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RESEARCH PAPER

Spontaneous Crystalline-to-Amorphous Phase Transformation of Organic or Medicinal Compounds in the Presence of Porous Media, Part 3: Effect of Moisture

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ABSTRACT

Purpose Amorphization of crystalline compounds using mesoporous media is a promising technique to improve the solubility and drug release of poorly-soluble compounds. The objective of this paper is to understand the effect of moisture on the capacity and performance of vapor-phase mediated amorphization.

Methods Mesoporous silicon dioxide (SiO_2) and crystalline naphthalene were used as the model system. The effect of moisture on the amorphization capacity of naphthalene was determined using adsorption chambers with various levels of relative humidity. Enthalpy and capacity of water vapor adsorption on SiO_2 were measured using isothermal microcalorimetry and thermogravimetry.

Results Moisture not only suppressed the amorphization capacity of naphthalene, but reversed an already-amorphized formulation as well. On the other hand, through the same competitive interaction, improved drug release and enhanced solubility were obtained. The initial supersaturation was followed by an entropy-driven crystallization. In addition, moisture-induced siloxane bond fracture was found at normal processing conditions, which led to the changes in silica surface chemistry. However, the implication in amorphization has not reached a definitive conclusion.

Conclusions Humidity during processing and storage must be carefully controlled for this type of amorphous formulation. Further investigation is needed to better understand the moisture-induced changes of silica.

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INTRODUCTION

Mesoporous materials (1), with mean pore diameter between 2 nm and 50 nm, have emerged as a novel amorphous drug delivery system in recent studies (2–6). A number of reports have shown that crystalline compounds became amorphous spontaneously after they were physically mixed with mesoporous silicon dioxide (SiO_2) (2,7,8) or magnesium aluminum silicate (e.g., Neusilin) (3). With naphthalene as a model compound, Qian *et al.* established that the pathway of amorphization occurs via the vapor phase, i.e., sublimation of the crystals, followed by physisorption of the molecules onto the porous excipients (7). The enthalpy of adsorption of naphthalene on SiO_2 was found to be more exothermic than the enthalpy of sublimation of naphthalene, which is in part responsible for the lowering of the Gibbs free energy and spontaneous phase transformation (7). Using nitrogen isotherms and semi-empirical calculations, Qian *et al.* further demonstrated that the amorphized molecules were residing inside of the pores of SiO_2, as capillary condensate, and multilayer (8). With an increasing number of new medicinal compounds having poor aqueous solubility, this type of amorphous system can be a new strategy to potentially enhance the bioavailability of drug molecules (9,10). Successful product development, therefore, requires a good understanding of how this novel drug delivery system would respond to environmental stresses, moisture in particular.

A neat amorphous solid can sorb a substantial amount of water. The sorbed water acts as a plasticizer to decrease the glass transition temperature of the glassy system, which in turn promotes nucleation and crystal growth. Recrystallization of amorphous solids through this mechanism is well recognized (11,12). However, the effect of humidity on the physical stability of an amorphous formulation using porous materials is not straightforward. For example, Konno studied the effect of moisture on the dissolution of amorphous Neusilin-flufenamic acid system (13). The formulation, containing 20 % drug, was subjected to 75 % relative humidity (RH) at 40°C for 1 month. Marked decrease in dissolution, both rate and extent, was observed; however, the formulation remained amorphous under powder X-ray diffraction (PXRD) and polarized-light microscopy (PLM). The absence of recrystallization was possibly due to the amount of flufenamic acid in the system being well under the amorphization capacity, although a satisfactory explanation regarding the conflicting observations, i.e., decrease in dissolution without the corresponding crystallization, was not provided.

Contrary to Konno's findings, Bahl *et al.* reported an opposite development (14). An amorphous formulation of Neusilin-indomethacin at 5:1 mass ratio, prepared using a low-energy ball milling method, was subjected to moisture at 40°C and 75 % RH for 3 months. Not only was the amorphous nature retained, but the amorphous content of indomethacin increased over time. Likewise, these samples showed greater dissolution and solubility. Salt formation of indomethacin with Mg^{2+} and Al^{3+} of Neusilin was suggested to be responsible for these observations. Nevertheless, these arguments do not adequately address Konno's findings.

Neusilin, being a type of magnesium aluminum silicate, arguably has a complex chemistry. Some investigators used a relatively simpler alternative for amorphization. An amorphous formulation of SiO_2-itraconazole, prepared using solvent impregnation method to achieve 20 % drug loading, was stored at 25°C and 97 % RH for 12 months (15). Dissolution studies showed that the stored samples exhibited greater concentration of itraconazole in solution than the initial sample. The authors proposed that water may react with SiO_2, and led to a change of silica surface chemistry. The evolving chemistry of SiO_2 could be responsible for the solubility enhancement.

The foregoing discussion illustrates the complex effects of humidity on the physical stability and performance of amorphous formulations prepared using porous media. Its understanding is of critical importance to product development. The three cases discussed above represent unique examples, of which the underlying mechanisms are compounded by factors such as preparation method (mechanical activation *vs.* solvent impregnation), chemistry of porous materials (with or without cations), and amount of drug (at or below the amorphization capacity). It is thus desirable to employ a simpler model system to elucidate a general guideline.

Herein, we examine the effect of humidity on amorphization using SiO_2-naphthelene system. Although this is not a pharmaceutical formulation, this model offers several advantages. First, the chemistry of SiO_2 is better understood and less complex than that of Neusilin. The surfaces of SiO_2 have both siloxane bridges (Si–O–Si) and hydroxyl (i.e., silanol, Si–OH) groups, the latter at an average density of 4.6 units/nm^2, measured using the hydrogen-deuterium exchange method (16). These surface functional groups can form hydrogen bonds or other types of van der Waals interactions with guest molecules. Second, since the vapor-phase mediated amorphization pathway of SiO_2-naphthelene has been established, we can measure the enthalpy of adsorption, and obtain a quantitative assessment regarding which molecule, water or naphthalene, interacts with the silica surfaces more favorably. Last but not the least, naphthalene has no known polymorphs, and is chemically stable even under high humidity. Therefore, any unexpected energetic events will likely due to SiO_2-water interactions. In summary, the objective of the current study is to investigate the effect of moisture on the capacity of vapor-phase mediated amorphization. A better understanding on the molecular level may explain the anomalous behavior reported in the literature.

MATERIALS AND METHODS

Materials

Mesoporous SiO_2 (Spherical silica gel, 62700) was obtained from Sorbent Technologies (Atlanta, Georgia). This grade of SiO_2 has an average pore diameter of 5 nm and specific surface area of 534 m^2/g, characterized using nitrogen isotherms. Its average particle size is 100 μm. Prior to use, SiO_2 was dried at 120°C for 12 h to remove surface-adsorbed water, without significant dehydroxylation. All subsequent sample handling was in a glove bag maintained at 0 % RH with a constant dry nitrogen purge.

