

SCIENCE OF HUMIDITY IMPACT ON DEGRADATION RATES IN SOLIDS

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Summary: *The rate of chemical reactions in multi-component, solid systems such as drug products depends exponentially on the water activity (equilibrium relative humidity). It is proposed that this dependence is directly linked to an exponential increase in water content as a function of relative humidity at amorphous (non-crystalline) regions. Such exponential sorption is attributed to cooperative water binding where water-water interactions are predominant. This condensation tendency as a function of relative humidity adjusts for temperature based on the change in water partial pressure in air at saturation. The result is that the exponential condensation (sorption) as a function of water activity is relatively temperature independent. Reaction rates overall increase proportionately to the amount of water condensed due to an increased amount of active in its more reactive dissolved, semi-solid and potentially admixed state. Since the dissolved state itself is independent of RH in character, though not in amount, the activation energy is independent of RH. Temperature effects on solubility, which themselves tend to be exponential for organic materials, are suggested to contribute to the activation energy for the degradation.*

GENERAL

In the solid state, a high fraction of chemical reaction rates depend on humidity to at least some extent. In this paper, we examine the origin of this humidity dependence. We define some relevant terms, discuss the nature of moisture's interactions with solids, describe the general mathematical form of the humidity dependence of chemical reactions in the solid state, and finally consider the key mechanisms for this dependence.

TERMINOLOGY

Relative Humidity: The amount of water that air can hold (i.e., water concentration for moisture-saturated air) varies exponentially with temperature, as described by the August-Roche-Magnus formula¹, shown in Equation 1,

$$P_{saturated} = 6.1094e^{\left(\frac{17.625T_c}{T_c+243.04}\right)} \quad (1)$$

where $P_{saturated}$ is the saturated partial pressure of water, and T_c is the temperature in Celsius. The actual moisture content at a given condition can be expressed in terms of its ratio to this saturated concentration. This ratio (as a percentage) is the "relative humidity" (RH). The RH is important since it reflects the thermodynamic energy of the water in air. For example, moisture transfer rates (e.g., into a bottle) and drying rates depend on RH differences rather than the moisture content.

Dew Point: One way to express the RH is in terms of what temperature the air would need to be lowered to in order to reach saturation. The higher the dew point, the closer to saturation the air is and the higher the corresponding RH must be.

Water Activity: At equilibrium, a solid and the air above it must have the same water activity (a_w). The water activity for the solid (expressed as a decimal) is therefore the same as the RH of the solid (expressed as a percentage) and the air in equilibrium above the solid. The water activity reflects the reactivity and mobility of the water in the solid. Water molecules bound as hydrates do not contribute to the water activity since they do not participate in chemical reactions or increase mobility.

Deliquescence: Highly soluble materials can impact the energetics (actually the entropy) of water solutions, lowering the water

activity of the solution.² The RH corresponding to the water activity of a saturated solution of the solid is called the "critical relative humidity" (CRH). When materials are placed in RH conditions above their CRH values, they will pull moisture out of the air in a process called "deliquescence". Deliquescence will continue until the water activity of the solution formed is above that of the air; i.e., water will be picked up until the solution is sufficiently dilute to have an activity above that of the environment. In general, the CRH of a solid is a colligative phenomenon depending on the solubility of the material; however, in certain circumstances, there can be local or metastable effects that serve to lower the CRH below the thermodynamic value. For example, an amorphous material will have a metastable solubility substantially higher than its crystalline form such that the CRH will be lower. Even in crystalline materials, the CRH can be lowered by capillary condensation: in confined defect sites deliquescence can occur below the CRH of the bulk solid. However, in most cases, the capillary size needed to induce capillary condensation is below the molecular size itself. Mixtures of solids can synergistically lower the CRH below that of any of the individual materials.³

