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Research Paper

Effect of Small Levels of Impurities on the Water Vapor Sorption Behavior of Ranitidine HCl

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Purpose. Deliquescence is the process by which a solid undergoes dissolution by sorbing moisture from its surroundings when a characteristic relative humidity, RH_0, is reached. For mixtures of two or more deliquescent solids, RH_0 will generally be lowered. The goal of this research was to investigate the effect of small amounts of impurities or degradants on RH_0 for a model deliquescent pharmaceutical salt.
Materials and Methods. The model salt chosen for this work was ranitidine HCl, which has two polymorphic forms. Moisture sorption profiles for each polymorph and samples of different purities were obtained using a gravimetric water vapor sorption balance.
Results. Polymorphs of a similar purity yielded virtually identical moisture sorption profiles. In contrast, samples containing higher levels of impurities had both enhanced moisture sorption below RH_0 and a lowered value of RH_0.
Conclusions. It was concluded that small levels of degradants and/or impurities can drastically affect the moisture sorption profile of a deliquescent material, both through affecting the deliquescence relative humidity and by altering the overall interaction of the substance with moisture. Such changes in behavior may have significant effects on both active pharmaceutical ingredient and drug product stability during both processing and storage.

KEY WORDS: deliquescence; impurities; moisture sorption; ranitidine HCl.

INTRODUCTION

It has been widely documented in the pharmaceutical literature that the presence of moisture may have deleterious effects on both the active pharmaceutical ingredient (API) and drug product (1–6). Such effects include phase transformations, chemical degradation and changes in powder flow and mechanical properties (1–9). Moisture can interact with pharmaceutical solids via a number of different mechanisms (10). One mechanism, of particular significance for pharmaceutical salts and many excipients, is the phenomenon of deliquescence, the process by which highly water soluble crystalline solids undergo dissolution when the relative humidity of the surroundings exceeds a certain characteristic critical relative humidity, termed RH_0. Deliquescence has been reported for a number of pharmaceutical salts and excipients (7,8,11,12). Methods for determining RH_0 of a substance include measuring the relative humidity above a solution saturated with respect to the solid, establishing plots of the equilibrium moisture uptake rates at fixed relative humidities above RH_0 and extrapolating back to a zero moisture uptake rate, and by gravimetric moisture sorption (13–15).

At low relative humidities, solid particles will adsorb moisture to form a monolayer or multilayer at the surface (10,14). The basis of the deliquescence process is the formation of a film of saturated solution on the surface of water-soluble solids with a lower vapor pressure than that of pure water (10). The chemical potential, μ, of pure liquid water in equilibrium with its vapor can be expressed as:

$$\mu = \mu_0 + RT \ln p_0 \tag{1}$$

where p_0 is the vapor pressure, μ_0 is the standard chemical potential, R is the gas constant and T is the temperature. For saturated aqueous solution at the same temperature, which has a vapor pressure p_s which is less than p_0, and a chemical potential μ_s, the difference in chemical potential between water in the solution and pure water can be expressed as:

$$\mu_s - \mu = RT \ln \left(\frac{p_s}{p_0} \right) \tag{2}$$

Water in the film of saturated solution will have a lower thermodynamic activity relative to pure water, providing the driving force for condensation of water when the vapor pressure exceeds p_s. Water vapor condensing into the film raises the vapor pressure of the film to that of the surrounding water vapor pressure which results in further dissolution of the solid until saturation is achieved. Equilibration with the atmosphere is reached when complete dissolution and some degree of solution dilution has occurred (16).

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Although deliquescence of most compounds tends to occur at high relative humidities, it has been reported in the aerosol literature (17–21) that mixtures of two or more deliquescent solids will deliquesce at a lower relative humidity than the individual components. The effect of a second component on the deliquescence relative humidity of organic pharmaceutical salts has also been reported (13), where it was shown that inorganic salts and sugars resulted in a lowering of RH_0 for three deliquescence APIs. Such lowering of the deliquescence RH can have drastic implications for the chemical and physical stability of the API during processing and storage.

It would seem tenable that minor amounts of impurities might cause a significant lowering of the RH_0 for deliquescent pharmaceutical salts. The main objective of this study was to investigate if the impurity level had any influence on the deliquescence behavior of ranitidine HCl, a model deliquescent salt. These investigations were motivated by observations in our laboratory that samples of ranitidine HCl, obtained from two different suppliers, showed noticeable differences in their moisture sorption profiles as depicted in Fig. 1. By extrapolating the linear parts of the plot before and after the deliquescence event, it can be seen that the deliquescence point of the two different samples are different, with that of one being approximately 5% RH lower than the other. It was hypothesized that such differences in the observed RH_0s of the two samples may be a result of the different levels of impurities; possibly residual by-products from the synthesis or degradation products. Numerous ranitidine-related compounds, which originate during synthesis or upon degradation, have been identified (22–25), and several of these are listed in Table I together with their structures and selected physical properties.