Naphthalene (scintillation grade with >99 % purity) and methanol (high-performance liquid chromatography grade) were obtained from Fisher Scientific (Fairlawn, New Jersey). Lithium chloride and magnesium nitrate hexahydrate, both certified American Chemical Society grades, were also obtained from Fisher Scientific and used as received. Purified nitrogen (extra-dry grade) was obtained from Airgas (Radnor, Pennsylvania). Naphthalene was passed through a 100-mesh screen to remove large particles and agglomerates prior to use. Vapor pressures of naphthalene, water and saturated salt solutions are listed in Table I (17–20).

Table I Vapor Pressures of Materials in the Adsorption Chambers

Material	Condition	Vapor Pressure of Naphthalene or Water at 40°C (Pa)	Relative Humidity (%)	Reference
Naphthalene	Solid	45	N/A	17–19
Water	Liquid	7400	100	20
Lithium chloride	Saturated solution	829	11.2	20
Magnesium nitrate	Saturated solution	3582	48.4	20

Amorphization Capacity in the Presence of Moisture

Chambers were set up to determine the relationship between humidity and amorphization capacity of crystalline compound on mesoporous SiO_2. Naphthalene was used as a model crystalline organic compound. The configurations of the chamber and its dimensions are similar to those described elsewhere (7,8). In brief, crystalline naphthalene, SiO_2 and water or a saturated salt solution were placed inside a chamber on separate dishes. Vapors of naphthalene and water diffused through the headspace of the chamber and came in contact with SiO_2. The headspace of the chamber was filled with dry nitrogen initially. The pressure inside the chamber was then reduced using the laboratory vacuum line for 5 min. Once the chamber was prepared, samples were stored at 40°C. The reduced pressure and elevated temperature were intended to accelerate mass transfer.

Periodically, each chamber was opened to withdraw and weigh samples of SiO_2 (m_1), after which each was sealed and evacuated as before and stored again at 40°C. Adsorbed naphthalene was extracted from SiO_2 using 50-mL of methanol, followed by centrifugation to separate the solid. The supernatant was assayed using ultraviolet (UV) absorbance (GENESYS 5, Thermo Electron, Waltham, Massachusetts) at 276 nm to determine the amount of naphthalene adsorbed (m_2). The accumulated mass of adsorbed naphthalene over time was calculated by $m_2/(m_1–m_2)$, in g naphthalene per g SiO_2. This procedure was repeated for each adsorption chamber until a constant value was obtained.

Recrystallization of Amorphized Compound in the Presence of Moisture

Physical mixtures of SiO_2 and crystalline naphthalene at 3:1 mass ratio were prepared at room temperature, as described earlier (7,8). Briefly, ingredients were accurately weighed and gently mixed using a mortar and pestle to ensure content uniformity. The mixtures were then transferred to scintillation vials, in which the powder mixtures occupied between one-third and one-half of the vial volume. The vials, with nitrogen in the headspace, were then sealed tightly with a rubber stopper and aluminum crimp, and placed in a sealed container. The container, also with nitrogen in the headspace, was stored at 40°C.

The change in crystallinity of naphthalene was monitored using PXRD (Scintag XDS Diffractometer, XDS 2000, Scintag, Inc., Cupertino, California) with CuKα radiation at 45 kV and 40 mA. Samples were scanned from 5° to 50° at the rate of 1° per minute. PLM (Zeiss, Micro-tech optical, Oberkochen, Germany) was also used to detect any birefringence due to crystallinity. Once the sample became amorphous as confirmed by PXRD and PLM, it was subjected to 100 % RH at 40°C in a closed chamber. The recrystallization of previously-amorphized naphthalene was monitored using PXRD and PLM.

At each time point where a vial was withdrawn for X-ray analysis, a small sample was assayed for adsorbate as described above. The purpose of this analysis was to assure no loss of naphthalene from the vial during storage.

Enthalpy of Water Vapor Adsorption

The enthalpy of water vapor adsorption was determined using isothermal microcalorimetry (Thermal Activity Monitor or TAM, 2277, TA Instruments, New Castle, Delaware) and a dynamic vapor sorption (DVS) apparatus (Q5000, TA Instruments, New Castle, Delaware), as described elsewhere (21). A sample of accurately weighed SiO_2, dried at 120°C prior to use, was placed in a stainless-steel ampoule. The ampoule was then tightly attached to a perfusion shaft. The shaft was connected to a computer-controlled flow regulator which was connected to a dry, purified nitrogen gas cylinder. The flow regulator nominally controls the flow rate of dry nitrogen from the gas cylinder and splits the gas into dry and wet lines. The gas from both lines proceeded to the perfusion shaft. Upon entering the shaft, the gas was first warmed up to the same temperature as the calorimeter (e.g., 25°C). The dry line fed the gas, at 0 % RH, directly into the sample ampoule. The wet line passed the gas through two successive water reservoirs so that the exit gas was saturated with water vapor (i.e., 100 % RH). The dry and wet gases then mixed in the headspace of the sample ampoule. By adjusting the proportion of the two streams, a specific RH in the sample ampoule was obtained. Gas then exited the shaft through the exit line.

The shaft was lowered into a calorimeter and the system was allowed to reach thermal equilibrium at 25°C, at which time a zero baseline was attained. The flow rate of dry nitrogen was set at 150 mL/h during the equilibration, which took approximately 8–10 h. Once equilibrium was obtained, the RH of the incoming gas was adjusted to 10 %, and adsorption of water vapor on SiO_2 took place in the ampoule. When the adsorption was completed and the power signal returned to baseline, the RH of the incoming gas was changed to 20 % and the process was repeated in 10 % RH increments to 90 % RH. Power was integrated over time using the trapezoidal rule to obtain enthalpy of water vapor adsorption over each RH increment, in mJ per mg SiO_2.

The amount of water vapor adsorbed at each corresponding RH was determined using a DVS. An accurately weighed sample of dried SiO_2 was placed inside the sample chamber at 25°C. The equilibrium moisture uptake was measured as a function of RH from 0 to 90 % at 10 % increments, in mol of water per mg SiO_2. With this particular instrument, 90 % RH was the upper limit of the humidity level, and hence measurements at 100 % RH were not performed. The molar enthalpy of water vapor adsorption on SiO_2 was obtained by taking the ratio of these two measurements, in kJ per mol of water, as previously described.

