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RESEARCH PAPER

Salt Stability – The Effect of pH_{max} on Salt to Free Base Conversion

Yi-Ling Hsieh[1,2] • Jeremy M. Merritt[3] • Weili Yu[4] • Lynne S. Taylor[1]

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ABSTRACT

Purpose The aim of this study was to investigate how the disproportionation process can be impacted by the properties of the salt, specifically pH_{max}.

Methods Five miconazole salts and four sertraline salts were selected for this study. The extent of conversion was quantified using Raman spectroscopy. A mathematical model was utilized to estimate the theoretical amount of conversion.

Results A trend was observed that for a given series of salts of a particular basic compound (both sertraline and miconazole are bases), the extent of disproportionation increases as pH_{max} decreases. Miconazole phosphate monohydrate and sertraline mesylate, although exhibiting significantly different pH_{max} values (more than 2 units apart), underwent a similar extent of disproportionation, which may be attributed to the lower buffering capacity of sertraline salts.

Conclusion This work shows that the disproportionation tendency can be influenced by pH_{max} and buffering capacity and thus highlights the importance of selecting the appropriate salt form during the screening process in order to avoid salt-to-free form conversion.

KEY WORDS buffering capacity · mathematical modelling · pH_{max} · salt disproportionation

✉ Lynne S. Taylor
lstaylor@purdue.edu

[1] Department of Industrial and Physical Pharmacy, Purdue University, 575 Stadium Mall Dr., West Lafayette, Indiana 47907, USA

[2] Present address: Novartis Pharmaceutical Corporation, 201 Industrial Rd., San Carlos, California 94070, USA

[3] Eli Lilly & Co, 1400 W. Raymond St., Indianapolis, Indiana 46221, USA

[4] Pfizer Global Research and Development, Eastern Point Road, MS 8156-007, Groton, Connecticut 06340, USA

ABBREVIATIONS

API	Active pharmaceutical ingredient
PXRD	Powder X-ray diffraction
RH	Relative humidity
TGA	Thermogravimetric analysis
TSPd	Tribasic sodium phosphate dodecahydrate

INTRODUCTION

Salt formation is widely used to improve the physicochemical properties of active pharmaceutical ingredients (APIs) with ionizable groups. Advantages of pharmaceutical salts can include improved dissolution rate and solubility, as well as more desirable solid state properties such as higher melting points. The conversion of the salt to the free form, a process known as disproportionation, during processing or on storage is particularly undesirable. Several examples of disproportionation have been reported (1–3), most recently for the platelet inhibitor, prasugrel, which was observed to convert from the hydrochloride salt to the free base, raising concerns about lower bioavailability in certain patient populations with raised gastric pH (4). In addition to bioavailability concerns, many free forms have poor physicochemical properties, for example they may form oils at room temperature (5) and therefore conversion to the free form may compromise the physical integrity of the solid dosage form. In addition, the free form resulting from disproportionation may have a different susceptibility to chemical degradation relative to the salt form. For example, sertraline salts that underwent salt-to-free form conversion induced by excipients were more susceptible to oxidation as compared to salts that resisted conversion (6).

The phenomenon of disproportionation for the salt of a weak base can be understood by considering the pH solubility profile of a basic ionizable compound, as illustrated in Fig. 1. When the pH is significantly lower than

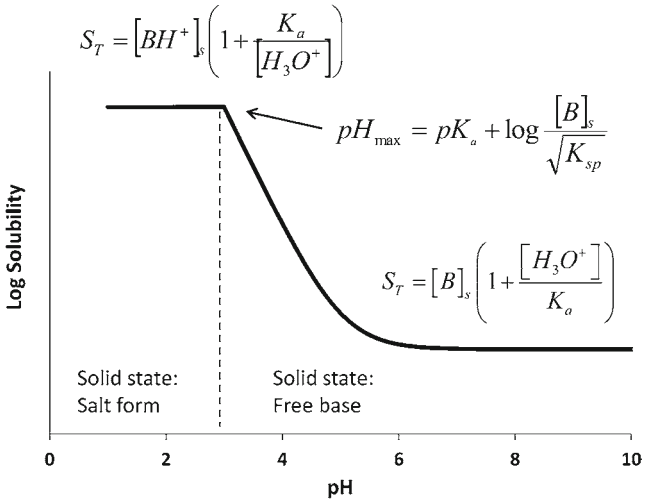

Fig. 1 Theoretical pH solubility profile for a basic compound with pK_a of 5.

the pK_a of the compound, the pH solubility profile can be described by:

$$S_T = [BH^+]_s\left(1+\frac{K_a}{[H_3O^+]}\right) \quad (1)$$

where $[BH^+]_s$ denotes the solubility of the salt form, K_a is the acid dissociation constant and $[H_3O^+]$ is the hydronium ion concentration which can be calculated from the pH using the following equation:

$$[H_3O^+] = 10^{-pH} \quad (2)$$

In this pH region, the dissolved compound is predominantly ionized and the solution is in equilibrium with the crystalline salt form. At higher pH, the pH solubility profile can be expressed by Eq. 3, whereby the solution is in equilibrium with the crystalline free base:

$$S_T = [B]_s\left(1+\frac{[H_3O^+]}{K_a}\right) \quad (3)$$

where $[B]_s$ denotes the solubility of the crystalline free base.

