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Research Paper

Deliquescence in Binary Mixtures

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Purpose. Deliquescence is a first-order phase transformation from solid to solution and occurs at a specific relative humidity (RH) that is characteristic to the solid. The goal of this research was to investigate the reduction in critical relative humidity (RH_0) in binary solid mixtures of deliquescent active pharmaceutical ingredients (APIs) and deliquescent excipients.

Methods. The RH where deliquescence is induced, RH_0, was measured using a gravimetric water vapor sorption balance. Values were obtained for model deliquescent APIs and excipients as well as for their binary mixtures. Model APIs included ranitidine HCl and diphenhydramine HCl, and sucrose and sodium chloride were examples of excipients investigated. To probe the thermodynamics of this phenomenon, water activity (a_w) of various saturated solutions of API and excipient systems was measured using a water activity meter. Optical microscopy was used to observe visually the phenomenon under investigation. The Ross equation was used to estimate RH_{0mix}, and predicted values were compared with experimental results.

Results. There was close agreement between RH_0 measurements (single-component RH_0, and RH_{0mix}) and a_w measurements of the corresponding saturated solutions. In addition, RH_{0mix} values were always lower than RH_0 for the API and excipients alone. In general, experimentally observed RH_{0mix} values were higher than those predicted using the Ross equation.

Conclusions. Mixtures of deliquescent API and deliquescent excipient are more hygroscopic (i.e., have lower RH_0) than either the API or the excipient alone. This might have significant effects on API and drug product stability.

KEY WORDS: critical relative humidity; deliquescence; mixtures; sorption; water activity.

INTRODUCTION

The presence of water in pharmaceutical systems can produce many undesirable effects on the physical and chemical properties of raw materials and drug products. These effects include phase transformations, chemical degradation, variation in disintegration or dissolution rate, and changes in flow and compactability. Pharmaceutical solids interact with water through a number of different mechanisms (1–3). One such mechanism is the phenomenon of deliquescence, a phase transformation whereby a substance absorbs water vapor from the atmosphere, leading to the dissolution of the solid and the presence of bulk water in the system at partial vapor pressures less than 1 (3). Deliquescent materials are typically crystalline solids that are highly water soluble and capable of producing a significant reduction in colligative properties (1,3). The relative humidity (RH) where deliquescence occurs is a characteristic of the solid and has been found to be the same as the RH produced by a saturated aqueous solution (1,3). The deliquescence point is commonly termed the critical relative humidity (RH_0). At relative humidities below RH_0, deliquescent solids adsorb minimal amounts of moisture at the surface by virtue of hydrogen bonding (4). Upon increasing the relative humidity to above RH_0, the solid starts dissolving in the condensate film. Solid will continue to dissolve and saturate the film, leading to further absorption of water. The absorption process stops when the vapor pressure of the resultant solution is equal to the vapor pressure of the atmosphere. Thus, if the atmospheric vapor pressure is equal to that of a saturated solution, the solid will dissolve until saturation is achieved. If the vapor pressure is further increased, complete dissolution of solid material and solution dilution will ultimately occur (1).

The deliquescence behavior of a number of pharmaceutically relevant materials has been described previously (5–8). From a survey of the literature, it appears that the most common category of materials likely to exhibit deliquescence is salts, most notably hydrochloride and sodium salts. Reported RH_0 values for some deliquescent active pharmaceutical ingredients (APIs) and pharmaceutical excipients are shown in Table I.

It can be observed from Table I that the deliquescence of many compounds occurs at quite high relative humidities and is therefore avoidable through careful choice of storage conditions. However, it is important to note that RH_0 values can be decreased by mixing with other deliquescent compounds. This was first observed for mixtures of fertilizers (i.e., mixtures of inorganic salts) (9) and has also been demonstrated

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Table I. RH_0 and a_w Values of Deliquescent Model Compounds and Excipients

Compound	RH_0 (%), 25°C	$a_w * 100$, 25°C	Literature RH_0 (%) values
Ranitidine HCl	76	75	76, 25°C (19) 67, 40°C (20)
Diphenhydramine HCl	82	82	77, 37°C (21)
Thiamine HCl	89	90	88, 37°C (21)
Sucrose	85	85	84, 25°C (22)
Lactose anhydrous	95	97	95, 40°C (23)

for sugars mixed with vitamins (8) and sugars with inorganic salts (10).

