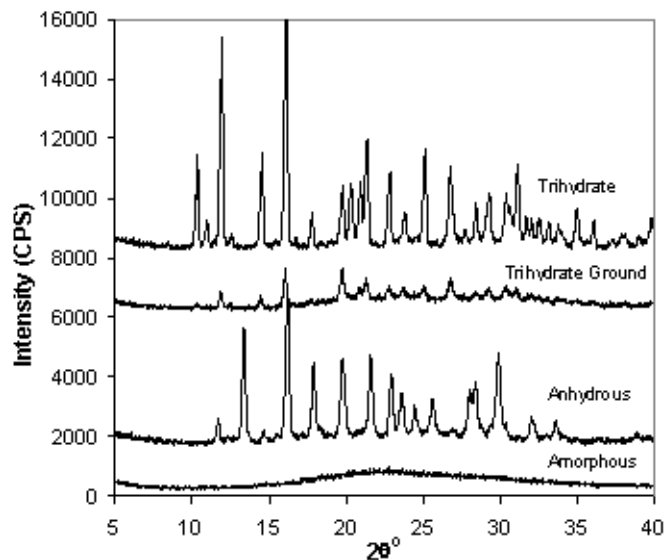


Figure 2. XRPD patterns of trihydrate, anhydrous, and amorphous NaIMC.

To confirm the phase transformation of amorphous NaIMC upon hydration, the amorphous NaIMC samples stored at 30°C in desiccators of 21%, 56%, and 83% RH were checked for crystallinity. A visual observation showed that there were no signs of crystallization for the samples in the 21% RH desiccator. However, the sample color was slightly darkened with storage. Upon exposure to RH of 56% and 83%, the fluffy amorphous cake quickly collapsed into a tightly packed structure, with obvious color darkening that worsened with extended storage. Figure 3 shows the change in XRPD patterns of freeze-dried amorphous NaIMC samples after storage at 30°C, for different periods of time, at 21%, 56%, and 83% RH, respectively. The data confirm the visual observation. At RH of 56% and 83%, the XRPD patterns at time (t) > 14 days resemble that of the ground crystalline NaIMC in Figure 2, confirming the formation of crystalline trihydrate.

Furthermore, closer comparison of the x-ray diffraction patterns of hydrated amorphous NaIMC to that of the trihydrate showed that hydration of amorphous NaIMC ultimately leads to the formation of NaIMC trihydrate. In all cases, however, only low levels of crystallinity resulted, as reflected by the low peak intensities observed in the XRPD patterns. However, a close examination of the change in