Sorption Isotherm: Solids will hold, at equilibrium, a different amount of water as a function of RH (discussed in detail below). The water can be sorbed into a matrix (absorption) or on surfaces (adsorption). At the same water activity, some solids will have significantly greater amounts of water present. With a sorption isotherm, one can convert a water content to a water activity, and vice versa. Sorption isotherms generally show small changes as a function of temperature in the range of 20-70°C.⁴ Traditionally, moisture sorption isotherms have been described by the Guggenheim-Anderson-de Boer (GAB) equation (Eq. 2), which has been shown to fit the sorption of most materials.⁵

$$Wt\%_{H_2O} = \frac{W_m C K (RH)}{[1-K(RH)][1-K(RH)+CK(RH)]} \quad (2)$$

Here W_m , C and K are three parameters related to the sorption, and RH is the equilibrium RH of the sample. RH can be replaced by a_w with the corresponding differences in units for the parameters. While these parameters may describe physical aspects of water sorption, they are generally used as fitting parameters based on experimental data.

THERMODYNAMICS OF WATER ACTIVITY

Before delving into the influence of moisture on reaction kinetics, it is worthwhile discussing the structures and transitions between water vapor, liquid water, adsorbed water, and absorbed water.

Pure Liquid vs. Vapor

We can start with the interplay between the liquid and vapor phases of water in the absence of any surfaces. When water molecules are added to dry air, at the low concentration limit, each molecule will fill the space as an ideal gas; i.e., $PV = nRT$ (P is the water partial pressure, V the volume, n the number of moles of water, R the gas constant, and T the temperature). Entropy is high since the water molecules have little correlation. As more water molecules are added, the attractive energy between the water molecules starts to offset the entropic benefit of keeping the molecules as far apart as possible. Water molecules in the center of water droplets have lower energy (more stabilized) than waters at the water-air interface. This is why water has a high surface energy (surface tension): water molecules arrange to minimize the number at the surface. However, to achieve the significant energy benefit of waters in the center of a grouping, a relatively large number of waters need to form an association. The result is that the entropic cost of association is high. The equilibrium constant (K) between water agglomeration as condensation

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(favored by enthalpy) or staying as individual water molecules in the gas phase (favored by entropy) is decided by the overall free energy (ΔG) of the process as shown in Equation 3.

$$K = e^{-\frac{\Delta G}{RT}} \quad \Delta G = \Delta H - T\Delta S \quad (3)$$

where K is the equilibrium constant between $H_2O(g)$ and $H_2O(l)$, ΔG is the free energy difference, ΔH is the enthalpy difference, and ΔS is the entropy difference between the states (with liquid water being the standard state). In a closed container, if there is liquid water present, the vapor above the liquid will be at the saturated pressure for that temperature (independent of the amount of water present). Basically, some water molecules will have enough energy to escape the liquid state and gain the entropy benefit. At ambient temperatures and pressures, gaseous water involves almost no agglomerations such that the density of the gas (g/L) even at saturation is almost exactly that predicted for an ideal gas (i.e., the fugacity ratio is approximately 1). As temperature increases, the equilibrium shifts more to the gas form since the entropy-favored vapor phase is multiplied by temperature (Eq. 3). When no liquid water is present, the activity of the water in the gas phase is defined in terms of the ratio of the partial pressure of water (or density) to that for the partial pressure above liquid water at that temperature. This means that as temperature increases, more water needs to be in the air to maintain the same water activity (relative humidity).

Adsorption/Absorption

When a solid surface is present, the energy associated with interactions with water molecules can be attractive or repulsive. The tendency for water molecules to associate with a surface in an attractive way (to “wet” the surface) is defined as the surface energy. When the attractive energy between the solid surface and water molecules is sufficiently large, it can offset the entropy disadvantage of condensation to enable condensation at water activities (RHs) below saturation at that temperature. As the waters bind to the surface, a layer of water molecules is now available to bind further waters in multilayer structures. In essence, we gain the enthalpy advantage of both water-surface and water-water interactions without having the disadvantage of many water molecules being at an air interface.