MATERIALS AND METHODS

Materials

Ranitidine HCl was obtained from Sigma (St Louis, MO, USA) and from Hawkins Pharmaceutical (Minneapolis, MN, USA). These materials were termed sample A impure and sample B pure, respectively, for the purposes of distinguishing between these and other samples to be discussed (see Table II). Magnesium chloride, which was used to achieve a saturated salt solution for an elevated temperature/humidity study, was obtained from Mallinckrodt AR (Paris, KY, USA).

Methods

High Performance Liquid Chromatography

The high performance liquid chromatography (HPLC) system utilized consisted of an Agilent 1100 with a variable-wavelength UV absorbance detector operated at a wavelength of 228 nm. An ACE 5 C_{18} 4.6 mm × 25-cm column was used, with a mobile phase of acetonitrile and 0.1 M ammonium acetate pH 5.0 (8:92%v/v), with a flow rate of 1.0 ml/min and an injection volume of 35 µl. Each run was performed in triplicate; relative standard deviations for each sample were no more than 0.2%.

Forced Degradation Study

The degradation study was carried out exposing sample B pure to an environment of 70°C (±0.5°C), 28% RH. The

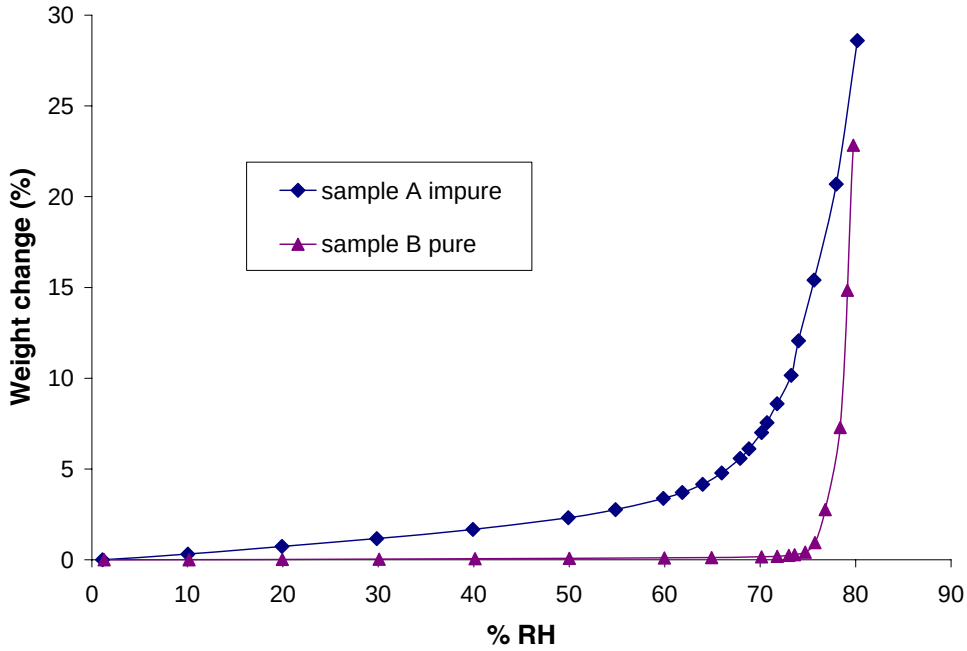


Fig. 1. Vapor sorption profiles at 25°C for ranitidine HCl sample A impure (polymorphic form I) and sample B pure (form II).