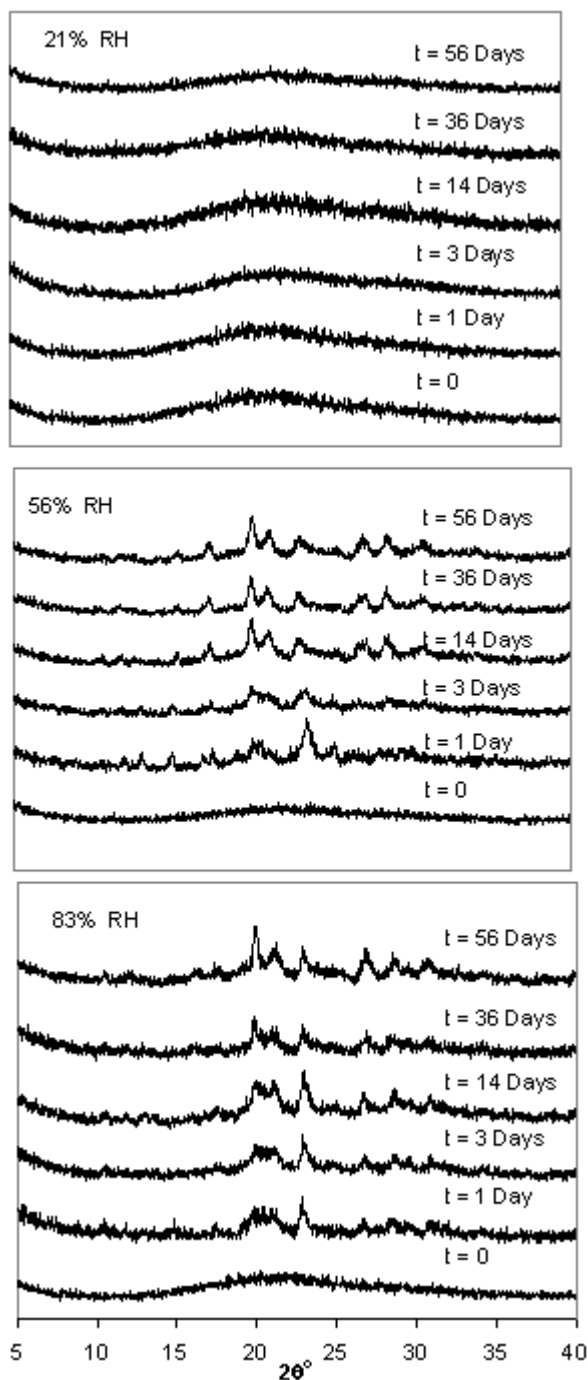


Figure 3. XRPD patterns of amorphous NaIMC when stored at 21% RH (upper panel), 56% RH (middle panel), and 83% RH (lower panel) at 30°C for different amounts of time (t).

crystalline form for amorphous NaIMC exposed to an intermediate humidity level (eg, 56% RH) showed that the transition from the amorphous phase to the trihydrate form may not be direct. Figure 4 represents a recording of the XRPD pattern for the amorphous sample exposed to 56% RH. Despite the poor resolution because of the low crystal-

linity, it can be seen clearly by numerous new peaks, which are absent for the trihydrate, that a new form different than the trihydrate occurs. The transformation from the new form to the trihydrate between 48 hours and 7 days is evidenced by the disappearance of diffraction peaks that are due to the new form and to the appearance of peaks that are characteristic of the trihydrate. The appearance of this new form may be due to the formation of an intermediate structure during the stage of crystal structure expansion and the accommodation of the gaseous water molecules. The other possibility is the formation of a metastable polymorphic trihydrate that subsequently transforms to the stable trihydrate form. However, at this point it is not possible to examine this form more clearly because of the difficulties associated with the isolation of the pure crystal form of the trihydrate and the "intermediate" form from solution.

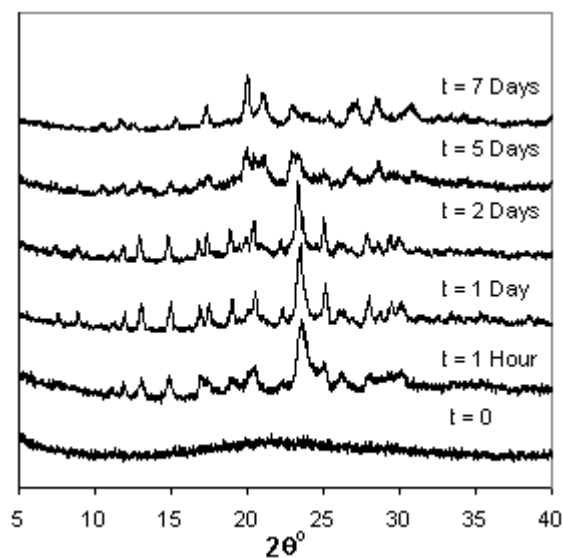


Figure 4. In situ x-ray diffraction patterns for freeze-dried amorphous NaIMC upon exposure to moisture. Samples were stored at 56% RH for different time (t) periods. The appearance of a new crystalline form before the formation of the trihydrate is shown at $t = 1$ day (scanned at 2.5° $2\theta/\text{min}$).

Glass Transition Temperature of Amorphous Sodium Indomethacin Exposed to Water Vapor

As has been demonstrated earlier (see Figure 3), amorphous NaIMC stored at 30°C and 21% RH can remain in the amorphous state for up to 56 days. To determine the extent to which water might plasticize amorphous NaIMC, samples were equilibrated under different conditions before they were subjected to DSC analysis. The experiments were carried out in 2 different ways. In the first case, the amorphous sample was loaded into a DSC pan and was allowed to

equilibrate for 2 days in desiccators containing salt-saturated solutions to provide RH of 7.6%, 11.3%, 16.5%, and 21.6% at 30°C . The equilibrated sample was weighed and scanned by DSC to 120°C to obtain the T_g values. The amount of water sorption is taken as the difference before and after the DSC scan. In the second case, in order to improve the accuracy of sample weighing, larger amounts of amorphous sample (200 mg) were put in scintillation vials and allowed to equilibrate in the above desiccators at 30°C for 2 days. The results of water content and T_g vs RH, measured in both ways, were in excellent agreement (up to 21% RH) and are shown in Table 1. It can be seen that at water contents up to almost 5% wt/wt and at T_g values of $\sim 53^\circ\text{C}$, insufficient molecular mobility exists at 30°C to produce crystals over a time period of 56 days.