Depending on the the solid, moisture sorption will show three behavior patterns as a function of RH:

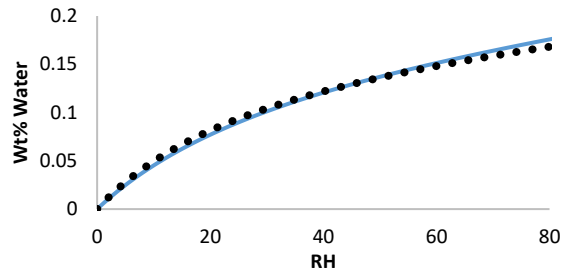
(1) In an ideal gas-ideal surface model, only surface bound waters are involved, and there is little water-water interactions of the bound waters. Adsorption where only waters are associated with the surface is known as Langmuir adsorption, which is described by the Langmuir equation (Equation 4).⁶

$$Wt\%_{H_2O} = \frac{K_{eq}(RH)}{1+K_{eq}(RH)} \quad (4)$$

In Equation 4, the only parameter, K_{eq} , is the equilibrium constant between adsorbed and gaseous water. In such systems, a limiting adsorption is reached as a function of RH. When the energetics of surface binding do not allow for large numbers of water molecules to adsorb, Langmuir behavior is observed at all RH values. This behavior is often the case for crystalline materials. For example, Figure 1 shows Langmuir adsorption for an average of 35 crystalline drug substances. As can be seen in the figure, even at 75%RH, water is only able to adsorb about 0.17% of the powder weight. At sufficiently low water activities, water sorption will behave according to Equation 4 for most solids that have at least some crystalline character; however, for pure amorphous materials, the

surface adsorption may be minimal; i.e., all waters will absorb into the matrix (as discussed below) rather than adsorb onto surfaces.

Figure 1 Example of surface adsorption in a monolayer described by the Langmuir equation. This example used an average sorption isotherm for 35 crystalline active pharmaceutical ingredients (APIs). The best fit coefficient for the sorption isotherm (Equation 4) is $K_{eq} = 1.15$ (shown as dotted black line).



(2) As water activity increases, multiple layers of water may associate with the bound waters. Favorable solid-water interactions make it easier for condensation to occur by eliminating the high energy, surface waters. As water molecules condense, “cooperative” water condensation occurs whereby groups of water molecules can readily add further waters. Water molecules condense into an amorphous solid matrix under conditions that liquid water does not form in the absence of the solid because of a combination of favorable enthalpy for the solid-water interaction (at least on the order of the matrix molecules with themselves), favorable enthalpy for water-water interaction, and favorable entropy due to disruption of the pure amorphous material. The favorable water-water interactions with cooperative water condensation mean that as more waters are sorbed, there are more sites for additional water molecules to be sorbed. This leads to an exponential increase in the amount of water sorbed as a function of water activity (RH). For most materials, this exponential cooperative water condensation occurs above about an RH of 15% as described by Equation 5,

$$\ln(Wt\%_{H_2O}) = \ln \alpha + \beta(RH) \quad (5)$$

where β is the coefficient for this interaction with an average value of 0.03, and α is related to the surface energy of the solid. Since the driving force for water sorption has a significant contribution from water-water associations, it is only partially dependent on the substrate, making the range in β relatively narrow (0.015 to 0.045). Four examples of excipients that have very different moisture sorption isotherms are shown in Figure 2. In Figure 3, these same isotherms are shown to be described by Eq. 5 (between 20 and 80%RH). The β values for a number of common excipients are shown in Table 1.

Figure 2 Moisture sorption isotherms for four common excipients with significant amorphous contents.