By combining Eqs. 1 and 3, Bogardus and Blackwood (7) derived the following equation to describe a characteristic pH, known as pH_{max}, where the two solubility curves merge:

$$pH_{max} = pK_a + log\frac{[B]_s}{\sqrt{K_{sp}}} \quad (4)$$

where K_{sp} is the solubility product of salt and hence $\sqrt{K_{sp}}$ is the intrinsic salt solubility. pH_{max} is the pH where solubility is maximized with an equilibrium formed between ionized and unionized drug in solution with both the crystalline base and the crystalline salt. At a pH below pH_{max}, the crystalline salt is the stable form present at equilibrium, while above pH_{max}, the crystalline free base is the equilibrium solid. The significance of pH_{max} arises from that fact that, for a basic drug forming a salt with an acidic counterion, the conversion from salt to free base can potentially occur when the pH is above the value of pH_{max}. Hence, it would be anticipated from a thermodynamic perspective that, for a given compound, a salt with a lower pH_{max} would have a greater tendency to disproportionate while disproportionation for a salt with a higher pH_{max} would be less likely.

Previous publications have shown that various environmental factors have significant impact on the extent of disproportionation (8, 9). Specifically, greater salt-to-free form conversion can be induced by higher temperature, higher relative humidity and greater extent of contact between salt and excipient. Interestingly, the impact of increased temperature on disproportionation extent was attributed to a lowering of pH_{max} due to the greater increase in salt solubility relative to base solubility, as well as effects on pK_a (8).

While several studies have postulated the importance of pH_{max}, there is still a lack of understanding about the susceptibility of different systems to disproportionation. To address this issue, the goal of this study was to study the impact of pH_{max} on the extent of salt disproportionation, using various salts of two basic model compounds, miconazole and sertraline, whereby disproportionation was induced in powders by mixing the salts with a base. The hypothesis to be tested is that the extent of disproportionation will be correlated to the pH_{max} of the salt, which in turn depends on free base solubility, salt solubility and pK_a, as shown by Eq. 4. Tribasic sodium phosphate dodecahydrate (TSPd), previously shown to induce disproportionation of basic salts (6, 8, 10), was chosen as a highly basic model excipient.

EXPERIMENTAL

Materials

Miconazole free base and miconazole nitrate were purchased from Spectrum Chemical (Gardena, CA). Sertraline HCl was donated by Pfizer Inc. Sertraline free base was prepared by titrating sertraline HCl in 1:1 *v/v* methanol/water mixture to a pH above 11.5 using 0.5 N NaOH. Tribasic sodium phosphate dodecahydrate (TSPd) and sodium bromide were purchased from Mallinckrodt Chemical (Phillipsburgh, NJ). Benzoic acid, phosphoric acid, methanesulfonic acid, p-toluenesulfonic acid monohydrate, (1S)-(+)-10 camphorsulfonic acid, L-(+)-tartaric acid were obtained from Sigma-Aldrich (St. Louis, MO).

Salt Formation

Miconazole mesylate was prepared as described by Guerrieri and Taylor (10). Miconazole nitrate and sertraline HCl were

used as received. All the other salts were formed by adding an equal molar amount of 2 M counterion solutions (1 M for benzoic acid stock solution) to sertraline or miconazole dissolved in acetonitrile. The solutions were stirred at 70°C for 1 h, cooled to room temperature and continuously stirred overnight. The salts were harvested using suction filtration, followed by overnight drying in under vacuum at room temperature.

Solid State Characterization and Solubility Measurement

To measure solubility, salts (except for miconazole mesylate) were stirred in water for 48 h at 25°C, maintaining an excess of solid. The solubility value of miconazole mesylate was obtained from Guerrieri and Taylor (10). Free base solubility at 25°C was obtained by stirring excess solid at 25°C for 48 h in a buffer solution with a pH at least two units higher than the compound pK_a. The supernatant and the excess solids were separated using ultracentrifugation and the saturated solutions were obtained by filtering through a 0.2 μm syringe filter. The excess solids were dried under vacuum at 25°C. The pH of the saturated solution was measured by an EasySeven pH meter equipped with an Inlab© 413 probe (Mettler Toledo International Inc., Columbus, OH). The solubility of free base and salt forms were measured by using a Waters Alliance 2690 high performance liquid chromatography (HPLC) system with a 4.6×100 mm SymmetryShield RP8 3.5 μ column (Waters Chromatography, Milford, MA). An isocratic method with flow rate of 1 ml/min was used with mobile phase consisting of a binary mixture of acetonitrile and pH 2.25 phosphate buffer. The mobile phase composition for miconazole and miconazole salts was 45% acetonitrile and 55% buffer, while the composition for sertraline and sertraline salts was 40% acetonitrile and 60% buffer. The injection volume was 100 μL. Both compounds were detected at wavelength of 230 nm. Linear calibrations were obtained with correlation coefficient (R^2) no less than 0.999. Samples with concentration exceeding the linear range were diluted accordingly.