Table 1. Water Vapor Sorption (30°C) Into Amorphous NaIMC and the Effect on T_g *

RH %	Water Fraction Absorbed	T_g ($^\circ\text{C}$)
7.6	0.026	72.3 ± 1.6
11.3	0.031	64.7 ± 0.5
16.5	0.041	56.0 ± 0.5
21.6	0.049	53.3 ± 1.4

*NaIMC indicates amorphous sodium indomethacin; T_g , glass transition temperature; and RH, relative humidity.

Chemical Stability of Sodium Indomethacin in Different Solid States

Even though crystallization of NaIMC to form the trihydrate occurred rapidly upon the exposure of amorphous NaIMC to $\text{RH} > 56\%$, the crystallization was never brought to completion even after up to 4 months of exposure. This finding is indicated by the low peak intensities and the diffusive background for all the XRPD patterns obtained for the hydrated amorphous material (Figures 3 and 4). The fact that water uptake is significantly higher than what is expected for the trihydrate also suggests that some proportion of amorphous content remains in the sample. One possible reason for such incomplete crystallization is the introduction of chemical impurities, because of degradation into the super-cooled liquid system, which might inhibit the growth of crystals. To clarify the relationship between crystallization and chemical stability of NaIMC, the chemical stability of amorphous NaIMC was studied under different hydration conditions.

Samples of amorphous NaIMC stored at 21%, 56%, and 83% RH at 4°C , 30°C , and 40°C were taken at different time intervals to check for any chemical degradation. Since these samples were not exposed to light, the major degrada

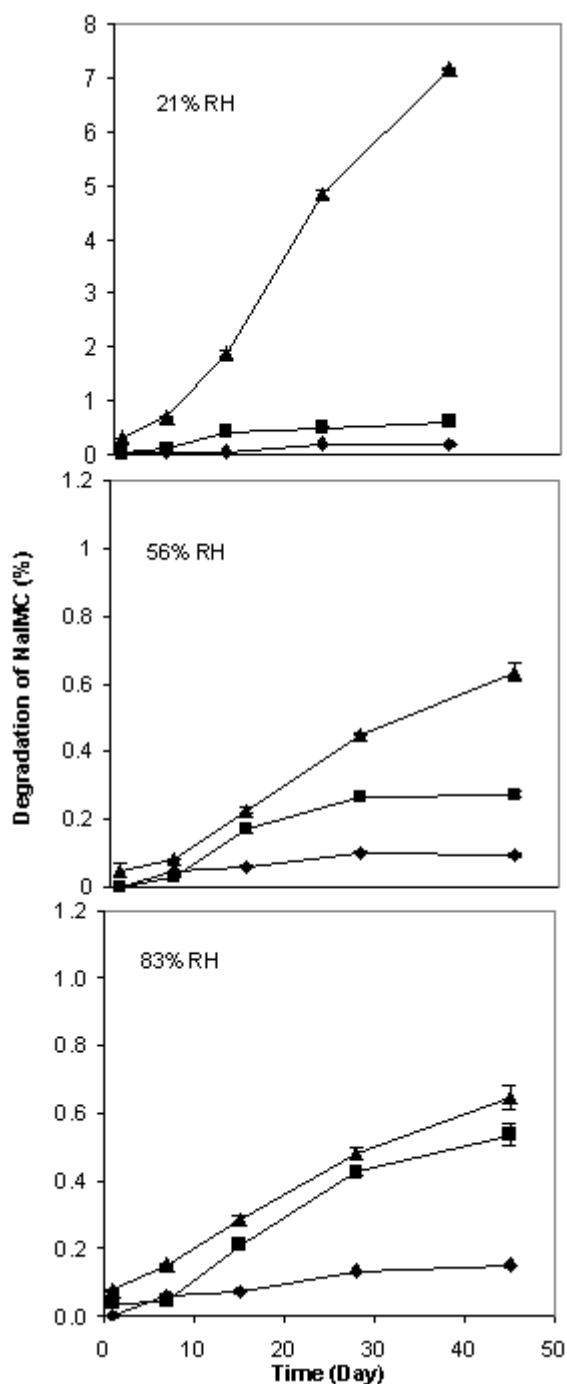


Figure 5. Percentage degradation of amorphous NaIMC as a function of time when stored at (upper panel) 21% RH, (middle panel) 56% RH, and (lower panel) 83% RH at different temperatures. Samples were stored at (■) 4°C, (●) 30°C, and (▲) 40°C. Lines are drawn to guide the eye.

tion observed during storage was expected to be due to hydrolytic degradation. The percentage degradation of NaIMC as a function of time when stored at different temperatures at 21%, 56%, and 83% RH is shown in Figure 5. At 21% RH, increasing temperature has a significant effect on the

degradation kinetics, as seen by the increase in rate of degradation when the temperature was raised from 30°C to 40°C. At higher RH, such as 56% and 83%, the samples also showed increased degradation with increasing temperature, but to a much lesser extent.