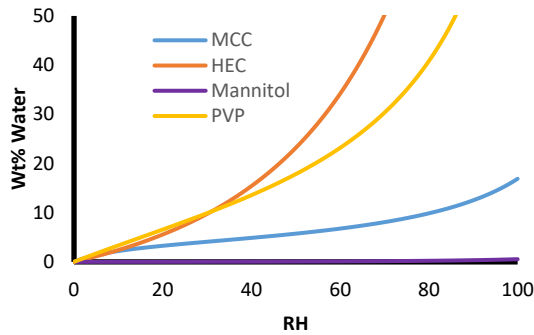


Figure 3 Moisture sorption isotherms for the four common excipients shown in Figure 2, now plotted according to Equation 5 (between 20 and 80%RH). The slopes (β) for the four excipients are 0.018, 0.042, 0.042 and 0.029 for MCC (microcrystalline cellulose), HEC (hydroxyethylcellulose), mannitol and PVP, respectively.

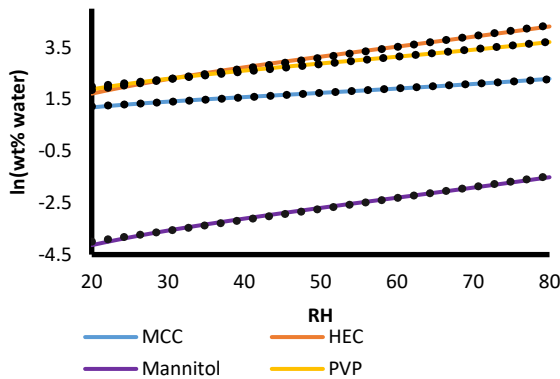


Table 1 Exponential increase in water absorption between 15 and 75%RH for common excipients.

Excipient	Exponential Factor (β)
Microcrystalline cellulose	0.018
Gelatin	0.021
Hydroxypropylcellulose	0.037
Mannitol	0.044
Hydroxyethylcellulose	0.045
Methylcellulose	0.028
Sodium starch glycolate	0.031
Lactose monohydrate	0.028
Croscarmellose sodium	0.027
Crospovidone	0.021
Povidone	0.029
Pregelatinized starch	0.016

In the region of exponential rise in sorption (Eq. 5), entropy still favors the gas phase; however, surface waters with their higher energy are now at least partially avoided by the water-solid interface. The result is that the energy for water to come out of the vapor phase to the liquid phase shifts to a lower partial pressure of water than without the solid present. The entropy and energy for the gas phase water molecules are not altered by the presence of the solid; therefore, the temperature impact on the saturation level for the moisture in the air remains the same. Since water activity (RH) takes into account this shift in the moisture saturation level in the air, there is no additional temperature dependence on the amount of water sorbed as a function of the water activity. In other words, as the temperature increases, the tendency for water to desorb from a condensed state based on the favorable entropy of the gas phase is exactly the same as the greater amount of water that the air holds at saturation at the increased temperature. The net result is a relatively temperature-independent sorption isotherm.

(3) At high RH values, some materials alter their structures to accommodate waters. The result is hysteresis in the sorption versus desorption curves; i.e., the material will hold more water once it has been exposed to high RH conditions than when it was originally exposed to the same water activity (RH). Most often, this irreversibility in the sorption isotherm is seen above 75%RH and therefore is of less significance for pharmaceutical stability studies which are generally limited to 75%RH.

GENERAL MOISTURE DEPENDENCE OF REACTIONS

Now that we have described the moisture sorption behavior of solids, we will shift to describing how chemical reaction rates (e.g., drug degradation kinetics) depend on water activity (RH), before linking the two.

ISOCONVERSION

While solution kinetics can be complex due to secondary degradation, autocatalysis and loss of inhibitors, processes in the solid state have the potential to be even more difficult to parameterize due to their heterogeneous nature. In solid mixtures, actives can be in multiple, non-equilibrating phases. These phases with distinct reactivity include crystalline domains, amorphous domains, surface molecules and molecules directly interacting with other solid components. The result is a superposition of reaction kinetics that are impractical to deconvolute. One approach to working with such systems is to use isoconversion, that is, the time to fail.⁷ In this method, the path to get to the failure point is less critical than the time to reach that point. An isoconversion rate is defined as the amount of degradation divided by the isoconversion time; however, this will not be a rate constant in the sense that for different failure points (specification limits), this value will change, except for the cases of true linear degradation. This principle can be applied to a range of temperature and RH conditions to build a model for the behavior of a particular degradation process. Use of isoconversion enables these models to be effective at predicting ambient behavior (shelf-life) even with complex kinetics by focusing the degradation level to be the same at the accelerated conditions (hitting the specification limit) as is relevant for the ambient shelf-life.