A TA Q500 thermogravimetric analyzer (TGA) (TA Instruments, New Castle, DE) was utilized to measure the weight loss of all salts upon heating from 25 to 300°C (except for miconazole mesylate and miconazole phosphate), both before and after stirring in water, in order to determine the existence of hydrate or solvates. Miconazole phosphate was evaluated from 25 to 200°C using a Seiko TGA220 (Seiko Instruments, Inc., Japan). A Shimadzu XRD-6000 (Shimadzu Scientific Instruments, Columbia, MD), equipped with a Cu- K_α source and set in Bragg-Brentano geometry, was utilized to evaluate any changes in solid state form before and after slurrying in water. The scan rate was 4°/min with a 0.04° step size and a scan range of 5 to 35° (2θ).

Sample Preparation

The materials were sieved to obtain a smaller range of particle sizes (lower than 53 μm) for the disproportionation study. The sieved materials were then stored over calcium sulfate (W.A. Hammond DRIERITE Co. LTD, Xenia, OH) for 10 days prior to mixing with TSPd. Each salt was blended with TSPd to give a composition of 50/50 *w/w* by geometric mixing using a spatula to lightly triturate the powders, with all samples handled in a glove box that was continuously purged with dry nitrogen. The relative humidity in the glove box was maintained below 20% RH. Each mixture was prepared in triplicate. The powder mixtures were placed in glass vials stored over saturated sodium bromide solution (57% RH) at 25°C and periodically removed for analysis using Raman spectroscopy. The weight gain of the powder mixtures was monitored over time.

Quantification of Disproportionation

The concept of utilizing Raman spectroscopy to detect and quantify salt disproportionation has been demonstrated previously (10). A RamanRxn1-785 Raman Spectrometer (Kaiser Optical Systems, Inc., Ann Arbor, MI) was utilized to obtain Raman spectra for the free bases and salt forms (except for miconazole phosphate) to identify the unique Raman shifts for each material. The system was equipped with fiber optics coupled with a MR probe with a spot size of 150 μm and the laser power was set to 200 mW. For miconazole phosphate, a RXN2 hybrid Raman Spectrometer equipped with a fiber-optically coupled PhaT probe head with spot size of 1 mm (Kaiser Optical Systems, Inc., Ann Arbor, MI) was used with a laser power of 200 mW. Calibration sets for this study were prepared by mixing free base and salt with a known molar ratio (5/95, 10/90, 30/70, 50/50, 70/30, 90/10 as free base/salt molar ratio). A calibration plot was generated by plotting the intensity ratio at the unique Raman shift of the free base divided by that of the salt as a function of the molar ratio of free base/salt. The resultant curves were linear and could be used to estimate the extent of disproportionation in the blends with TSPd which did not have any spectral overlap with the peaks used for determination of the free base/salt ratio.

RESULTS

Solubility and Solid State Characterization

The solubility values of the various compounds are summarized in Table I. The pH values of the saturated salt solutions are also summarized in Table I. A form change was observed for miconazole phosphate following slurrying in water, whereby Fig. 2 shows that the PXRD patterns for miconazole

Table I Summary of Relevant Physicochemical Properties of the Free Base and Various Salts

Salt	pK_a	pH_{max}	pH at saturation	Salt solubility (M)	Free base solubility (M)	Buffer concentration (M)	Buffer capacity (M)	% weight gain at 57% RH
Miconazole	6.9[a]	–	–	–	2.4×10^{-6} [b]	–	–	–
Miconazole camsylate	–	4.17	3.43	1.27×10^{-3}	–	1.27×10^{-3}	8.57×10^{-4}	0.04
Miconazole mesylate	–	1.44[a]	1.47[a]	6.88×10^{-1} [a]	–	6.88×10^{-1}	7.8×10^{-2}	0.2
Miconazole nitrate	–	4.75	4.37	3.36×10^{-4}	–	3.36×10^{-4}	1.01×10^{-4}	0.05
Miconazole phosphate monohydrate	–	3.35	2.23	8.53×10^{-3}	–	8.53×10^{-3}	1.36×10^{-2}	0.4
Miconazole tosylate	–	4.44	3.63	6.97×10^{-4}	–	6.97×10^{-4}	5.41×10^{-4}	0.07
Sertraline	9.06[b]	–	–	–	1.31×10^{-5}	–	–	0.04
Sertraline benzoate	–	7.11	6.79	1.17×10^{-3}	–	1.18×10^{-3}	1.50×10^{-5}	0.02
Sertraline HCl	–	6.04	5.56	1.38×10^{-2}	–	1.38×10^{-2}	1.64×10^{-5}	0.01
Sertraline hemitartrate	–	6.65	5.65	3.35×10^{-3}	–	3.37×10^{-2}	8.18×10^{-6}	0.04
Sertraline mesylate	–	5.68	5.55	3.11×10^{-2}	–	4.07×10^{-2}	3.55×10^{-5}	0.02