To the best of our knowledge, the effect of a second component on the deliquescence behavior of organic pharmaceutical salts has not been reported. The main objective of this study was therefore to evaluate RH_0 values of model pharmaceutical salts mixed with inorganic salts and sugars. These compounds are of interest because they may be in intimate contact with the API as impurities or excipients. In addition, we were interested in comparing two different methods of measuring RH_0; namely, water activity measurements of equilibrated saturated solutions and dynamic gravimetric measurement of water uptake by solids.

MATERIALS AND METHODS

Materials

Ranitidine HCl, diphenhydramine HCl, and thiamine HCl, were obtained from Hawkins Pharmaceutical (Minneapolis, MN, USA). Lactose anhydrous was obtained from Sheffield Products (Chicago, IL, USA). All inorganic salts (sodium chloride, potassium chloride, sodium bromide, and potassium bromide) were obtained from Mallinckrodt AR (Paris, KY, USA)

Methods

Vapor sorption isotherms of model compounds, excipients, and their physical mixtures were generated using a symmetrical gravimetric analyzer (SGA-100; VTI Corporation, Hialeah, FL, USA) at 25°C. Physical mixtures were prepared by geometric mixing of individual components such that the final sample weight was in the range 15–25 mg, and the entire sample was used for analysis. Samples were first dried at 50°C in the sorption analyzer. The equilibrium criterion for the drying step was 0.01% w/w in 2 min with a maximum drying time of 80 min. During the experiment, the sample was exposed to increasing RH, and 2–3 isotherms points were collected below and above RH_0. The step isotherm equilibrium criterion was 0.01% w/w in 15 min with a maximum step time of 90 min. RH_0 was measured from the vapor sorption isotherms by extrapolating the linear parts of the isotherm before and after the deliquescence event. To establish the repeatability of measuring RH_0 using the sorption analyzer, RH_0 of ranitidine HCl was determined in triplicate. Duplicate measurements of all other samples were obtained.

Water activity (a_w) of single and multisolute solutions were measured in duplicate at 25°C using an Aqua Lab 3TE (Decagon, Pullman, WA, USA). Aqua Lab 3TE is a chilled mirror dew-point instrument. The sample is equilibrated within the headspace of a sealed chamber containing a chilled mirror, an optical sensor, and an internal fan. A thermoelectrical cooler controls the mirror temperature, and the optical reflectance sensor detects the onset of condensation (dew point). The dew-point temperature is determined by a thermocouple attached to the mirror. In addition, sample temperature is measured by a thermopile sensor. a_w is determined by using dew-point and sample-surface temperatures. To measure a_w, saturated solutions were prepared by mixing approximately 2–3 g of physical mixture (prepared by geometric mixing) with small amounts of double distilled water (~300–500 μl). For the mixtures of ranitidine HCl and bromide salts, water was replaced with saturated solution of the bromide salt (~600 μl).

A VGI 2000M microscope stage with temperature and humidity control (Surface Measurement Systems Ltd., London, UK) was used to conduct an optical microscopy study to visually examine deliquescence in mixtures of diphenhydramine HCl and KCl. The stage was kept at 79% RH and 25°C throughout the study.

To study the effect of sample preparation on the deliquescence event, ranitidine HCl was ground using a pestle and mortar for 2 min. In addition, a compact was prepared from the material, as received, using a Carver Press (Craver Inc., Wabash, IN, USA) with 1-inch tooling and applying a compaction force of 3000 lb.

RESULTS

Single-Component Systems

Moisture Sorption Isotherms

Figure 1 illustrates the moisture sorption isotherm for ranitidine HCl, obtained in triplicate, using dynamic gravimetric analysis. The repeatability of the method is excellent, and RH_0 was estimated to be equal to 76% using the extrapolation method, with an RSD% (limited by the instrument resolution) of ±1%. In order to study the effect of sample presentation on the results, moisture sorption isotherms of ranitidine HCl were also obtained from material that had either been ground or formed into a compact. Only minor differences in the moisture sorption profiles were observed (data not shown) and, following extrapolation, the calculated RH_0 values for the different sample states were within the instrument resolution (±1% RH). Thus, we can be reasonably