MOISTURE AND TEMPERATURE DEPENDENCE

For a wide range of chemical degradation processes in the solid state (>300 examined), isoconversion rates (k_{iso}) have been empirically found to depend exponentially on the water activity (or equilibrium RH), as described in Eq. 6 (constant temperature):

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$$k_{iso} = \gamma e^{B \cdot RH} \text{ or } \ln k_{iso} = \ln \gamma + B \cdot RH \quad (6)$$

where B and γ are fitting parameters with B being the moisture sensitivity coefficient, and RH being the equilibrium relative humidity.⁸ For a large number of reactions, B ranges between about 0 (i.e., no RH dependence) to 0.10, with an average of 0.03. It should be noted that this RH dependence represents the equilibrium (open) condition that a sample is exposed to rather than reflecting an external environment to a packaged product. The impact of packaging can explicitly be accounted for based on the changing RH inside packaging due to the rate of moisture transfer into (or out of) a package and the equilibrium redistribution of moisture of the internal components.⁹ The exponential RH dependence is quite general, with exceptions to date only seen when there is a corresponding phase transition (e.g., change of hydrate state) within the experimental design space. It should be noted that RH dependence on rates is not particularly high for hydrolytic reactions.

When temperature is taken also considered, the modified Arrhenius equation (Eq. 7) accounts for the observed experimental data for isoconversion times in all cases studied (>300), again with the exception of phase transitions.⁸

$$\ln k_{iso} = \ln A - \frac{E_a}{RT} + B \cdot RH \quad (7)$$

In Eq. 7, A is the collision frequency, and E_a is the activation energy. As noted in the white paper "Origin of Temperature Sensitivity in Stability Studies", the activation energy in a solid is actually a composite of the activation energy for diffusion and that for the reaction itself. That there is no "cross-term" between temperature and RH is discussed in another white paper in this series. Again, Eq. 7 represents the equilibrium RH of the sample rather than the conditions external to the packaging. ASAPprime[®] explicitly takes into account the changing RH a sample is exposed to inside the packaging.

MECHANISM OF MOISTURE SENSITIVITY

Introduction

While Equation 7 has been shown to be operational over a wide range of solid-state chemical degradation reactions with different mechanisms, below we discuss potential mechanisms for moisture sensitivity. Before delving into these mechanistic aspects, it is worth emphasizing that solid-state systems will be very different in purely crystalline states and in mixed systems (i.e., combinations of crystalline, amorphous, active-exipient interfaces, etc.) common in formulated products such as pharmaceuticals. In the mixed systems, stability for an active is often much worse than for the pure crystalline active.¹⁰ Almost undoubtedly, this greater reactivity is due to loss of crystallinity either in the form of amorphous and defect site formation of the active (high energy form), or formation of a solid-solution with the other ingredients (low energy state).

Water as Reactant

With chemical reactions that involve an active reacting directly with water (e.g., hydrolyses) in the rate-limiting step one would expect the reaction to depend linearly on the water activity, a_w or equilibrium RH, rather than the water content:

$$k \propto a_w \quad (8)$$

The rate constant k is expected to be a pseudo-first order rate constant since even at low water contents, the amount of water consumed in a hydrolytic degradation reaction where the extent of