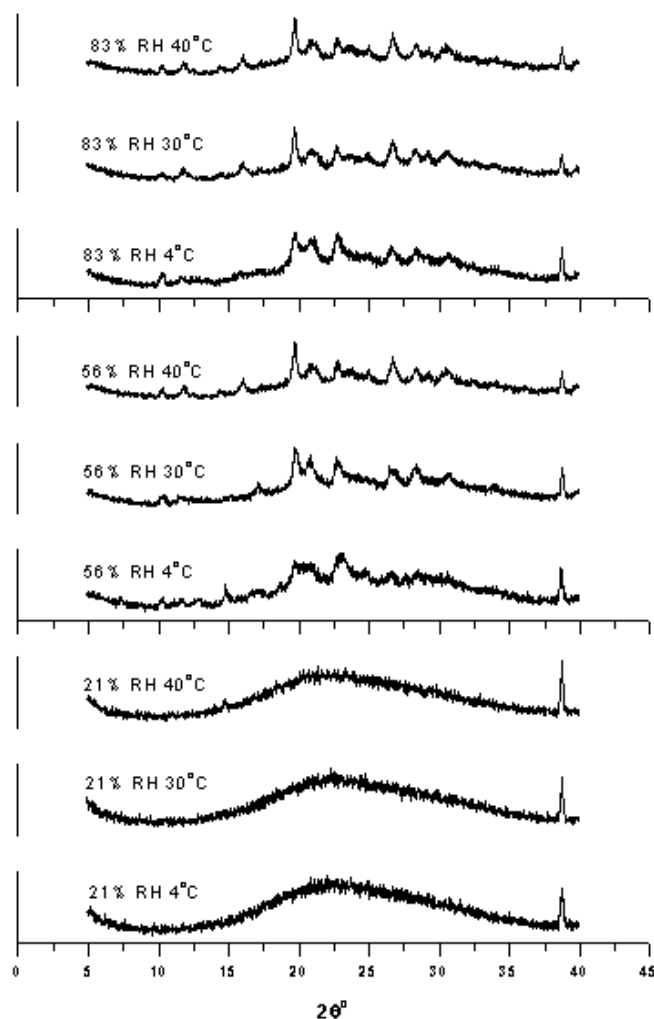


Figure 6. XRPD patterns for amorphous NaIMC exposed to 21%, 56%, and 83% RH at 4°C, 30°C, and 40°C for 15 days. Peak at 38.8° 2θ is due to the addition of 10% LiF.

Figure 6 shows the XRPD patterns for the above samples after 1 day of storage at the different conditions. As expected, the samples remained amorphous at 21% RH at all temperatures tested, but they crystallized immediately at 56% RH and 83% RH at all temperatures tested. It is noteworthy that crystallization of amorphous NaIMC when stored at 4°C and 30°C in a high humidity environment for 1 day gives rise to the new crystal form mentioned earlier. At high temperature (40°C), the trihydrate is formed more rapidly.

Chemical Reactivity vs Crystallinity

Degradation studies coupled with studies on crystallinity performed at different *RH* and different temperatures provide an interesting view of the chemical and physical stability of amorphous NaIMC. At *RH* of 21%, wherein crystallization did not take place in the experimental time scale, a strong temperature dependence of chemical degradation was observed. From the analysis of the plasticizing effects of water on amorphous NaIMC (Table 1), the T_g of NaIMC is reduced to $\sim 53^\circ\text{C}$ when the amorphous sample is equilibrated at 21% *RH* at 30°C . Ignoring the difference in water uptake caused by the difference in equilibrating temperature, the experimental temperatures of 4°C , 30°C , and 40°C , where percentage degradation was investigated, correspond to 49°C , 23°C , and 13°C , respectively, below the T_g value for NaIMC after plasticization by water. From the estimation of molecular mobility by enthalpy relaxation in previous studies,⁹ we know that at 16°C below T_g , significant molecular mobility can be detected, with structural relaxation times of approximately 6 hours. At 47°C below T_g , however, the molecular mobility becomes practically insignificant, as indicated by a relaxation time on the order of 10^6 hours. This finding may explain why at 40°C the degradation becomes prominent, whereas at 4°C the degradation is hardly detectable. It is interesting to note that at 21% *RH* and 30°C and 40°C , where it appears that degradation is enhanced because of increased molecular mobility, such increased molecular mobility increases do not lead to enhanced crystallization over the time scales of these experiments. Since crystallization results in the formation of the trihydrate, the higher activity of water (higher *RH*) needed to form the trihydrate is likely the reason that more crystallization does not occur despite an increase in molecular mobility.