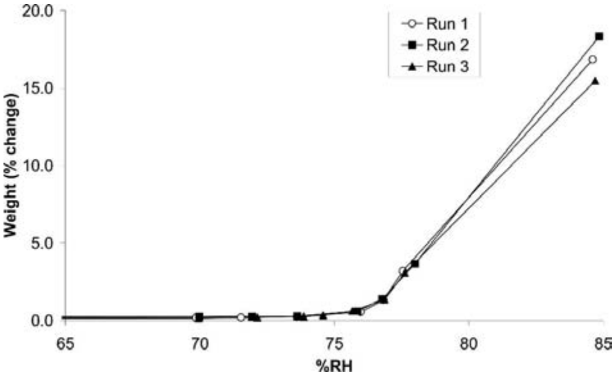

Fig. 1. Water vapor sorption isotherm for ranitidine HCl at 25°C showing the repeatability of the deliquescence event.

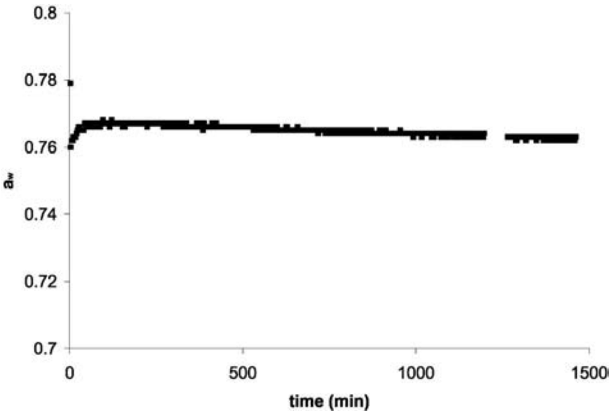

Fig. 2. Water activity vs. time profile for a saturated solution of ranitidine HCl at 25°C.

assured that any observed variations in the RH_0 values calculated using dynamic vapor sorption find their origin in differences in the properties of the systems rather than from sample presentation. RH_0 values for all individual components were measured, and results are shown in Table I. Literature values are also shown, and it can be seen that, in general, there is a good agreement between the values determined in this study and the published values.

Equilibrium Water Activity of Saturated Solutions

In addition to making the kinetic measurements described above, the equilibrium activity of water above saturated solutions of the individual components was measured at 25°C. An example of activity as a function of time is shown in Fig. 2 for a saturated solution of ranitidine HCl. It was assumed that the sample had reached equilibration with the headspace in the instrument when the reading varied by less than 0.001 over 60 min. Results for saturated solutions of the individual components are shown in Table I and are compared with the RH_0 values measured using dynamic water vapor sorption. It can be seen that, in general, there is an excellent agreement between a_w and RH_0 values for single-component systems.

Binary Systems

Moisture Sorption Isotherms

In Fig. 3, sorption isotherms are shown for ranitidine HCl, sucrose, and three physical mixtures of ranitidine HCl and sucrose consisting of 10:90, 50:50, and 90:10 w/w blends. The physical mixtures appear to undergo deliquescence at a lower relative humidity than either of the individual components (i.e., at a unique RH that can be designated RH_{0mix}). Furthermore, the composition of the physical mixture does not appear to influence RH_{0mix} within experimental limitations. The same phenomenon was observed for mixtures of diphenhydramine HCl and sucrose. In this case, the individual components have similar RH_0 values of 82% and 85% for diphenhydramine HCl and sucrose, respectively, whereas RH_{0mix} was around 76% (Table II). In contrast, anhydrous lactose was found to have minimal effect on the deliquescence behavior of ranitidine HCl, and mixtures of these two components were found to deliquesce close to RH_0 of ranitidine HCl, as shown in Fig. 4. For ranitidine HCl, in addition to investigating the effect of sucrose and lactose, a series of inorganic salts were also examined. For all of the salts, RH_{0mix} was lower than RH_0 of the individual components, and results are summarized in Table II.