Release of Naphthalene from Amorphous Formulations

An amorphous formulation consisting of SiO_2-naphthalene at 3:1 mass ratio was also used for release studies. A United States Pharmacopeia (USP) type II (paddle) dissolution apparatus (Vanderkamp 600, Vankel Industries, Chatham, New Jersey) was used. Similar to a previous report, paddle height was adjusted to 0.7-in. from the bottom of the vessel, and high rotation speed at 250 rpm was employed to prevent heap formation at the bottom of the vessel (14). Either crystalline naphthalene or an amorphous formulation containing 50 mg, 100 mg, 200 mg, or 300 mg of naphthalene was dispersed in 900 mL of water at 37°C. Aliquots were withdrawn and filtered through a 0.20 μm filter (Non-pyrogenic sterile syringe filter, 25-mm diameter, Corning Incorporated, Corning, New York) and analyzed by UV absorbance at 276 nm.

RESULTS AND DISCUSSION

In a pharmaceutical manufacturing facility, the moisture level is typically maintained between 40 and 60 % RH, not only to provide an acceptable working environment but also to ensure the proper processing conditions (e.g., prevent high static charges and powder sticking due to water condensation in exceedingly dry and wet air, respectively). This humidity level may affect a vapor-phase mediated amorphization process. Therefore, it is useful to determine a threshold RH level, below which sufficient amorphization capacity can still be achieved for practical considerations. On the other hand, a more favorable interaction between water and porous media would imply that, once an amorphous formulation is dispersed in a dissolution medium, water can displace the adsorbed drug molecules. The displaced drug compounds may go into solution and result in an improvement in solubility. A good understanding of these opposing effects of moisture will be important to develop a novel amorphous formulation with acceptable processability and reliable product performance.

Effect of RH on Amorphization of Crystalline Compounds

At equilibrium, water vapor significantly suppressed the capacity of mesoporous SiO_2 to amorphize naphthalene, from 0.53 g naphthalene per g SiO_2 at 0 % RH to 39 μg naphthalene per g SiO_2 at 100 % RH (Fig. 1). At 48 % RH, which is within the humidity range of a manufacturing facility, the amorphization capacity (0.19 g naphthalene per g SiO_2) is still adequate for product development.

Because of the faster rate of evaporation of water at 40°C, compared to the slower rate of sublimation of crystalline naphthalene at the same temperature, this observed relation of humidity-amorphization capacity might be confounded by kinetics. In other words, the adsorptive sites on the surface of SiO_2 could have been already occupied by water before naphthalene molecules entering the gaseous state. If the timescale of naphthalene replacing water molecules were much longer than that of the experimental procedure, a false conclusion might be reached that water had more favorable interaction with SiO_2.

In order to differentiate the kinetics and thermodynamics of competitive interaction, a physical mixture of SiO_2 and naphthalene at 3:1 mass ratio was prepared and stored. After it became amorphous as verified using PXRD, the

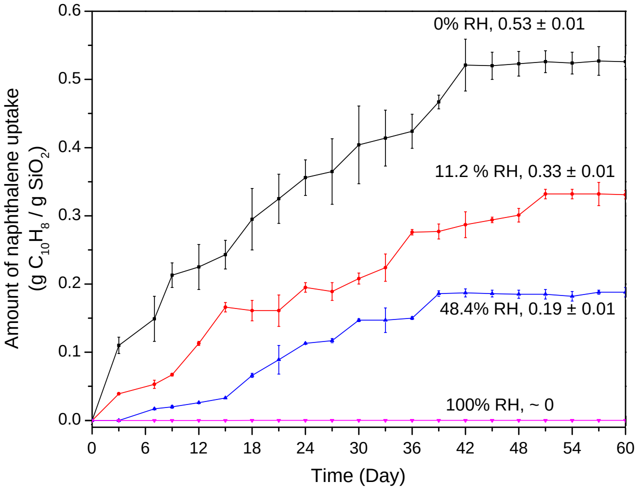

Fig. 1 Amorphization capacity of naphthalene on mesoporous SiO_2 (62700) at various levels of relative humidity.

formulation was stored at 100 % RH at 40°C. The reappearance of diffraction peaks (Fig. 2) and birefringence (data not shown) indicates the crystallization of naphthalene. As shown in earlier studies, in an amorphous mixture, naphthalene molecules were residing inside of the pores of SiO_2 (8). Therefore, a very likely scenario is that water has a stronger interaction with SiO_2 than naphthalene does. Once the naphthalene molecules were displaced by water, they diffused out of the pores and crystallized.

While we consider that most of the naphthalene molecules, if not all, crystallized out of the pores by this mechanism, it is desirable to quantify the crystallinity of naphthalene as a function of time once the amorphous formulation was subjected to moisture. One may potentially select a characteristic diffraction peak and compare the peak height or peak area to assess whether the moisture-induced recrystallization was complete; however, it should only be a rank-order consideration since diffraction peak intensity depends on the size of crystallite, as well as its orientation, which can lead to misleading conclusions. Another method one may consider is Fourier transform infrared spectroscopy coupled with chemometrics. Bahl and Bogner have shown this method can reliably quantify the crystallinity of a model compound in a partially-amorphous formulation, which can be used in future studies (22).

Furthermore, the moisture-induced recrystallization seen in the current investigation is distinctly different from the observations in the literature, i.e., moisture-induced further amorphization and improved solubility. Since each formulation is unique, the responsible mechanism is also different and requires additional studies. With our formulation, the favorable interaction of water vapor with SiO_2 is evident, and thus implies stronger energetics. This hypothesis was experimentally tested by measuring the enthalpy of water vapor adsorption, which is discussed below.

Thermodynamic Analysis of Competitive Adsorption Between Water Vapor and Naphthalene Molecules

Recognizing that the change of energy states of a phase transformation process is path-independent, this complex moisture-induced recrystallization of naphthalene may be viewed as a successive process of four simpler steps: 1) desorption of adsorbed naphthalene to the vapor phase; 2) vapor-solid condensation of naphthalene; 3) evaporation of water; and 4) adsorption of water vapor on SiO_2. Water, naphthalene and SiO_2 are denoted as 1, 2, 3 in the equations, respectively.