At *RH* above 56%, the temperature dependence still exists. However, the much reduced degradation can be correlated to the formation of a stable crystalline trihydrate, which is less chemically reactive than the amorphous form. Although it was not possible to quantitate the extent of crystallinity using the conventional x-ray diffraction method, a ratio of the peak intensity at $19.8^\circ 2\theta$ for NaIMC trihydrate to the intensity of LiF at $38.8^\circ 2\theta$, after subtracting the background, can be used as an index for crystallinity of the hydrated product. As can be seen from the comparison between the chemical degradation and crystallinity in Figure 7, the uncrystallized amorphous material stored at 21% *RH* for 15 days at both 30°C and 40°C showed the highest extent of degradation, especially at 40°C . At 56% and 83% *RH*, the percentage degradation at all 3 temperatures tends to decrease as the extent of crystallinity increases.

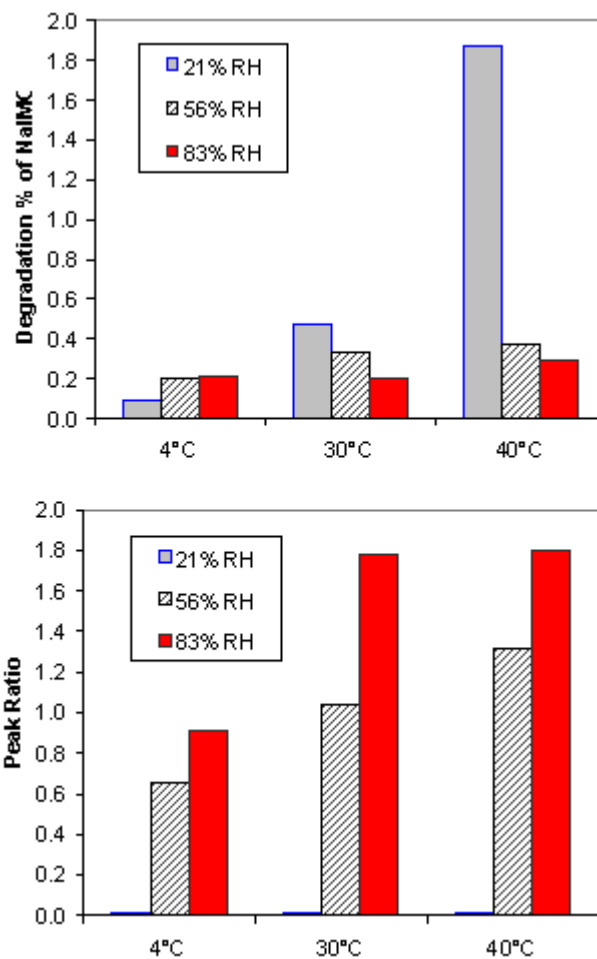


Figure 7. The relationship between chemical degradation (upper panel) and crystallinity (lower panel) of NaIMC at different *RH* as a function of temperature. Data shown are results at day 15. Peak ratio in the lower panel is calculated as the ratio of peak intensity at $19.8^\circ 2\theta$ (from the trihydrate) to $38.8^\circ 2\theta$ (from LiF).

CONCLUSION

Water vapor sorption studies for amorphous NaIMC at 30°C showed that below a critical *RH* of 30%, NaIMC can sorb up to 4% water while remaining in the amorphous state. However, below this critical *RH*, amorphous NaIMC becomes chemically unstable when the storage temperature is raised to 40°C , because of hydrolytic degradation caused by water sorption. At higher *RH*, water vapor sorption sufficiently plasticizes the amorphous system, also leading to rapid crystallization. Crystallization, however, tends to stabilize the system by forming the trihydrate, which does not undergo hydrolytic degradation on the timescale of these experiments. Of interest, crystallization from the amorphous phase results in the formation of an unknown form, which then transforms to the

stable trihydrate form in a temperature- and humidity-dependent manner. However, crystallization to form the trihydrate is not complete even after long-term exposure to high humidity. At all temperatures and humidities tested, upon crystallization, a significant amount of amorphous portion remains, retaining a substantial amount of water that is higher than would be expected to form the trihydrate. It is believed that the incomplete crystallization of the hydrated system is due to the interference of degradation product with the crystallization process.

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