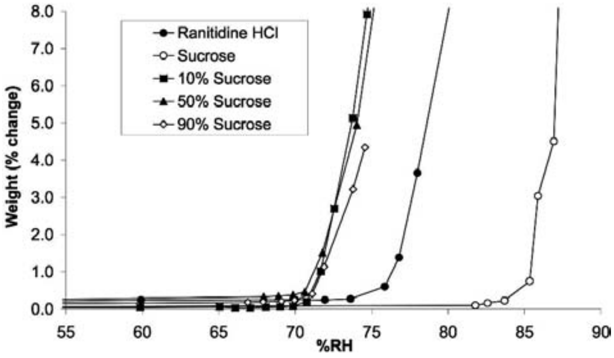

Fig. 3. Vapor sorption isotherms of ranitidine HCl, sucrose, and their physical mixtures (10, 50, and 90% w/w) at 25°C.

Table II. RH_{0mix} and a_w Values for Mixtures of Model Compounds and Excipients Measured at 25°C[a]

Mixture composition	RH_{0mix} (%) observed	$a_w * 100$	RH_{0mix} predicted	χ
Ranitidine HCl:sucrose	71	70	65	1.09
Diphenhydramine HCl:sucrose	76	75	70	1.09
Thiamine HCl:sucrose	76	74	75	1.01
Ranitidine HCl:NaCl	72	72	57	1.26
Ranitidine HCl:NaBr	41	35	44	0.93
Ranitidine HCl:KCl	75	75	64	1.17
Ranitidine HCl:KBr	72	73	61	1.18

[a] All mixtures were 50:50 w/w. RH_{0mix} was also predicted using the Ross equation. RH_0 of inorganic salts used in calculations are literature values.

Visualization of Deliquescence in Binary Mixtures

In order to confirm that the sharp increase in the sorption isotherm for binary mixtures at a lower RH_0 was due to deliquescence, a visual examination was undertaken. Two

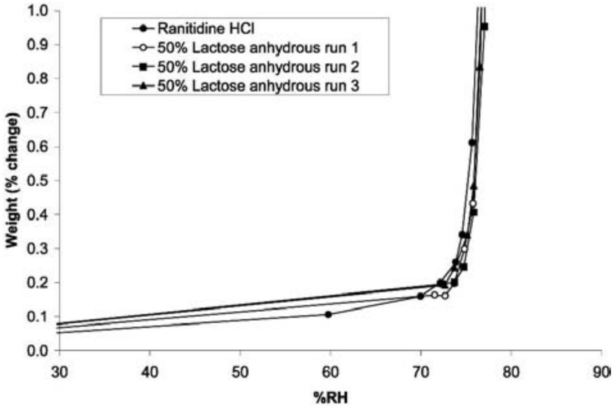

Fig. 4. Vapor sorption isotherms at 25°C for 50:50% w/w physical mixtures of ranitidine HCl and anhydrous lactose compared with the isotherm for ranitidine HCl alone.

crystals each of diphenhydramine HCl and KBr (which have RH_0 values of 82% and 81% at 25°C, respectively) were selected, and these are shown in Fig. 5a. One crystal of each substance was used as a control; the remaining two crystals were placed in contact with each other to simulate a mixture, as shown in Fig. 5b. The variable humidity stage was maintained at 79% RH, 25°C, and the crystals were monitored as a function of time for signs of deliquescence. Clear visual signs of deliquescence could be observed after 25 min as shown in Fig. 5c with a liquid film being apparent at the contact point between the two crystals. After 80 min (Fig. 5d), complete dissolution of the diphenhydramine HCl crystal was evident while the KBr crystal shape had rounded at the edges, indicating that some dissolution had occurred. The individual crystals of each component that were isolated showed no signs of deliquescence. The RH_{0mix} for this system was determined as 79% RH at 25°C from water sorption measurements.

Equilibrium Water Activity of Saturated Solutions

Table II shows a_w measurements for saturated solutions of binary mixtures. As with the single-component systems, there is a good agreement between RH_0 estimated from moisture isotherms and water activity measurements. In all cases, a_w is lower for the mixtures than for the individual components. These results provide further confirmation that the apparent decrease in RH_0 for the mixtures is due to a reduced deliquescence relative humidity.