The crystallization of naphthalene can be illustrated in Eq. 1, with naphthalene in the adsorbed state and crystalline phase as the initial and final states, respectively, and naphthalene vapor as an intermediate step:

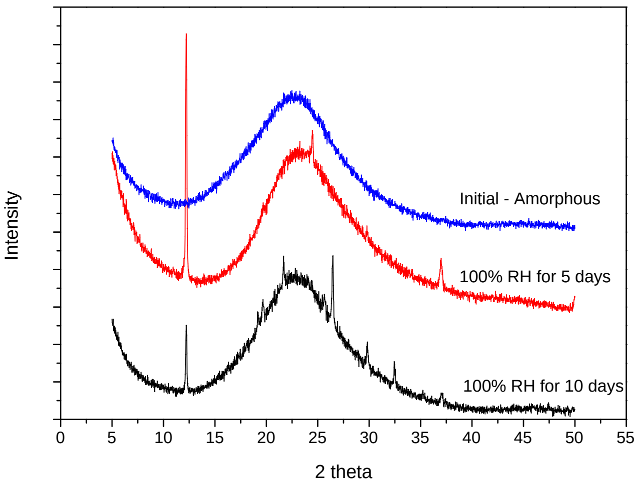

Fig. 2 Moisture-induced recrystallization of naphthalene once the amorphous formulation of SiO_2-naphthalene at 3:1 mass ratio was subjected to water vapor at 100 % RH at 40°C.

$$Naphthalene_{Adsorbed} \underset{Ads}{\overset{Des}{\rightleftarrows}} Naphthalene_{Vapor} + Adsorbent_{Substrate} \tag{1.a}$$

$$Naphthalene_{Vapor} \underset{Sub}{\overset{Cond}{\rightleftarrows}} Naphthalene_{Solid} \tag{1.b}$$

The Gibbs free energy of recrystallization of naphthalene, ΔG_2^{Crys} in J, can be expressed as:

$$\begin{aligned}\Delta G_2^{Crys} &= \Delta G^{Des,\,Naphthalene} + \Delta G_2^{Cond} \\ &= n_2 \cdot \left[\left(\Delta H^{Des,\,Naphthalene} + \Delta H_2^{Cond}\right) - T \cdot \left(\Delta S_2^{Des} + \Delta S_3^{Des,\,Naphthalene} + \Delta S_2^{Cond}\right)\right] \\ &= n_2 \cdot \left\{\left(\Delta H^{Des,\,Naphthalene} + \Delta H_2^{Cond}\right) - T \cdot \left[\left(S_2^S - S_2^{Ads}\right) + \Delta S_3^{Des,\,Naphthalene}\right]\right\}\end{aligned} \tag{2}$$

where $\Delta G^{Des,\,Naphthalene}$ and ΔG_2^{Cond} are the Gibbs free energies of desorption and condensation of naphthalene, respectively, both in J; $\Delta H^{Des,\,Naphthalene}$ and ΔH_2^{Cond} are the enthalpy of desorption and the enthalpy of vapor-solid condensation of naphthalene, respectively, both in J per mol of naphthalene; ΔS_2^{Des} is the change in molar entropy of naphthalene molecules upon desorption, in J/(mol·K); $\Delta S_3^{Des,\,Naphthalene}$ is the change in entropy of SiO_2 upon the desorption of 1 mol of naphthalene molecules, in J/(mol·K); ΔS_2^{Cond} is the change in molar entropy of naphthalene upon vapor-solid condensation, in J/(mol·K); S_2^S is the molar entropy of naphthalene in the solid state, in J/(mol·K); S_2^{Ads} is the molar entropy of naphthalene in the adsorbed state, in

J/(mol·K); n_2 is the amount of naphthalene desorbed and condensed, in mol; and T is the absolute temperature, in Kelvin.

The endothermic $\Delta H^{Des,\ Naphthalene}$ (159 kJ per mol of naphthalene) and the exothermic ΔH_2^{Cond} (−73 kJ per mol of naphthalene) were reported previously (7). At equilibrium ($\Delta G_2^{Crys} = 0$), the overall entropy change, $\left(\left(S_2^S - S_2^{Ads}\right) + \Delta S_3^{Des,\ Naphthalene}\right)$, is 288 J/(mol·K). A negative change in entropy for naphthalene molecules transitioning from an adsorbed state to an ordered crystalline phase is expected. However, its negative value is offset by an increase in entropy of the adsorbent, due to the restored vibrational motion of surface Si–OH of SiO_2 after the desorption of naphthalene.

Similarly, the adsorption of water vapor on SiO_2 can be illustrated in Eq. 3, with water in the liquid phase and adsorbed state as the initial and final states, respectively, and water vapor as an intermediate step:

$$Water_{Liquid} \underset{Cond}{\overset{Evap}{\rightleftarrows}} Water_{Vapor} \tag{3.a}$$

$$Water_{Vapor} + Adsorbent_{Substrate} \underset{Des}{\overset{Ads}{\rightleftarrows}} Water_{Adsorbed} \tag{3.b}$$

The Gibbs free energy of water vapor adsorption, $\Delta G^{Ads,\ Water}$ in J, can be expressed as:

$$\begin{aligned}\Delta G^{Ads,\ Water} &= n_1 \cdot \left\{\left(\Delta H_1^{Evap} + \Delta H^{Ads,\ Water}\right) - T \cdot \left(\Delta S_1^{Evap} + \Delta S_1^{Ads} + \Delta S_3^{Ads,\ Water}\right)\right\} \\ &= n_1 \cdot \left\{\left(\Delta H_1^{Evap} + \Delta H^{Ads,\ Water}\right) - T \cdot \left[\left(S_1^{Ads} - S_1^{L}\right) + \Delta S_3^{Ads,\ Water}\right]\right\}\end{aligned} \tag{4}$$

where ΔH_1^{Evap} and $\Delta H^{Ads,\ Water}$ are the enthalpy of vaporization of water and the enthalpy of water vapor adsorption on SiO_2, respectively, both in J per mol of water; ΔS_1^{Evap} is the change in molar entropy of water upon evaporation, in J/(mol·K); ΔS_1^{Ads} is the change in molar entropy of water vapor upon adsorption, in J/(mol·K); $\Delta S_3^{Ads,\ Water}$ is the change in entropy of SiO_2 upon the adsorption of 1 mol of water, in J/(mol·K); S_1^{Ads} is the molar entropy of water in the adsorbed state, in J/(mol·K); S_1^{L} is the molar entropy of water in the liquid state, in J/(mol·K); and n_1 is amount of water evaporated and adsorbed, in mol.