Table I. Related Substances of Ranitidine HCl

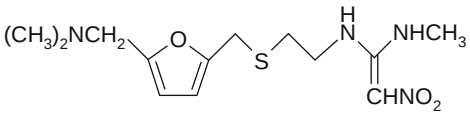
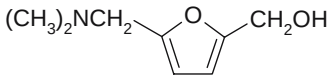
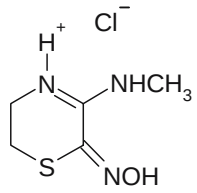
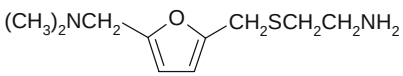
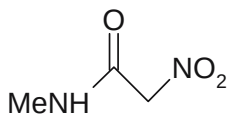
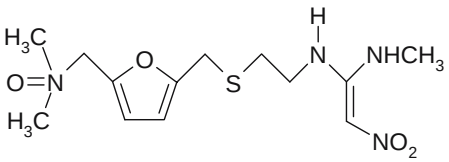
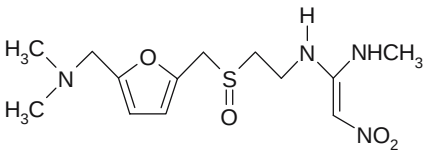
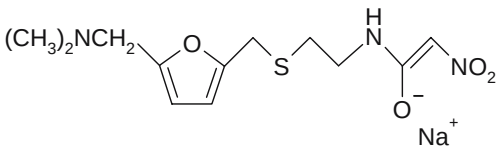
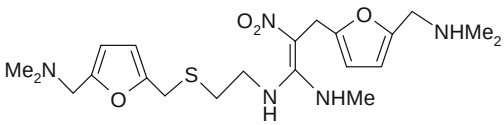
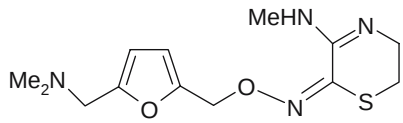
Structure and Name	Type of Degradant/ Synthesis Byproduct	Physical State at 25°C	bp/mp (°C)	Solubility/ Hygroscopicity
 Ranitidine **[1]**	NA	Solid	144–146.5 (decomposes)	Very soluble
 5-[(dimethylamino)methyl]-furfuryl alcohol **[2]**	Hydrolysis product/synthesis	Liquid	96–110	Very soluble[a]
 5,6-dihydro-3-methylamino-2H-1,4-thiazin-2-one oxime, monohydrochloride **[3]**	Hydrolysis product/synthesis	Solid	NA	Very soluble/ hygroscopic
 5-[[(2-aminioethyl)thio] methyl]-N,N-dimethyl-2-furanmethanamine **[4]**	Hydrolysis product/Synthesis	Liquid	130–137	Very soluble below pH 9[a]
 N-methyl-2-nitroacetamide **[5]**	Hydrolysis product/Synthesis	Solid	75–76	Very soluble below pH 7[a]
 Ranitidine-N-oxide **[6]**	Oxidation product	NA	NA	Very soluble[a]

Table I. (continued)

 Ranitidine-S-oxide **[7]**	Oxidation product	NA	NA	Very soluble below pH 7[a]
 Sodium N-[2-[[[5-[(dimethylamino) methyl]-2-furanyl]methyl]thio] ethyl]-2-nitroacetamide **[8]**	Hydrolysis product	NA	NA	NA
 3-[5[(dimethylamino) methyl]-2-furanyl]-N-[2-[[[5-[dimethylamino)methyl]-2-furanyl]methyl]thio] ethyl]-N'-methyl-2-nitro-1-propene-1,1-diamine **[9]**	Secondary degradation product	NA	NA	Very soluble below pH 7[a]
 2H-1,4-Thiazin-2-one, 5,6-dihydro-3-(methylamino)-O-[[5-[(dimethylamino) methyl]-2-furanyl]methyl] oxime **[10]**	Secondary degradation product	NA	NA	Very soluble below pH 7[a]

[a] Calculated using Advanced Chemistry Development (ACD/Labs) Software V8.14 for Solaris (© 1994–2006 ACD/Labs)
NA Not available (Information could not be found). The numbers in brackets correspond to impurities.

relative humidity was controlled by placing the sample in a desiccator containing a saturated solution of magnesium chloride (26), and the desiccator was then placed in an oven set to 70°C. The degraded sample of sample B pure was termed sample B impure.

Raman Spectroscopy

Raman spectra were collected using a Perkin Elmer Spectrum System 2000 (Perkin Elmer, Shelton, CT) instrument with near IR Nd/YAG laser operating at 1,064 nm. The results are the average of three scans collected over the wave number range of 3,500–100 cm^{-1} with spectral resolution of 4 cm^{-1}.

X-ray Powder Diffraction

Diffraction data were obtained using a Shimadzu LabX XRD-6000 diffractometer (Kratos Analytical, Chestnut, NY) equipped with a CuKα anode operating at a wavelength of 1.5406 Å and a polycapillary optic (XOS, Albany, NY). All

Table II. Purities on the Basis of Percent of Total Area by HPLC for Ranitidine HCl Polymorphs: Comparison with Degraded Sample of Form II and a Sample of Recrystallized Form I from Form II

Sample	Polymorph	Purity (Percent of Drug Peak Area to Total Area)	Percent Total Area of Ranitidine-related compound			
			[6] or [7]	[3]	[10]	[9]
Sample A Impure (Initial Sigma Material)	Form I	97.7	0.69	0.62	0.30	0.19
Sample B Pure (Initial Hawkins Material)	Form II	99.2	0[a]	0[a]	0[a]	0[a]
Sample A Pure (Recrystallized from Sample B Pure)	Form I	99.1	0[a]	0[a]	0[a]	0[a]
Sample B Impure (Sample B Pure Degraded for 2 Weeks at 70°C/28% RH)	Form II	97.5	0.25	1.20	0.46	0.19

[a] This peak was not found on the chromatogram.

diffraction patterns were collected at 4°/min with an angular step size of 0.04° using an operating voltage and amperage set to 40.0 kV and 40.0 mA, respectively.