DISCUSSION

Water-solid interactions in pharmaceutical systems are typically interrogated using gravimetric analysis, and automated moisture sorption balances have grown in popularity in recent years. Samples measured with such automated systems may or may not be in thermodynamic equilibrium with the surroundings, depending on the kinetics of the process under investigation relative to the equilibration time at each condition. Our results indicate that gravimetric measurements of moisture uptake as a function of increasing relative humidity can provide reasonable estimates of the deliquescence point of both single components and mixtures of materials. Only minor differences were observed between the relative humidity present above saturated salt solutions (which is an equilibrium measurement) and the point in the moisture sorption isotherm characterized by a dramatic increase in weight gain resulting from dissolution (a kinetic phenomenon). Interestingly, studies on single crystals of sodium chloride have shown a significant hysteresis in the deliquescence point of the solid as compared to the RH above a saturated solution, leading to the suggestion that deliquescence is a nucleated phenomenon most likely initiated at high-energy sites on the crystal surface (11). For the powdered samples investigated in this study, no such hysteresis was observed, presumably as a consequence of the polycrystalline nature of the model compounds and the availability of high-energy sites where deliquescence can be initiated. Hence, we observed that the deliquescence phenomenon is triggered at or near the point where the ambient RH reaches that found above the corresponding saturated solution. In addition, we observed that deliquescence of a mixture of two chemically different solids is triggered at a relative humidity that is lower than either of the individual RH_0 values, although again corresponding to the RH above a solution saturated with respect to both compounds.

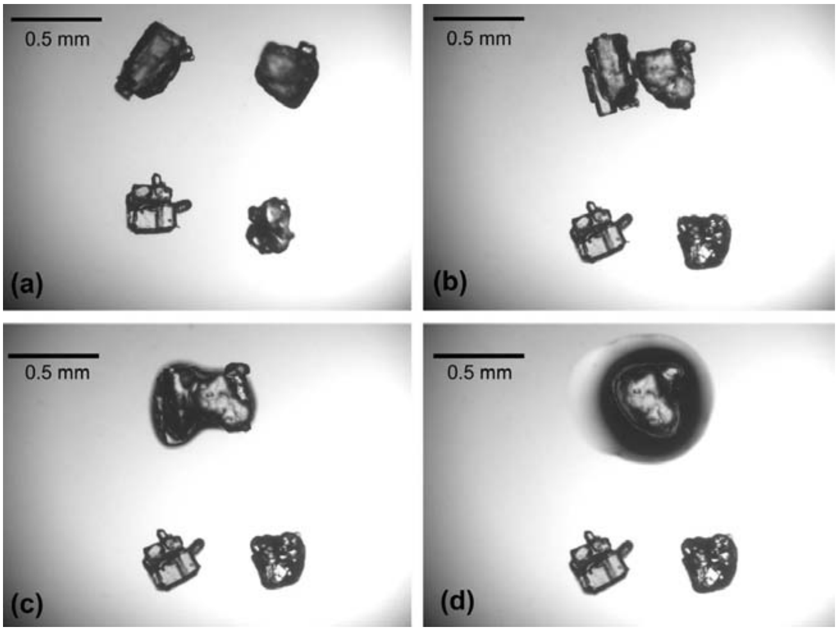

Fig. 5. Photomicrographs illustrating deliquescence in a simulated binary mixture: (a) Diphenhydramine HCl crystals (left) and KBr crystals (right) exposed to 79% RH, 25°C. (b) A crystal of each compound is placed in contact with each another to simulate the mixture; the other two isolated crystals are used as controls. Time = 0 min, exposure to 79% RH. (c) After 25 min. (d) After 80 min. Complete deliquescence of the diphenhydramine HCl crystal in contact with KCl is observed, and the KCl crystal has undergone rounding of the edges. The control crystals are unchanged.