Overall, the change in the total Gibbs free energy of moisture-induced recrystallization of naphthalene, $\Delta G^{Overall}$, can be obtained from Eqs. 2 and 4:

$$\Delta G^{Overall} = \sum n_i \cdot \Delta H_i - T \cdot \sum n_i \cdot \Delta S_i \tag{5.a}$$

where

$$\sum n_i \cdot \Delta H_i = n_2 \cdot \left(\Delta H^{Des,\ Naphthalene} + \Delta H_2^{Cond}\right) + n_1 \cdot \left(\Delta H_1^{Evap} + \Delta H^{Ads,\ Water}\right) \tag{5.b}$$

$$\sum n_i \cdot \Delta S_i = n_2 \cdot \left(\left(S_2^S - S_2^{Ads}\right) + \Delta S_3^{Des,\ Naphthalene}\right) + n_1 \cdot \left(\left(S_1^{Ads} - S_1^{L}\right) + \Delta S_3^{Ads,\ Water}\right) \tag{5.c}$$

The enthalpy terms in Eq. 5.b are either obtained from the literature or previously measured, with the exception of $\Delta H^{Ads,\ Water}$, which was experimentally determined in this investigation, as discussed below.

Differential Enthalpy of Water Vapor Adsorption on SiO_2

For adsorption on an energetically-heterogeneous surface, the first molecule would have a higher probability of adsorbing on the most energetic site and result in the most exothermic enthalpy of adsorption. The second molecule would adsorb on the next most energetic site, and so on. With increasing relative pressure of adsorbate, the differential enthalpy of adsorption gradually approaches the enthalpy of vapor–liquid condensation due to multilayer formation. This trend can be expected if and only if the thermal events are due to physisorption alone. As shown in Fig. 3, at each RH interval, the heat released due to adsorption of water vapor on SiO_2 was measured using isothermal microcalorimetry (column 2 of Table II). Correspondingly, the amount of water vapor adsorption was measured using a gravimetric method (DVS) (column 4 of Table II). By taking the ratio of the two measurements (columns 2 and 4), a differential enthalpy of adsorption was obtained (column 6 of Table II).

From the experimental data (Fig. 3 and Table II), the interaction between water vapor and SiO_2 was more complex than physisorption alone. First, at RHs above 40 %, it took much longer for the heat signal to reach equilibrium while the weight gain attained constant values much more rapidly. Second, as expected, the differential enthalpy of adsorption was slightly more exothermic than the enthalpy of water condensation, ΔH_1^{Cond}, (−44 kJ/mol) at low RHs (<30 %); and at RH between 80 and 90 %, the enthalpy of adsorption (−50 kJ/mol) was similar to that of condensation. However, at RHs between 30 and 80 %, the enthalpy of adsorption became less exothermic (column 6 of Table II). Therefore, the presence of moisture likely induced chemical reaction and structural change of SiO_2. As shown in the Appendix (Eq. 7), the amount of water adsorbed at 40 %

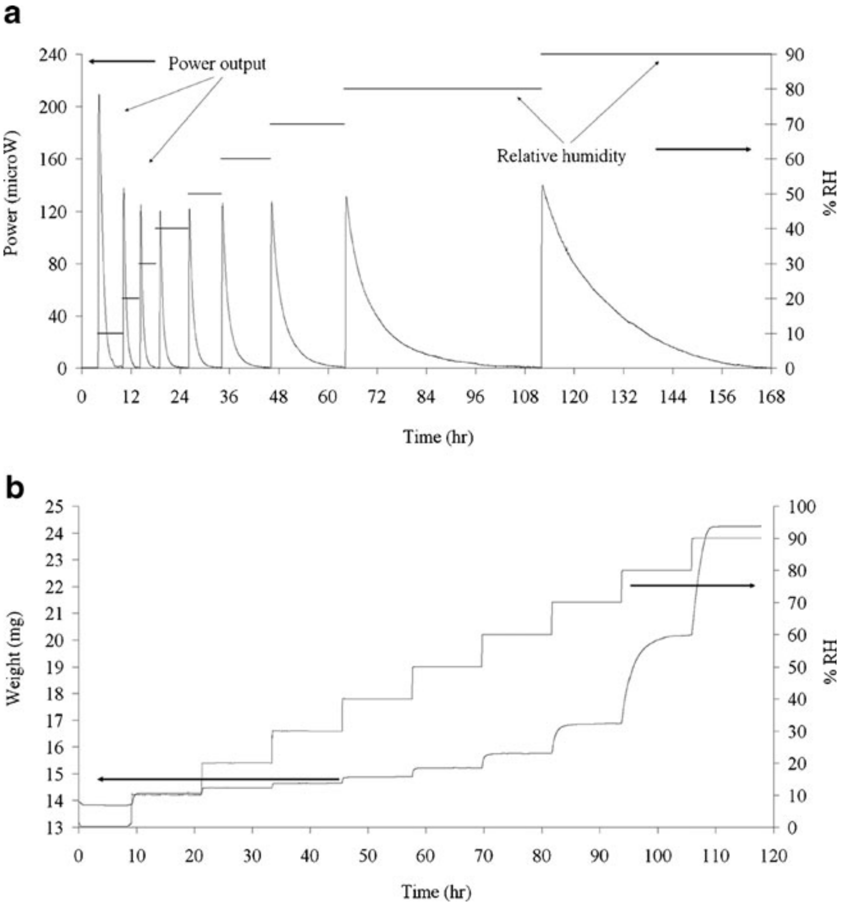

Fig. 3 Experimental measurements of the enthalpy of water vapor adsorption on SiO_2 as a function of RH. (**a**) Heat released due to adsorption in an isothermal microcalorimetry; (**b**) amount of water adsorbed in a dynamic vapor sorption apparatus.

RH (4.2×10^{-6} mol of water/mg SiO_2) approximately corresponds to monolayer coverage on the surface of SiO_2, assuming one water molecule interacting with one silanol group and the density of silanol groups is 4.6 units per nm^2. The onset of reaction may begin well before the monolayer was completed (23).

Network silica, with the empirical formula of SiO_2, is composed of $[SiO_4]$ tetrahedral units linked at their corners by bridging Si–O–Si bonds. The surface Si–O is terminated with a hydrogen atom (H). The Si–OH groups are normally the sites for adsorption, i.e., water vapor interacts with Si–OH via hydrogen bonding between the hydrogen atom of Si–OH (H_{Si-OH}) and oxygen atom of water (O_{H_2O}). The siloxane bridge (Si–O–Si), although hydrophobic in nature, can also interact with water vapor, and lead to water-mediated siloxane bond rupture (24–26). In this case, the

Table II Enthalpy of Adsorption of Water Vapor on SiO_2 (62700)