Liquid Chromatography Combined with Mass Spectrometry

The liquid chromatography/mass spectrometry (LC/MS) experiment was carried out using electrospray ionization on a LCQ Classic (ThermoFinnigan, San Jose, CA) mass spectrometer system. The electrospray needle voltage was set at 3.5 kV; the heated capillary voltage was set to 10 V and the capillary temperature was 220 °C. Typical background source pressure was 1.2×10^{-5} Torr as measured by an ion gauge. The drying gas was nitrogen. The instrument was scanned from 50 to 1,000 amu for these experiments. Samples were dissolved in water and injected into a 20 µl injection loop prior to separation on an ACE 5 C18 4.6 mm × 25-cm column using a Dionex P580 liquid chromatography pump (Dionex, Sunnyvale, CA). The LC mobile phase was 0.1 M ammonium acetate pH 5.0 and acetonitrile (92:8 v/v). The sample was separated using a 1.0 ml per minute flow rate run isocratically. The model UVD340U UV detector was set at 228 nm.

Crystallization of Form I Polymorph from Sample B Pure

Sample B pure was dissolved in 20 ml of pure ethanol in a 100 ml Erlenmeyer flask with stirring at a temperature of 80°C until excess solid remained even with continued stirring. The temperature was raised to 90°C, and stirring continued until the remaining solid had dissolved. The solution was then refrigerated overnight, after which a layer of off-white solid had recrystallized at the bottom of the flask. The excess ethanol was decanted, and the residual solid was heated at 50°C for approximately 3 h to remove any remaining ethanol. The recrystallized material was analyzed by XRPD to confirm the polymorphic form. This material was termed sample A pure.

Moisture Sorption

Water vapor sorption profiles of all samples were generated using a symmetrical gravimetric analyzer (SGA-100; VT, Hialeah, FL, USA) at 25°C. The sample weights used for analysis were in the range of 10–15 mg. 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 60 min. During the experiment, the sample was exposed to increasing RH. The step equilibrium criterion was 0.01% w/w in 5 min with a maximum step time of 90 min. RH_0 was measured from the vapor sorption profiles by extrapolating the linear parts of the plot before and after the deliquescence event (13).

RESULTS

Characterization of Samples

The XRPD patterns of each sample are shown in Fig. 2. It is immediately apparent that sample A impure and sample B pure, although both crystalline, have different powder diffraction patterns, suggesting that they are not the same crystal modification. Reference to the literature indicates that the powder pattern for sample A impure is consistent with that reported for polymorph I while that of sample B pure is the same as for polymorph II (27). The powder diffraction pattern for the material recrystallized from sample B pure (form II) was identical to that of the form I polymorph (sample A impure; Fig. 2). For this sample, there was no observable amorphous halo or significant loss in intensity of the diffraction peaks suggesting that the recrystallized material had a comparable crystallinity to the original samples. Raman spectra were also obtained from these three samples (data not shown) and are supportive of the XRPD data. Sample B impure material, prepared by sample B pure subjected to forced degradation, was characterized by Raman spectroscopy and XRPD to determine if any polymorphic conversion had occurred under stress conditions. Based on both the diffraction patterns and the Raman spectra, it was concluded that no polymorphic conversion occurred following storage at 70°C/28% RH (data not shown). Since no new peaks were seen for the degraded sample, any interconversion between polymorphic forms was below the detection limits of the techniques. These results are in good agreement with those of Wu *et al.* (27) who reported no new diffraction peaks upon analysis by XRPD for samples of ranitidine HCl stored under various conditions of elevated temperature (20, 30, 42°C) and relative humidity (45, 55, 75% RH).