For these binary systems, both the deliquescence behavior and the opposite phase transition of efflorescence (12) (crystallization induced by lowering of the ambient water activity), are more complex than for single-component systems. Consider a hypothetical solution with two solutes. As the ambient relative humidity is decreased, the solution will become more concentrated with respect to both solutes as water evaporates from the solution to maintain equilibrium with the atmosphere. Eventually, one of the solutes will reach saturation and begin to precipitate out as the crystalline phase. As RH is lowered further, more of the solid phase of this component forms, and the solution becomes more concentrated with respect to the second solute. At a certain relative humidity, referred to as RH_{0mix} (13) or the mutual deliquescence relative humidity (14,15), the two compounds crystallize together and form a mixed solid phase at what has been termed the eutonic composition (14,16,17). RH_{0mix} is always lower than RH_0 of individual solutes (14). For aerosols composed of mixed electrolytes, it has been shown that the resulting dried particles are composed of a pure salt core surrounded by a mixed salt coating (14,15). For these systems, the core composition is determined by the original aerosol composition (i.e., is composed of the phase present in excess of the eutonic composition) while the coating is identical to the eutonic composition and is independent of starting composition. If this dried particle is exposed to increasing relative humidity, little moisture will be taken up until RH_{0mix}, at which point the relative humidity of the atmosphere is equal to the partial pressure above the eutonic and the solid coating having the eutonic composition will dissolve, leading to a step change in the aerosol mass. Increasing relative humidity results in more water absorption and dissolution of the salt core. A second stage of particle growth can occur at the relative humidity where the salt core completely dissolves (14,17).

The systems investigated in our research are somewhat different from the example described above in that we start with physical blends of particles, not heterogeneous dried particles where crystallites of the two components are in intimate contact with one another at the surface. This is analogous to eutectic that has formed from the melt compared with a physical blend of the components. Despite the lack of intimate contact in our systems, a lowered deliquescence point is still observed for all mixtures. Furthermore, as predicted by theory (14,18), RH_{0mix} is independent of composition, although the amount of material entering the solution phase at RH_{0mix} will obviously depend on the composition of the eutonic and the ratio of the two components. Thus, if the composition of the mixture was equal to the eutonic composition, all solid material would be dissolved at RH_{0mix}. However, if there was only a very small amount of a second deliquescing component, only a small proportion of the major component would be dissolved at the lower relative humidity. Based on the preceding discussion, it would be expected that a binary mixture, not at the eutonic composition would show a complex water vapor sorption profile, with a step change at RH_{0mix} and potentially an abrupt change in slope at the RH where the component in excess of the eutonic composition dissolves completely. Figure 6 illustrates the water vapor sorption profile for a mixture of 10% sodium bromide and 90% ranitidine HCl that have widely separated RH_0 values. For this mixture, in addition to the change at RH_{0mix} (around 41% RH), there are changes in slope at around 55% RH and 70% RH. This suggests that not all of the minor component is able to deliquesce at the eutonic point, presumably due to incomplete contact with the second component. Thus, some portion of sodium bromide has no contact with ranitidine HCl and therefore continues to dissolve above RH_{0mix}. Another contributing factor might be that the kinetics of dissolution at RH_{0mix} are extremely slow. Solid ranitidine HCl is also present and is probably responsible for the change in slope at around 70% RH. This observation indicates that the intimacy of mixing will have a profound effect on the extent of deliquescence at RH_{0mix}. This subject is under further investigation.

Given, the potential consequences of a lowered deliquescence point in mixtures, it is important to consider the thermodynamic explanation for this phenomenon and the applicability of prediction models. RH_{0mix} is determined by the water activity at the eutonic point, which is the point in the

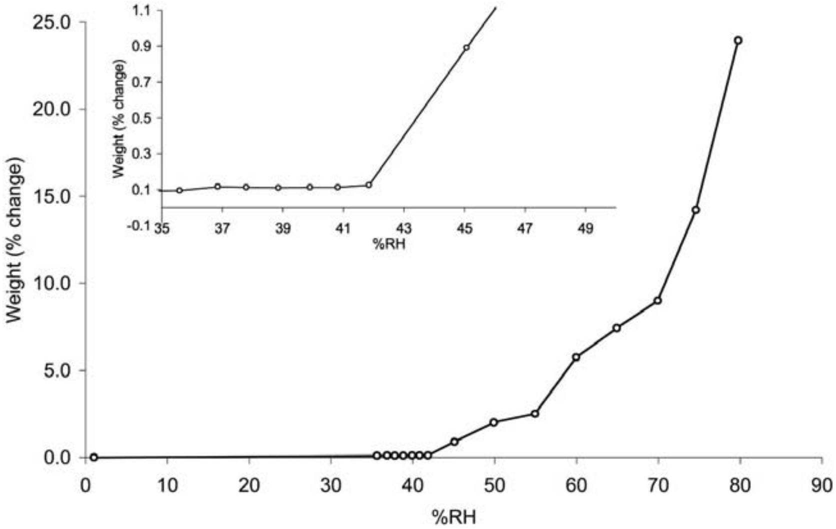

Fig. 6. Deliquescence of a ranitidine HCl:NaBr (90:10, w/w) mixture at 25°C showing 3 stages of water vapor sorption. The inset shows an enlarged view of the 40% RH region of the isotherm.