[a] Values obtained from Guerrieri and Taylor (10)

[b] Value obtained from Box and Comer (5)

phosphate were distinctively different before and after stirring in water. TGA measurements revealed 3.4% weight loss at around 85°C, which corresponds to a weight loss of one molecule of water per salt molecule suggesting the formation of a monohydrate. Further analysis using HPLC to obtain the assayed value of samples of known concentration confirms the results obtained from TGA, confirming monohydrate formation for miconazole phosphate after slurrying in water. Since the solubility of the monohydrate is likely to be different from the anhydrate initially prepared, miconazole phosphate monohydrate produced from slurrying was used for the disproportionation study. The value of pH_{max} for each salt was calculated using Eq. 4 and data are summarized in Table I. Miconazole free base has a much lower solubility than sertraline, and is also a weaker base. For both compounds, the mesylate salt has the highest solubility, being approximately 5 orders of magnitude more soluble than the free base for miconazole and 3 orders of magnitude more soluble for sertraline. The lower pK_a of miconazole, combined with a larger difference in salt and free base solubility leads to lower pH_{max} values for the miconazole salts relative to the sertraline salts.

Extent of Disproportionation

The unique Raman shifts that were identified for the free bases and their salt forms are summarized in Table II. An example calibration curve used for estimating the extent of disproportionation is shown for miconazole camsylate in

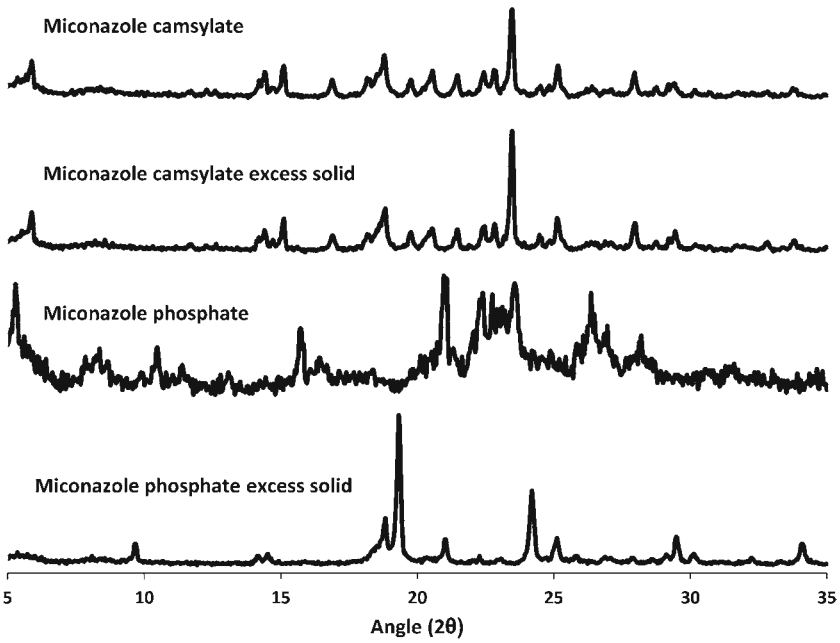

Fig. 2 PXRD data for miconazole camsylate and miconazole phosphate, before and after stirring in water. The intensity was adjusted to an arbitrary value.

Fig. 3. The extent of disproportionation and the weight gain data for each salt in the presence of TSPd after storage at 57% RH for 4, 9 and 14 days are shown in Fig. 4. The initial time points were assumed to be zero for both weight gain and disproprotionation data. The percent conversion to free base appeared to have reached a plateau for all samples within 4 days with no further increases being observed at extended times, as shown in Fig. 4a. The water vapor sorption likewise had reached a plateau value by the 4 day time point (Fig. 4b). The amount of disproportionation varied considerably between salts, from being not detectable in sertraline benzoate to about 80% for miconazole mesylate. The relationship between pH_{max} and the extent of disproportion (% conversion) at day 14 is demonstrated in Fig 5.