HPLC of Original Samples of Ranitidine HCl

An initial impurity profile for each sample A impure and sample B pure was obtained by HPLC. Based upon the

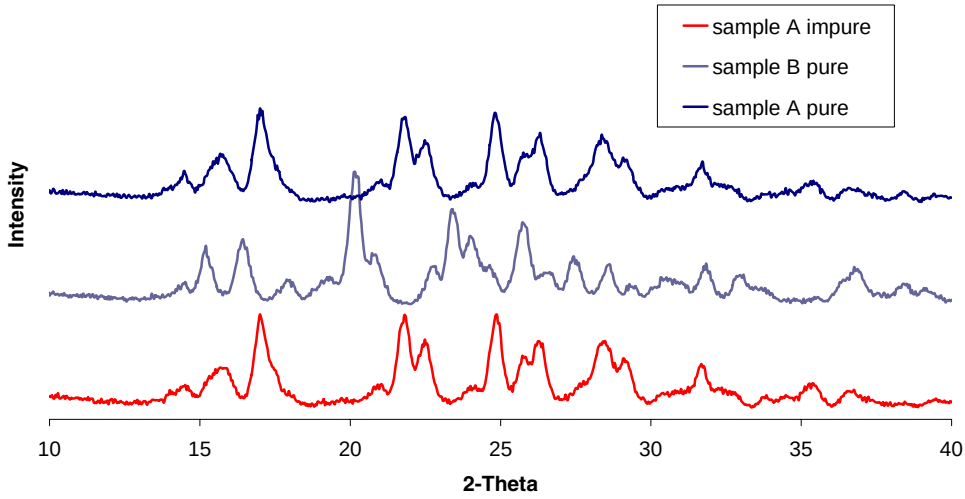


Fig. 2. XRPD patterns of ranitidine HCl sample A impure (form I) and sample B pure (form II) compared with the pattern for sample A pure (recrystallized form I from form II).

knowledge that the response factors of some of the known impurities of ranitidine are approximately identical to that of ranitidine, the purities of the samples were calculated based on the percentage of total peak area integrated of the drug peak area. By visual analysis of the chromatographs obtained for the samples (see Fig. 3), it was evident that sample A impure had a higher level of impurities, as evidenced by the presence of additional peaks. Based on percentage of total area, sample A impure had a purity of 97.7%, while that of sample B pure was 99.2% (see Table II).

HPLC of Processed Ranitidine Samples

In order to obtain a higher purity sample of ranitidine HCl sample A impure (form I), sample A pure was prepared through crystallization from a solution prepared from sample B pure (form II). Purity analysis was performed using HPLC. Based on the area of the drug peak as a percent of total area of all integrated peaks, it was found that the purity of this recrystallized sample A pure (form I) material was virtually identical to that of the sample B pure (form II) material,

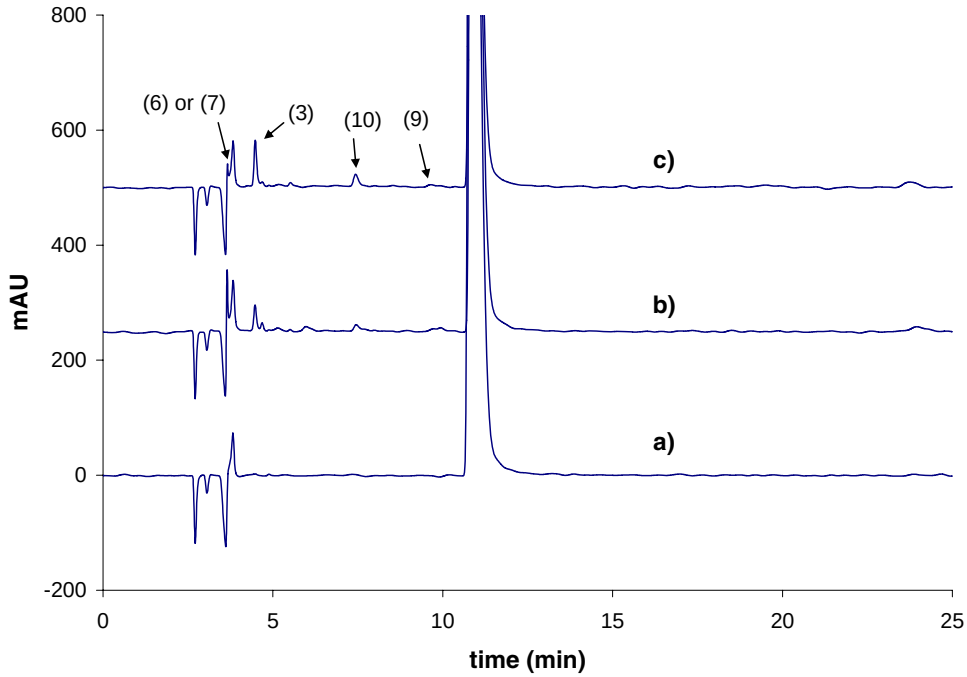


Fig. 3. Comparison of HPLC profiles of ranitidine HCl polymorphic forms and degraded sample of form II: (a) sample B pure (form II), (b) sample A impure (form I), (c) sample B impure (sample B pure degraded at 70°C/27% RH for 2 weeks). Chromatograms (b) and (c) are offset by 10 and 20 mAU, respectively.