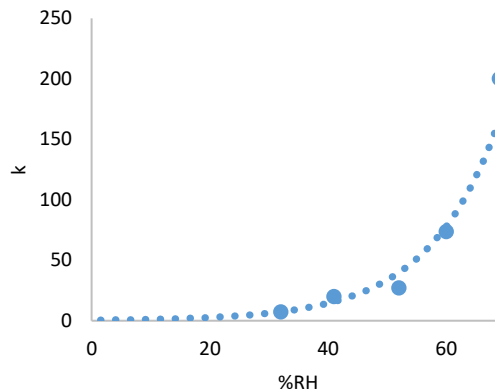
degradation just hits the specification limit is generally quite small. For example, with 0.50% of the active hydrolyzing to give the specification limit of a degradant, assuming a molecular weight of 500 and 0.2 weight percent water, only about one tenth of the water is consumed at the specification limit:

$$\frac{0.005 \text{ mol } H_2O \text{ consumed}}{\text{mol active}} * \frac{\text{mol active}}{500g \text{ active}} * 100\% = 0.018\% H_2O \quad (9)$$

The predicted behavior of Eq. 8 is not in fact observed. Rather, exponential dependence described in Eq. 7 fits observed data in all cases where careful data were generated. For example, in Figure 4, hydrolysis of nitrazepam shows a clear exponential dependence on equilibrium RH, with a B term (Eq. 7) of 0.084.¹¹

That the dependence of hydrolytic reactions is not linear with water activity, and indeed is not significantly differentiated from non-hydrolytic reactions suggests that any explanation for humidity dependence on reactivity should be more general than reactions with water itself.

Figure 4 Diazepam hydrolytic degradation kinetics as a function of equilibrium relative humidity.¹¹



Water Plasticization

Absorbed moisture in amorphous materials lowers the glass transition temperature (T_g) in a process of plasticization. This glass transition temperature depression by moisture is predicted by the Fox equation:¹²

$$\frac{1}{T_g} = \frac{x_w}{T_{g,w}} + \frac{(1-x_w)}{T_{g,s}} = \frac{x_w}{135K} + \frac{(1-x_w)}{T_{g,s}} \quad (10)$$

where x_w is the mole fraction water, $T_{g,w}$ is the glass transition temperature of water (-138°C), $T_{g,s}$ is the glass transition temperature of the dry solid.

Local mobility of an active should increase as a function of this plasticization (corresponding to an increase in free volume). One could postulate that there could be a corresponding reactivity increase as T_g is lowered by moisture. A study was reported where a series of T_g values were used to look at degradation rates at different RH conditions for homogeneous polymer-active dispersions.¹³ There was a clear RH dependence, but little evidence of a T_g dependence. In other words, the reactivity was changed by RH but did not give the same rate when using different molecular weight polymers to match T_g values. While we earlier saw that amorphous moisture sorption is exponential, the resulting plasticization does not appear to be a general primary cause of

increased reactivity as a function of RH, even when moisture plasticization as a function of RH drops the T_g below the temperature of the study.

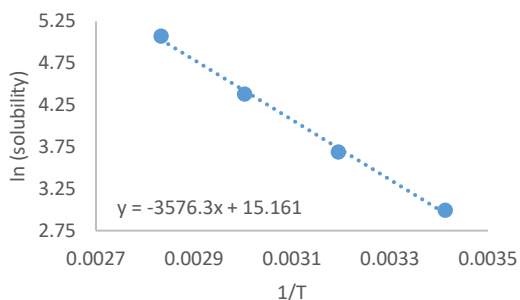
Moisture Inducing Intermixing

One could suggest that in heterogeneous solid mixtures of an active and inactive component, moisture could enable two materials to form a phase compatible, solid solution which would have a corresponding higher reaction rate as a function of RH. Since this moisture-induced solid solution formation would be expected to be irreversible when moisture is removed, an examination of the reversibility of the RH dependence would indicate whether this is a dominant mechanism. When a reaction was examined under such conditions (i.e., low RH, high RH, back to low RH), the reaction rate returned to a relatively low value with only a slight impact of the high RH exposure on the rate.¹⁴ This result is inconsistent with the dominant source of RH dependence being the formation of a new, amorphous phase of two materials induced by moisture.