DISCUSSION

Salt solubility and pH_{max}

One of the many reasons to formulate an ionizable API as a salt is to improve its aqueous solubility as the ionized form usually exhibits higher solubility. However, in the context of disproportionation, the higher the solubility of the salt relative to that of the base, the lower the pH_{max} value, and consequently, the more susceptible the salt is to disproportionation. This can be clearly seen from Fig. 6 which summarizes the pH-solubility profiles of all of the miconazole salts studied. Here, it is apparent that the pH_{max} of the miconazole salt decreases significantly as salt solubility increases, consistent with what is suggested by Eq. 4. This can be exemplified by comparing miconazole mesylate and nitrate; the mesylate salt has more than three orders of magnitude higher solubility relative to miconazole nitrate, and consequently, pH_{max} is three pH units lower (Table I). Table I also demonstrates the large variation in salt solubility with different counterions as well as between the salts of the two compounds. The measured salt solubility corresponds to the concentration of the ionized form, $[BH^+]$, which is determined by the solubility product of the salt, the K_{sp}:

$$K_{sp} = [BH^+][X^-] \quad (6)$$

where $[X^-]$ is the concentration of counterion. In the absence of excess counterion and hence no common ion effect, the solubility product can be determined by measuring the solubility of the salt. The salt solubility is difficult to predict *a priori* (11). For example, despite having a similar pK_a value to methanesulfonic acid (pKa −1.89) (12), the nitrate salt of miconazole (pKa of nitric acid = −1.3) (13) exhibits a significantly lower solubility. Furthermore, sertraline hydrochloride, formed from hydrochloric acid with significantly lower pK_a of −6.1, has lower solubility in comparison to sertraline mesylate. It is therefore evident that solubility of salt cannot be easily deduced from the pK_a of the counterion. In turn, relative disproportionation tendency can thus only be predicted following determination of salt and free form solubility. Likewise, it is only feasible to obtain a pH-solubility profile, shown in Fig. 6 with miconazole salts as example, after the salt solubility has been measured.

Table II Summary of Raman Shifts for the Free Bases and Salts

Material	Raman shift (cm^{-1})	Calibration R^2
Miconazole	1506	–
Miconazole camsylate	1743	0.9994
Miconazole mesylate	780	0.9973
Miconazole nitrate	1328	0.9880
Miconazole phosphate monohydrate	896	0.9933
Miconazole tosylate	1124	0.9992
Sertraline	783[a], 2785	–
Sertraline benzoate	1385	0.9938
Sertraline HCl	1405	0.9824
Sertraline hemitartrate	2875	0.9956
Sertraline mesylate	3010	0.9981

[a] 783 cm^{-1} was used as unique Raman shift for sertraline free base in comparison to sertraline HCl due to interference at 2785 cm^{-1}

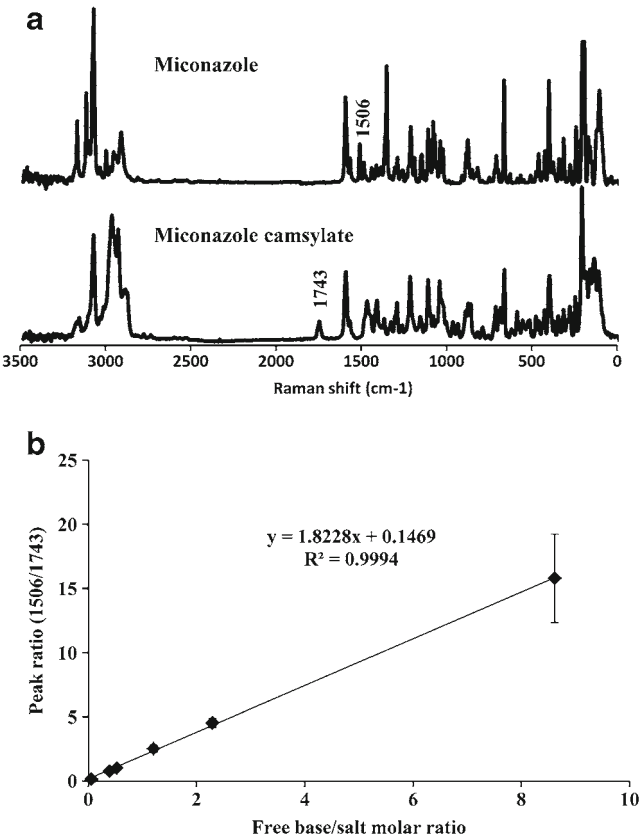

Fig. 3 Example calibration plot built using unique Raman shifts for miconazole and miconazole camsylate.