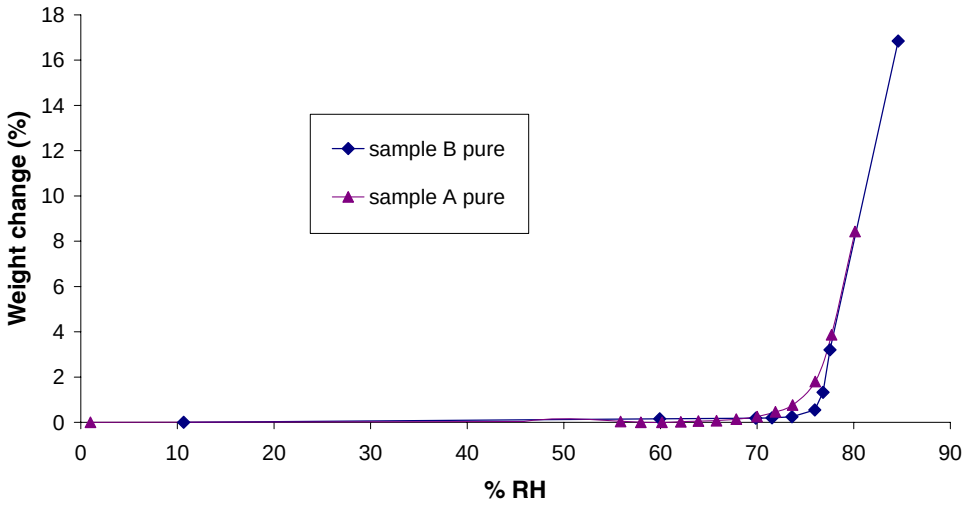


Fig. 4. Vapor sorption profiles at 25 °C for ranitidine HCl sample B pure (form II) and sample A pure (recrystallized form I from form II).

within the uncertainty in peak area attributed to the HPLC method (Table II).

Similarly, to produce a sample of the sample B polymorph (form II) with a similar impurity level to that of sample A impure (form I), sample B pure was subjected to a stress condition of elevated temperature and humidity (70°C/28% RH). The material was observed over time and pulled after 2 weeks of storage, when the color of the sample resembled that of the original sample A impure material. Analysis by HPLC showed the total purity of the degraded sample (sample B impure) was very similar to that of the sample A impure (see Table II). Furthermore, based on elution times, the major impurities in sample A impure and sample B pure appear to be identical (Fig. 3), although a comparison of peak areas leads to the conclusion that the levels of each impurity are different (Table II).

LC/MS of Original and Degraded Samples of Ranitidine

Sample A impure, sample B impure and sample B pure were analyzed by LC/MS in order to attempt to identify the major impurities. Four of the impurity peaks were successfully identified. These corresponded (in order of elution time) to ranitidine-related compounds [6] and/or [7], [3], [10] and [9], as shown in Fig. 3. The first peak had a molecular ion of mass m/z 331, which could correspond to the $(M + H)^+$ ion of