solubility diagram where each component has reached its solubility limit in the solution. At this composition, the water activity reaches a minimum value. Ross derived an equation to predict this water activity from the water activities of each individual component (18). The Ross equation, derived from the Gibbs-Duhem equation, assumes that solute activity coefficients in mixtures are not significantly different from the activity coefficients in simple solutions. The equation for a binary solute system is as follow:

$$a_w = (a_w)_1 \cdot (a_w)_2 \tag{1}$$

where a_w is the water activity in the binary solution, and $(a_w)_1$ and $(a_w)_2$ are the water activities for solutions of components 1 and 2, respectively. Ross also suggested an empirical interaction parameter to represent the contribution of solute-solute interactions to a_w.

$$\chi = \frac{a_w \text{ (observed)}}{(a_w)_1 (a_w)_2} \tag{2}$$

Assuming that a_w can be approximated by RH/100, then the Ross equation can be written in terms of RH_0 for the individual components. A binary mixture is therefore predicted to undergo deliquescence at a RH value equivalent to the product of the individual deliquescence relative humidities of each individual component divided by 100. The predictions of the Ross equation for all the binary systems investigated are shown in Table II. It is apparent that there are significant solute-solute interactions for the systems under investigation, which is unsurprising given the high concentrations involved. Ross tested his model in multisolute solutions of electrolytes (inorganic salts) and nonelectrolytes (sugars) and found that χ increased as a function of solute concentration, although in general errors of predictions were less than 3% for the solutions studied. χ values observed in our studies are higher than this, indicating a greater degree of solute-solute interaction, which may arise from the greater concentration in the deliquescing systems or enhanced solute-solute interactions relative to the systems studied by Ross. In general, positive deviations from predicted values are observed, hence the mixtures tolerate a higher RH than predicted. It does appear that the inorganic salts result in greater nonidealities as compared to sucrose: for the latter substance, χ values were much closer to unity for all three APIs investigated. We had expected that HCl API salts might exhibit greater χ values with chloride salts due to a common ion effect, but χ values were found to follow no particular trend depending if chloride or bromide salts were used, as shown in Table II.

At lease two scenarios can be imagined where deliquescence lowering would be of pharmaceutical importance. First, a deliquescent salt API may be formulated either with a deliquescent excipient or with another deliquescent API as in a product intended for combination therapy. In this instance, the ratio of the two components may be similar or the excipient may be in excess and significant dissolution of API will occur at a lowered RH. Second, a deliquescent API might contain small levels of deliquescent impurities such as a related substance or sodium chloride, which will result in a small proportion of the API deliquescing at a lower RH. Both of these situations may remain undetected because moisture sorption studies are not always performed on formulations and even if they are, moisture sorption by other formulation components may mask that of the API. The presence of dissolved material will likely have a significant impact on the chemical stability of the API and for the latter situation; this may vary from batch to batch depending on the amount of the impurity. In addition, the physical stability of the formulation may change if cycles of deliquescence and recrystallization occur, and the crystal form of the API that precipitates from solution on lowering of the RH may not be the same as the starting form.

CONCLUSIONS

The deliquescence behavior of deliquescent API and deliquescent excipient binary solid mixtures has been investigated. The final RH_{0mix} values of all API-excipient mixtures were found to be lower than the RH_0 values of either the API or the excipient alone. Thus, mixtures of deliquescent API-excipient commence deliquescence at a lower RH, hence these mixtures are more hygroscopic in nature than the API and the excipient alone. These observations are of significance because two or more deliquescent compounds may be present in close proximity in a variety of pharmaceutical systems. In conclusion, lowering of the deliquescence relative humidity in API-excipient systems has potential implications for the physical and chemical stability of the drug product that will be dependent on composition, storage relative humidity, and temperature.

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