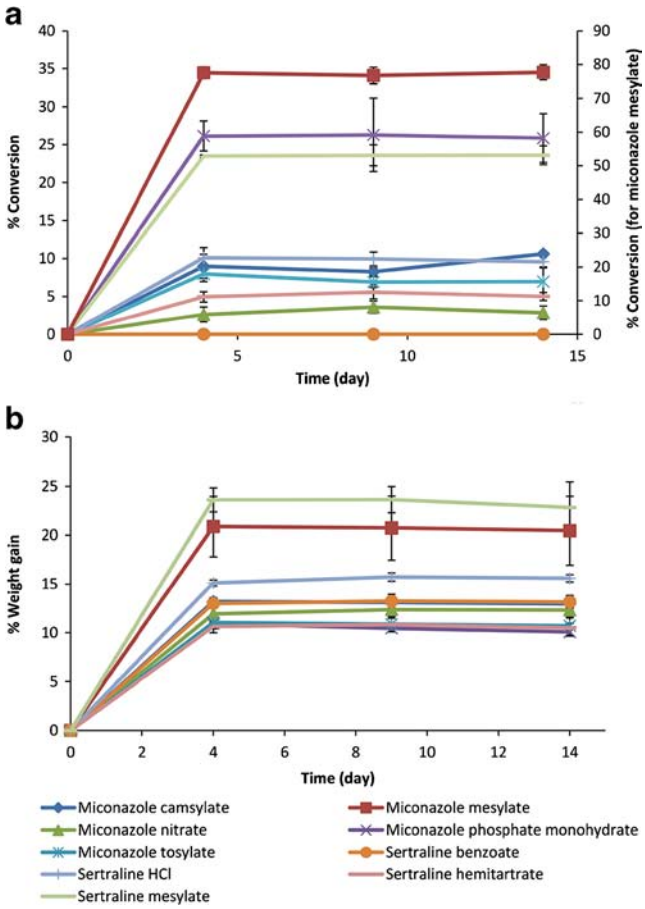

Fig. 4 Disproportionation (**a**) and percent weight gain (**b**) of each salt/TSPd binary mixture as function of time at 57%RH.

Extent of Disproportionation *vs.* pH_{max}

The conversion of an ionized species to a neutral species in the solution phase upon increasing pH is a well-established principle. In the solid state, the concept of microenvironmental pH to describe the surface of the solid has been proposed, and extended to pharmaceutical applications (14–17). Although the exact characterization of microenvironmental pH is difficult, particularly in blends (17), it is clear that disproportionation can occur if the excipients selected for the formulation create a pH environment which favors the conversion from salt to free form; hence it is important to select appropriate excipients. Alternatively, since the selection of excipients approved for pharmaceutical use is somewhat limited, one may select the most robust salt form by considering the disproportionation tendency, along with other important physicochemical properties, during the salt screening process. Figure 5 clearly illustrates the strong correlation between the extent of disproportionation and the value of pH_{max}. The trend illustrates that the salts with lower pH_{max} (miconazole mesylate and sertraline mesylate) exhibited a much higher extent of conversion to the free base in the presence of a basic excipient, while salts with a higher pH_{max}, such as miconazole nitrate and sertraline benzoate, underwent significantly less or no disproportionation. The pH_{max} of a salt thus becomes an important parameter that may be used for evaluating the likelihood of a given salt to disproportionate. During salt selection, the disproportionation tendency must be balanced against the need to utilize a salt with the desired solubility. Since salt solubility values are routinely obtained during salt screening measurements, it would be straightforward to rank the disproportionation tendency of the various salts by using the obtained data to calculate pH_{max}.

Buffering Capacity

While there is a clear trend within a given series of salts between pH_{max} and the extent of disproportionation, there are differences between the two compounds that cannot be

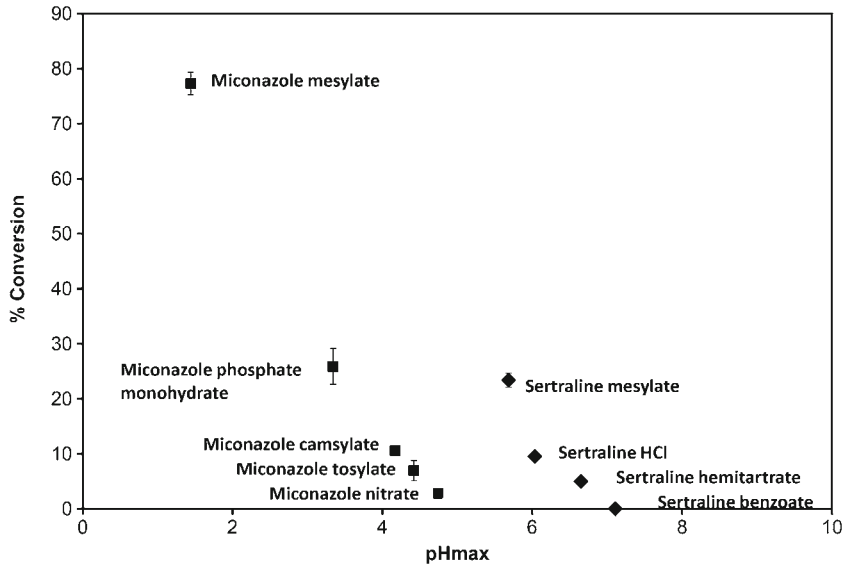

Fig. 5 Relationship between pH_{max} and the extent of disproportionation for a series of miconazole and sertraline salts.