Water as Solvent

Water has the potential to dissolve active and inactive ingredients in a solid matrix. This can serve to increase mobility and enable greater interactions between components (e.g., active and inactive ingredients). Materials mobilized in the solution/semi solid state could reasonably be expected to show greater reactivity for most degradation mechanisms. Since the amount of condensed moisture in amorphous solids is exponentially dependent on the RH, the amount of this semi-solid phase present should also follow an exponential dependence on RH. The end-result is that reactivity (degradation kinetics) should increase correspondingly. In this explanation, one would expect that most often the components are saturated in the limited amount of water present. More reaction would occur not by dilution from saturation, but from increasing the amount dissolved. In this scenario, one would expect the activation energy for the chemical degradation to not change with a change in RH since the reactive material would always be in the same saturated semi-solid, only the amount present would change. This is consistent with the observed experimental data (Eq. 7). However, we also have to factor in any change in solubility of the components with temperature. The impact of temperature on water solubility of a range of organic solids has been found to be exponential in temperature ($^{\circ}\text{C}$), with the average behavior shown in Figure 5.¹⁵

Figure 5 Aqueous solubility change as a function of temperature for an average organic material reflected in an Arrhenius plot (based on ref. 15).



The average solubility of organic solids increases by a factor of two every 20 $^{\circ}\text{C}$ ("Black's Rule"), which corresponds to an effective activation energy of 7 kcal/mol, assuming reaction rates depend directly on the amount of material dissolved.

Combining the temperature impact the reaction ($E_{a\text{ rxn}}$), the temperature impact on diffusion, $E'_{a\text{ dif}}$ (from the white paper "Origin of Temperature Sensitivity in Stability Studies"), the temperature dependence on solubility reflected above ($E''_{a\text{ sol}}$), with the RH sensitivity due to increased moisture condensation yields the following equations:

$$\ln k = \ln A - \frac{(E_{a\text{ rxn}} + E'_{a\text{ dif}} + E''_{a\text{ sol}})}{RT} + B(\text{RH}) \quad (11)$$

In carrying out experimental determinations of the T and RH sensitivity, the contributions to the overall temperature dependence will appear as a single activation energy. Because of the added terms, there is a likely to be significant deviation in the activation energy of a reaction in the solid versus solution states.

While it may be tempting to rationalize or predict the B-term for specific systems based on the sorption isotherm or even the solubility, this exercise is probably difficult to employ successfully. Materials that have high water solubility would be expected to be more susceptible to reactions in the presence of moisture, this does not mean that the B-term (Eq. 7) will be high since this reflects the change in behavior as a function of RH. This change would be more related to the sorption isotherm. While we would predict a correlation between the B-term (Eq. 7) and the sorption β -term (Eq. 5), the sorption of the interfacial area between active and other ingredients (excipients) may not be reflected in the overall sorption isotherm for the mixture. Effectively, the microenvironmental sorption behavior will be the critical parameter, but is difficult to assess in practical experiments.

CONCLUSION

Moisture sensitivity of chemical reactions in the solid state is ubiquitous. While several explanations have been advanced for this sensitivity in the past, we believe the presence of dissolved solid as a function of RH is the best explanation for the observed behavior. In this explanation, condensation of water in non-crystalline domains occurs via cooperative water-water binding. This leads to exponential moisture sorption as more waters present make further water binding sites more available. As more water condenses, more of the active can dissolve thereby creating additional material in its reactive semi-solid state and admixed with other ingredients which can also induce reaction. Since this material in solution is not changed in character, only in amount present, as a function of RH, the activation energy (temperature dependence) is independent of the RH. Changes in solubility as a function of temperature are likely to contribute to the effective activation energy for the reaction.

ACKNOWLEDGMENTS

I would like to acknowledge discussions, suggestions and edits of Dr. Garry Scrivens and Dr. Steve Baertschi.

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