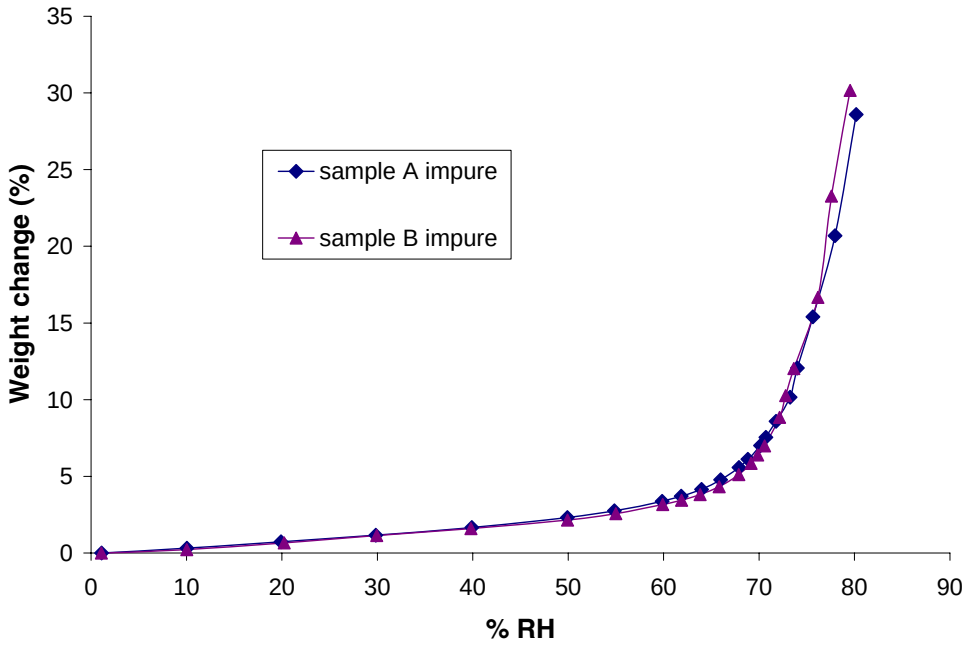


Fig. 5. Vapor sorption profiles at 25°C for ranitidine HCl sample A impure (form I) and sample B impure (degraded sample of form II).

either ranitidine–N-oxide [6] or ranitidine–S-oxide [7]. None of the identified peaks were seen on the chromatograms for sample B pure (see Fig. 3) or sample A pure (chromatogram not shown).

Moisture Sorption Behavior

Figure 1 illustrates the moisture sorption profiles for the two original sample A impure and sample B pure materials. RH_0 for sample A impure (form I) was determined to be 71% RH by use of the extrapolation method (13), while for sample B pure (form II), RH_0 was found to be 76% RH. In addition, the sample A impure material gained approximately 3% w/w at relative humidities just preceding the point on the isotherm where the sample shows a dramatic increase in moisture gain rate, representative of deliquescence. The isotherm for the sample B pure material shows a nearly negligible weight gain prior to deliquescence.

The moisture sorption profiles for sample B pure (form II) and the recrystallized sample A pure (form I) powder are illustrated in Fig. 4. Since the recrystallized sample A pure (form I) had similar impurity levels as sample B pure (form II), any change in the moisture sorption profiles for the two samples can be attributed to the polymorphic form. As can be seen from Fig. 4, the moisture sorption profiles were virtually identical, with the only minor difference being a slightly sooner onset of deliquescence for sample B pure. RH_0 for both samples was approximately 76% RH.

Figure 5 illustrates the moisture sorption profiles for sample A impure and degraded form II (sample B impure). The weight gain for each sample is similar in the pre-deliquescence region with a maximum uptake of around 3–4%. RH_0s were also very similar for the two samples and were estimated as 71 and 70% for sample A impure and sample B impure, respectively.

DISCUSSION

The presence of deliquescent additives has been reported to cause lowering of the RH_0 of organic drug compounds (13). The purpose of this study was to determine whether small amounts of impurities or degradants could also cause a significant reduction in RH_0 for a model deliquescent salt, ranitidine HCl. An additional goal was to evaluate the influence of polymorphic form, if any, on RH_0.

Based on data shown in Fig. 4, it can be seen that, for samples of equivalent purity, the polymorphic form does not have a significant effect on either RH_0 or the overall moisture sorption isotherm. RH_0 has been reported to vary depending on the solid state form of the compound with hydrates having a higher deliquescence point than the anhydrous form (28,29). This variation in RH_0 has been explained by the different kinetic solubility of the various forms whereby the more soluble form will start deliquescing at a lower RH. In the context of these literature reports, the results shown in Fig. 4 can be explained by the similar solubilities of the two polymorphic forms of ranitidine HCl, which are so close that the two polymorphs have been termed isoenergetic (30).

Sample A impure shows enhanced water vapor sorption prior to the deliquescence event, and in this region of the isotherm, sorbs more moisture than is typical for highly crystalline solids (15). Many studies have shown that small amounts of amorphous material can lead to increased moisture sorption (31–35). For example, in one study by Saklatvala *et al.* (32), it was observed that separate batches of a drug had markedly different moisture uptake profiles. The authors determined that the difference was due to the presence of relatively minor amounts of amorphous content. In this study, no amorphous material could be detected in any sample by XRPD, indicating that any disordered material present was below the detection limits of the technique. Attempts to prepare amorphous ranitidine HCl, e.g., by freeze-drying were unsuccessful. In addition, previous studies have shown that the moisture sorption profile of ground ranitidine HCl is similar to that of the unprocessed material (13). These results suggest that it is not facile to form amorphous ranitidine HCl and hence the increased water sorption below the deliquescence point is not thought be explained by the presence of amorphous ranitidine HCl.