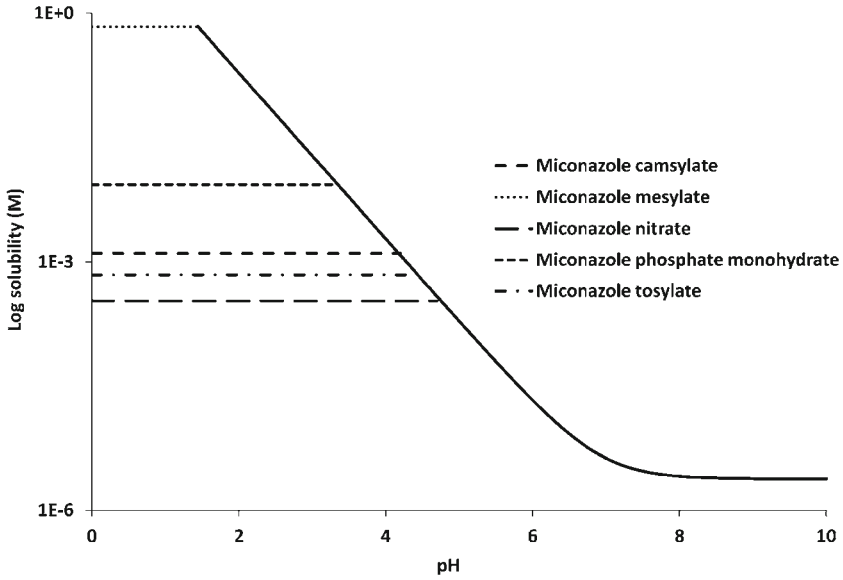

Fig. 6 pH solubility profile of miconazole salts calculated using Eqs. 1 and 3 and ignoring common ion effects that would come into play at pH values lower than pH_{max}. pH_{max} for each salt is given by the pH at the intersection of the horizontal lines with the continuous line.

explained using this parameter. Considering the phosphate salt of miconazole and the mesylate salt of sertraline, the extent of disproportionation is approximately the same for both salts, even though the pH_{max} values vary by more than 2 units. Similar trends can be seen for other salts. It has been noted previously that buffer capacity may play an important role in influencing the extent of disproportionation (10). The buffer capacity of a salt, estimated for the solution, may be relevant for disproportionation as it indicates how well the solvated salt may resist changes in pH. Although it may be counterintuitive to apply the concept of buffering capacity to complex powder mixtures, previous studies have suggested that small amounts of water molecules may adsorb onto the surface of the crystalline solid at relative humidity conditions lower than the deliquescence point, leading to increased mobility and solvation of surface species (18–20); furthermore, the pH of the aqueous layer on the surface of the solid was shown to correspond to the pH of the saturated solution (21). To evaluate how buffering capacity may affect the extent of disproportionation observed in powders, it is therefore reasonable to assume that the conversion takes place in a region of localized moisture on the surface of the solid where the salt is saturated. The free base concentration, [B], in a solution where the salt is at saturation can be expressed by the following equation:

$$[B] = \frac{[BH^+]_s K_a}{[H^+]} \tag{7}$$

where $[BH^+]_s$ denotes the salt solubility and, K_a, is the acid dissociation constant. The concentration of buffer, C_{buf}, is the sum of the molar concentration of the ionized and the unionized species:

$$C_{buf} = [B] + [BH^+]_s \tag{8}$$

Buffer capacity (β) is defined as the moles of acid or base that needs to be added to the solution in order to change the pH of the buffer of 1 liter by one unit. The equation to calculate the buffer capacity of a solution, saturated with respect to the

Table III Summary of Disproportionation Extent Estimated by the Mathematical Model Described in ref (25)

Material	pK_a (of acid)	Original model (%Fb)	0.0025x H2O model (%Fb)	Experimental (%Fb)
Miconazole camsylate	−0.8	100	12.2	10.6
Miconazole mesylate	−1.9	100	100	77.7
Miconazole nitrate	−1.4	100	2.2	2.9
Miconazole phosphate	2.1	100	55.2	25.9
Miconazole tosylate	−2.8	100	5.2	7.0
Sertraline benzoate	4.2	100	0.27	0
Sertraline HCl	−7.0	100	2.9	9.6
Sertraline mesylate	−1.9	100	11.7	23.6

salt can be expressed by Eq. 9, derived from the Van Slyke equation (22, 23):

$$\beta = 2.303\left(\frac{K_w}{[H^+]} + [H^+] + \frac{C_{buf}K_a[H^+]}{(K_a + [H^+])^2}\right) \quad (9)$$