% RH	Heat Evolved due to Adsorption Measured by Isothermal Microcalorimetry (mJ/mg SiO_2)		Amount of Water Uptake Measured by DVS (mol of Water/mg SiO_2, $\times10^{-6}$)		Differential Enthalpy of Adsorption (kJ/mol) [b, c]
	Differential Quantity [a]	Cumulative Quantity	Differential Quantity [a]	Cumulative Quantity	
0–10	−90.2 (3.2)	−90.2	1.7 (0.0)	1.7	−53 (1.8)
10–20	−40.2 (1.5)	−130.4	0.80 (0.0)	2.5	−50 (1.9)
20–30	−32.9 (2.2)	−163.3	0.71 (0.0)	3.2	−46 (3.0)
30–40	−40.4 (0.6)	−203.7	0.94 (0.0)	4.2	−43 (0.6)
40–50	−54.1 (1.7)	−257.8	1.3 (0.0)	5.5	−42 (1.3)
50–60	−85.1 (0.9)	−342.9	2.2 (0.0)	7.7	−39 (0.4)
60–70	−151 (1.4)	−493.9	4.5 (0.0)	12	−34 (0.3)
70–80	−368 (3.1)	−861.9	13 (0.0)	25	−28 (0.2)
80–90	−795 (2.8)	−1656.9	16 (0.0)	41	−50 (0.2)

[a] Average of three measurements with standard deviation in the parenthesis

[b] Values obtained by taking the ratio of columns 2 and 4

[c] Standard deviation calculated using error propagation

water molecule is aligned by 1) formation of hydrogen bond between the hydrogen atom of water (H_{H_2O}) and the oxygen atom of Si–O–Si ($O_{Si-O-Si}$); and 2) interaction between the lone-pair electrons of O_{H_2O} and the silicon atom of Si–O–Si ($Si_{Si-O-Si}$) (Fig. 4a). This mode of interaction transforms the 4-coordinated Si to a transient 5-coordinated Si.

When Si is attacked by the lone-pair electrons of O_{H_2O}, the adjacent Si–O bond ruptures. The transient 5-coordinated Si relaxes to a 4-coordinated Si and creates a non-bridging oxygen (NBO) (Fig. 4b). Through a dual electrophiloic/nucleophilic process, the original water molecule dissociates and a hydrogen ion attaches to the final NBO, thus creating two new silanols (Fig. 4c). The water-mediated siloxane bond rupture is an endothermic event. Depending on the nature of Si–O–Si bond (e.g., crystalline or amorphous silica, bond angle and bond length), the energy to fracture a Si–O bond can range from 38 to 403 kJ/mol (27).

The water-mediated siloxane bond fracture and subsequent creation of new silanols introduce complications to the measurement of enthalpy of adsorption, i.e., observed heat flow is not due to physisorption only. Therefore, it might explain the less-exothermic enthalpy of adsorption. A similar mechanism was suggested by Mellaerts *et al.* in studying the possible changes in surface chemistry when SiO_2 was exposed to moisture at 97 % RH (15). By using ^{29}Si solid-state nuclear magnetic resonance equipped with magic angle spinning, the linkage of a Si atom of SiO_2 was probed. The Q^n notation indicates the number of –O–Si linkages of a Si atom (Fig. 5). After their mesoporous SiO_2 was stored at 97 % RH for 12 months, the content of Q^4 was reduced from 68 to 64 %, while the contents of Q^2 and Q^3 were enhanced from 3 to 4 % and 29 to 32 %, respectively. These data corroborate the formation of new silanol groups during storage in the presence of water vapor.

Since amorphization of crystalline compounds in the presence of mesoporous SiO_2 is facilitated through interaction with silanol groups, the newly created silanol groups would further amorphization. However, moisture-induced recrystallization of naphthalene was observed in this investigation (Fig. 2). A possible explanation is that Si–O bond rupture is a highly endothermic event. The number of newly created silanol groups might not be sufficient to significantly enhance amorphization. This is evidenced by the very slight increase in Q^2 and Q^3 contents. However, comparisons of the two studies are limited because the silica samples were from different sources. The different impurity levels, catalytic effects, difference in the density and distribution of surface functional groups and presence of cations can all contribute to the complex interaction. While the differential enthalpy of water vapor adsorption elucidates some details on the interaction mechanism, more investigation is needed to gain a better understanding.

Integral Enthalpy of Water Vapor Adsorption on SiO_2

At 90 % RH, the total amount of heat evolved due to adsorption and total amount of water vapor adsorbed are −1659.6 mJ per mg SiO_2 and 41×10^{-6} mol per mg SiO_2, respectively. The integral enthalpy of adsorption is calculated to be −40 kJ per mol of water. The amount of

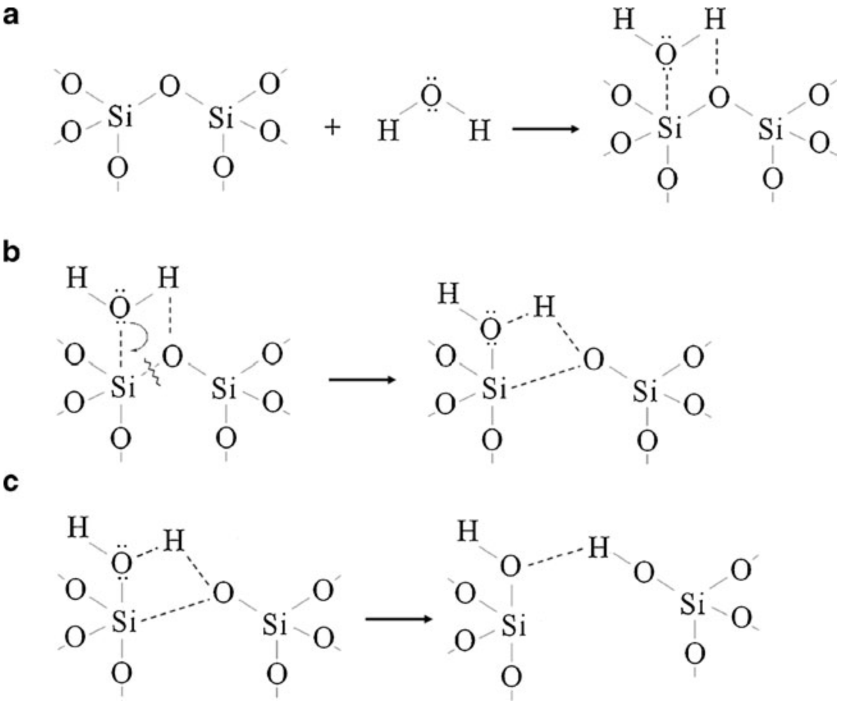

Fig. 4 Schematic representation of water-mediated siloxane bond rupture.