Instead, based on the chromatographic analyses (Table II), it is proposed that the increased moisture uptake below the deliquescence point and the lowering of the deliquescence RH are linked to the purity of the sample. Strong evidence for this supposition is provided by data shown in Figs. 4 and 5. It can be seen that moisture sorption is enhanced and RH_0 is reduced for the two samples of lower purity (Fig. 5), relative to the more pure samples (Fig. 4) regardless of the polymorphic form. Interestingly, sample B pure had an identical moisture sorption profile to that obtained for the USP reference standard (data not shown). To the best of our knowledge, changes in deliquescence point with impurity/degradant levels have not been reported previously. Yoshioka *et al.* (6) reported an increase in moisture sorption at constant RH for meclofenoxate HCl as degradation proceeded, consistent with our results that indicate impurities/degradants can increase the level of moisture associated with a solid.

As discussed above, a relatively small decrease in the purity of ranitidine HCl corresponds to a noticeable reduction in the value of RH_0. The reduction in RH_0 from 76 to 71% RH is of a similar magnitude to that reported for ranitidine HCl with various deliquescent excipients (13). Furthermore, for the two samples with higher impurity levels (sample A impure, sample B impure), although the chromatographs shown in Fig. 3 indicate that the identity/quantity of each the impurities/degradants may vary somewhat between samples, their effect on moisture sorption is reasonably similar. The latter observation can most likely be explained by the fact that all of the impurities identified by the LC/MS study seem to have a high affinity for moisture, as reflected by their high aqueous solubilities (Table I). Indeed, all of the known ranitidine degradants have very high water solubilities. Thus, even though ranitidine is known to undergo a complex degradation process with degradants prone to subsequent breakdown (24), the related substances observed in this study seem to have similar effects on the moisture sorption. Consequently, for the case of ranitidine HCl, it appears that the total level of related substances is important in influencing the moisture sorption profile rather than the specific amounts of individual compounds. Obviously

this is unlikely to be true if the various degradation products have vastly different interactions with moisture. Since specifications for a batch of API may allow a window of a few tenths of a percent in overall purity, these results are of significance. Hence, even a small variation in impurity content could potentially lower RH_0 enough to cause deliquescence or significant moisture uptake at conditions of relative humidity conditions previously believed to be a safe storage condition. In addition, a batch of API which undergoes even slight amounts of degradation may be more susceptible to deliquescence (6). Since it has been shown previously that the degradation rate of ranitidine HCl increases dramatically once deliquescence occurs (7), such a lowering of RH_0 followed by deliquescence would have negative consequences for chemical stability.

In addition to the lowered RH_0, and perhaps of even greater significance, a large increase in moisture content at relative humidities below the deliquescence point was also observed for the lower purity samples. For example, at 60% RH, the presence of an additional 1.5% level of impurities/degradants raises the moisture content of the sample from below the detection limits of the instrument to approximately 2% w/w (Fig. 1). Thus, even if the sample is stored below the critical RH, there is a considerable amount of moisture associated with the solid. This observation raises several interesting points. For example, during early stages of drug development, it is fairly typical to produce batches of a low purity (e.g., around 97%). Observations of apparent "hygroscopicity" may lead to searches for alternative salt forms when in reality, a purer material may have significantly reduced moisture sorption. Furthermore, of greater importance is the possibility that the additional moisture associated with the solid may compromise chemical stability, even if the material is stored below the deliquescence point.

One issue that should also be considered for the specific example of ranitidine HCl is the origin of the enhanced moisture sorption below the deliquescence point. If all the moisture is associated with the impurities/degradants, then this implies that these substances are capable of sorbing at least their weight in water. This level of moisture sorption is not typical of crystalline solids, suggesting that the impurities/degradants are probably disordered or if crystalline, deliquescent. Moreover, formation of these substances may induce disorder in ranitidine HCl (36,37), resulting in enhanced sorption in this region (38,39).

Thus the presence of small quantities of impurities/degradants would most likely result in localized regions of very high water content with enhanced molecular mobility. Such "hot spots" will most likely significantly affect the chemical stability of the API. Further investigations of the increased moisture uptake at relative humidities lower than the RH_0 are currently underway.

CONCLUSION

The effect of small amounts of impurities or degradants on the deliquescence behavior of a model deliquescent pharmaceutical API has been investigated. RH_0 was found to be lowered in the presence of small levels of impurities. In contrast, the polymorphic form of the API was found to have a minimal effect on RH_0. A significant increase in moisture uptake at relative humidities below the observed RH_0 was also observed for samples of ranitidine HCl of lower purity. Such an effect can have significant implications during drug development, potentially posing risks to physical and chemical stability.

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