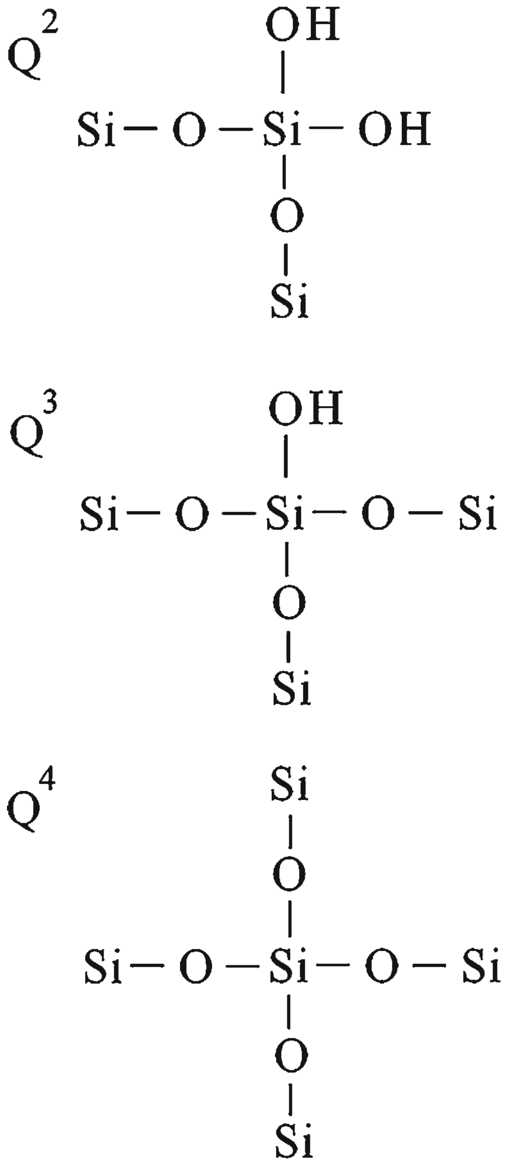

Fig. 5 –O–Si linkage of a silicon (Si) atom.

naphthalene in an amorphous formulation of SiO_2-to-naphthalene ratio being 3-to-1 (w/w) is 2.6×10^{-6} mol per mg SiO_2 (Eq. 8 in Appendix). The net enthalpy in Eq. 5.b is thus 0.39 J (Eq. 9 in Appendix), which is endothermic. Therefore, is the "enthalpy-driven displacement" hypothesis wrong? A more detailed explanation is necessary to address this complex and seemingly counter-institutive phenomenon.

The measured enthalpy reflects the net of all thermal events rather than solely physisorption of water vapor. Even with this particular example, the measured enthalpy (−40 kJ/mol) is very close to ΔH_1^{Cond} of −44 kJ/mol. If the endothermic siloxane-bond fracture does not take place, $\Delta H^{Ads,\ Water}$ would be more exothermic than ΔH_1^{Cond}. The limiting case in this argument is that the surface of SiO_2 behaves just like water, or $\Delta H^{Ads,\ Water} = \Delta H_1^{Cond} = -44$ *kJ/mol*. Based on this assumption, the enthalpic and entropic contributions are re-evaluated.

The net enthalpy (Eq. 5.b) in the limiting case is now 0.22 J (Eq. 10 in Appendix). The entropy terms in water vapor adsorption on SiO_2 (second part of Eq. 5.c), $\left(\left(S_1^{Ads} - S_1^{L}\right) + \Delta S_3^{Ads,\ Water}\right)$, is zero at equilibrium (Eq. 11 in Appendix); while the entropy terms in naphthalene desorption from SiO_2 (first part of Eq. 5.c), $\left(\left(S_2^{S} - S_2^{Ads}\right) + \Delta S_3^{Des,\ Naphthalene}\right)$, is 288 J/(mol·K). This value was not measured at the 3-to-1 ratio, and hence, not rigorously accurate. We nevertheless argue that it is adequate for estimation. Therefore, the net entropy (Eq. 5.c) in the limiting case is 7.5×10^{-4} J/K (Eq. 12 in Appendix). The $\Delta G^{Overall}$ (Eq. 5.a) in the limiting case is thus -4×10^{-3} J (Eq. 13 in Appendix).

The negative and near zero value of $\Delta G^{Overall}$ is consistent with the underlying assumptions of the limiting case. It is very likely that $\Delta H^{Ads,\ Water}$ is under-estimated to a large extent. Since the spontaneous displacement and recrystallization was indeed observed, water undoubtedly interacts with SiO_2 more favorably than naphthalene or an amorphized drug molecule. However, the process may not be merely due to the changes in enthalpy. Rather, interplay of enthalpy and entropy is responsible for the competitive interaction.

While the integral enthalpy of water vapor adsorption due to physisorption only could not be obtained in this study, the experimental evidence collectively suggests a favorable interaction between water vapor and SiO_2. This competitive interaction is responsible for the suppressed amorphization capacity of naphthalene in the adsorption chambers, as well as the recrystallization of naphthalene once the amorphous formulation was exposed to 100 % RH. Such competition may again be observed in the study of drug release, in which water can effectively displace the amorphized drug compound and produce an improved solubility.

Release of Naphthalene from Amorphous Formulations

Dissolution of a dosage form is a critical test to ensure product performance and quality. It is necessary to point out that the drug release mechanism from an amorphous formulation using porous media is different than the dissolution of a drug from a tablet or a solid dispersion formulation. Once the amorphous formulation is dispersed in water, its thermodynamic state is perturbed, i.e., water displaces adsorbed drug molecules. The displaced drug molecules go into solution and diffuse out of the pores, at a concentration that is higher than the equilibrium solubility of the crystalline state. This supersaturation is thermodynamically unstable and the drug eventually crystallizes. Using various formulation methods, one may potentially sustain the supersaturation to delay the onset of crystallization. If the duration of supersaturation can be extended to a pharmaceutically relevant time scale (e.g., 2-hour gastrointestinal transit time), this type of amorphous formulation would have significant practical importance.

Similar to the thermodynamic analysis of competitive adsorption (Eqs. 2, 4 and 5), a simplified model can be proposed to study the dissolution of amorphous formulations, based on several assumptions. First, adsorbed drug molecules would desorb from the surface and go into solution, at least for a short period of time. The enthalpy of solution is often exothermic. Second, water, in the liquid state with unit activity, would adsorb on the surface of SiO_2 and result in monolayer coverage. This successive process can be illustrated as:

$$Naphthalene_{Adsorbed} + Water_{Solution} \leftrightarrow Naphthalene_{Solution} + Water_{Adsorbed} \tag{6}$$

At a hypothetical equilibrium before crystallization occurs, the dissolved medicinal compound in an aqueous medium disrupts the three-dimensional network of water molecules, which form a highly-ordered structure around the nonpolar solute and brings about a decrease in entropy. In order to restore the random motion of water molecules, which will cause an increase in the entropy of the system, dissolved compound would crystallize from the solution (28).

Using an amorphous formulation of SiO_2-naphthalene at 3:1 mass ratio, the release of naphthalene from amorphous formulations was performed (Fig. 6). As the amount of naphthalene was increased, the peak concentration increased as well. This is consistent with the prediction that the initial higher concentration was achieved by competitive interaction and water displacement. However, the higher degree of supersaturation eventually led to the faster recrystallization, as in the case of formulation with 300 mg of naphthalene. Naphthalene is a drug-like compound with poor aqueous solubility (29). It would be of great interest and importance to carefully select drug compounds with known fast or slow crystallization tendency and perform the dissolution studies from mesoporous silica.

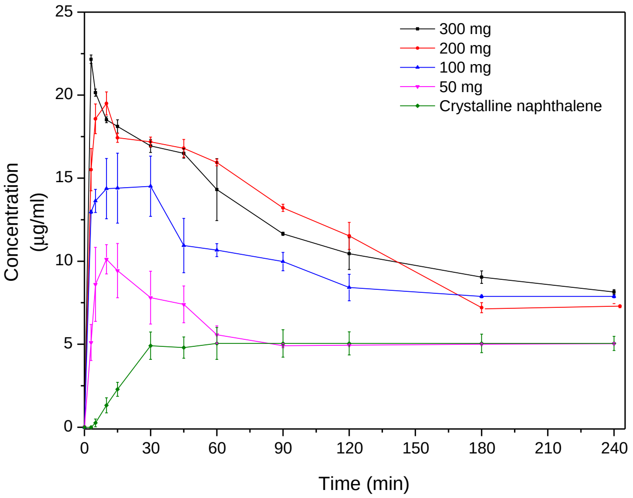

Fig. 6 Release of naphthalene from amorphous formulation of SiO_2-naphthalene at 3:1 mass ratio in 900-mL water at 37°C.

CONCLUSIONS

The effect of moisture on the capacity of amorphization was investigated. Water vapor can significantly decrease the amount of drug amorphized. The amorphization capacity of naphthalene at 48 % RH was approximately 0.2 g per g SiO_2, which is still sufficient for product development. However, this type of amorphous formulation should be prepared under capacity, because moisture can also reverse an already-amorphized formulation due to competitive interaction. Blister-packaging to avoid moisture prior to administration would be critical to maintain the performance of these dosage forms. On the other hand, through the same competitive interaction, improved drug release and an enhancement of apparent solubility were obtained. The initial supersaturation was followed by crystallization, driven by the entropy.

During the course of this investigation, SiO_2 was found to react with water at normal processing conditions (e.g., temperature, pressure and RH). The reaction may lead to the changes in its surface chemistry. However, the implication of such changes in amorphization, both capacity and performance, has not been well established. As the current study still cannot fully address the "moisture-induced further amorphization", additional study is thus needed. Advanced analytical techniques, such as *in situ* Raman spectroscopy, may be applied in the investigation.

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APPENDIX

Amount of water adsorbed by forming a monolayer on the surface of SiO_2:

$$\begin{aligned}&\mathit{Monolayer\ of\ water\ molecules}\\&=4.6\,\frac{Sites}{nm^2}\cdot\frac{10^{18}nm^2}{m^2}\cdot 534\,\frac{m^2}{g\ of\ SiO_2}\cdot\frac{1\ mol}{6.022\times10^{23}molecules}\cdot\frac{1\ g}{1000\ mg}\\&=4.1\times10^{-6}\,\frac{mol\ of\ water}{mg\ SiO_2}\end{aligned}\tag{7}$$

Amount of naphthalene molecules in an amorphous formulation of SiO_2:naphthalene = 3:1 (w/w):

$$\begin{aligned}&\mathit{Amount\ of\ naphthalene\ molecules}\\&=0.33\,\frac{g\ naphthalene}{g\ SiO_2}\cdot\frac{g\ SiO_2}{1000\ mg\ SiO_2}\cdot\frac{1\ mol}{128\ g\ naphthalene}\\&=2.6\times10^{-6}\,\frac{mol\ of\ naphthalene}{mg\ SiO_2}\end{aligned}\tag{8}$$

Evaluation of net enthalpy (Eq. 5.b):

$$\begin{aligned}\sum n_i\cdot\Delta H_i=n_2\cdot\left(\Delta H^{Des,\ Naphthalene}+\Delta H_2^{Cond}\right)+n_1\cdot\left(\Delta H_1^{Evap}+\Delta H^{Ads,\ Water}\right)&=(2.6\times10^{-6})\cdot(159-73)\cdot1000\\&\quad+(41\times10^{-6})\cdot(44-40)\cdot1000\\&=0.39J\end{aligned}\tag{9}$$

Net enthalpy in the limiting case (Eq. 5.b):

$$\begin{aligned}\sum n_i\cdot\Delta H_i=n_2\cdot\left(\Delta H^{Des,\ Naphthalene}+\Delta H_2^{Cond}\right)+n_1\cdot\left(\Delta H_1^{Evap}+\Delta H^{Ads,\ Water}\right)&=\left(2.6\times10^{-6}\right)\cdot(159-73)\cdot1000\\&\quad+\left(41\times10^{-6}\right)\cdot(44-44)\cdot1000\\&=0.22\,J\end{aligned}\tag{10}$$

Entropy terms in water vapor adsorption on SiO_2 in the limiting case (Eq. 4 at equilibrium):

$$\left[\left(S_1^{Ads}-S_1^L\right)+\Delta S_3^{Ads,\ Water}\right]=\frac{\left(\Delta H_1^{Evap}+\Delta H^{Ads,\ Water}\right)}{T}=\frac{(44-44)}{298.15}\cdot1000=0\,\frac{J}{mol\cdot K}\tag{11}$$

Net entropy in the limiting case (Eq. 5.c):

$$\begin{aligned}\sum n_i\cdot\Delta S_i=n_2\cdot\left(\left(S_2^S-S_2^{Ads}\right)+\Delta S_3^{Des,\ Naphthalene}\right)+n_1\cdot\left(\left(S_1^{Ads}-S_1^L\right)+\Delta S_3^{Ads,\ Water}\right)&=(2.6\times10^{-6})\cdot288\\&\quad+(41\times10^{-6})\cdot0=7.5\times10^{-4}J/K\end{aligned}\tag{12}$$

Change in the Gibbs free energy in the limiting case (Eq. 5.a):

$$\begin{aligned}\Delta G^{Overall}&=\sum n_i\cdot\Delta H_i-T\cdot\sum n_i\cdot\Delta S_i\\&=0.22-298.15\cdot\left(7.5\times10^{-4}\right)=-4\times10^{-3}J\approx0\,J\end{aligned}\tag{13}$$

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