The equilibrium constant for autoionization of water, K_w, is 10^{-14} at 25°C. The pH of the solution at saturation for each salt was measured and therefore can be used to calculate the proton concentration, $[H^+]$, in Eqs. 7 and 9. The buffer capacity for each salt calculated using Eq. 9 is summarized in Table I. Generally, a buffer with optimal buffer capacity constitutes equal molar amount of ionized and unionized species in solution and usually the pH of the buffer would be close to the pK_a of the drug. Since salt formation is favored to occur when the pH is at least two units below pK_a, the buffer capacity of the saturated solution of the salts selected in this study therefore would be naturally weak, depending on the solubility and pH of the solution at saturation. However, it can be seen that there is still considerable variation among the buffer capacity of the different salts. Clearly, for those salts with lower buffering capacity, the pH on the surface of the salt will be more easily increased by a strongly basic excipient and as a result, the salt would be expected to be more susceptible to disproprotionation. The considerably lower buffer capacity of the sertraline mesylate salt relative to that of the miconazole phosphate salt helps explain why a similar extent of disproportionation is seen for these two salts even though the former compound has a much higher pH_{max}.

Although not evaluated in the current study, the buffer capacity of the excipient may also impact the extent of disproportionation. This was demonstrated in a study by John *et al.* where the impact of different excipients on the disproportionation of a weakly basic model HCl salt was probed (24). It was observed that certain excipients containing a carboxylate functional group, such as magnesium stearate and sodium croscarmellose, induced significant amounts of disproportionation and this was attributed to the higher "buffering" or proton uptake capacity of these excipients.

Salt Disproportionation Modeling

A theoretical model of disproportionation has been recently described by Merritt *et al.* (25) and was applied to the current results. The salt and freebase water solubility and also the pK_a of the free base and acidic salt former are inputs to the model. The pK_a of miconazole and also sertraline have already been discussed while the pK_a of all acidic formers were calculated using Marvin Sketch (version 5.2.6). The pK_a values of acids used in the calculations are given in Table III. In the original model, a semi-empirical method was used to calibrate the effect of different excipients on the micro-environmental pH, namely measuring the pH of an excipient slurry directly and calibrating the model parameters to reproduce the pH. In this case, the solid–liquid and acid–base equilibria were input directly in the model. A solubility of 28.3 g/ 100 ml H_2O (0.58 mol/L solution) (26), and pK_a of 12.319 (27) were used in the model for TSPd (only the 1st ionization constant was used for simplicity). One of the main assumptions in the model is that the solid state disproportionation is solution (water) mediated, and that the API and TSPd dissolve to their respective solubility levels in this water layer. Previously, the water volume was estimated from moisture sorption measurements and this approach was also implemented here, with some modification.

The results from the model are given in Table III. Using the raw moisture sorption data, the model predicts all the compounds should completely disproportionate, clearly overestimating the effect. One hypothesis for the overestimation was due to the large water uptake used in the model. As the blends of API and TSPd were stored in a dry environment before the stress test, much of the weight gain could be due to rehydration of TSPd which forms multiple hydrates (8). During rehydration of TSPd, most of this water would be incorporated in the crystal lattice and would not be available to mediate the disproportionation. Due to this observation, we attempted to scale the water content in the model to get more sensitivity of the predictions, and these results are also given in the Table III. After scaling the water content by 0.0025x, which brings the moisture sorption more in line with the pure salts, we find the model predictions are in good qualitative agreement with experimental data for both miconazole and sertraline salts. The correct prediction of the relative rank ordering of the disproportionation tendency is encouraging support for the model assumptions.

One of the key discussion points of this work is the effect of buffering strength of the API to understand the disproportionation extent. This effect is also built in to the model using the acid–base equilibrium and salt and free base solubility, which is possibly one reason why the model is able to capture the effect nearly quantitatively. It should be pointed out that an additional effect, the buffering strength of the excipients was also discussed previously (25), but has not been included in the model and could also play an important role, especially when comparing disproportionation across a range of excipients or formulations.

Considerations for Salt Selection

While it is typically the aim of a salt screen to identify a salt form with high solubility, the risk of undergoing salt-to-free base conversion, which may lead to further physical/chemical instability, will be much greater as the pH_{max} is significantly lower for the more soluble salt form. Although no free base was observed following slurrying for the salts studied, which suggests that the salt by itself should remain its integrity in

terms of ionization state even under high relative humidity, the ionization state of the API may be potentially changed in the presence of excipients in the formulation. Thus the salt with the highest solubility advantage might not be the most ideal candidate for formulation and processing, in particular if unit operations involving water are used. This study has shown that pH_{max} has a significant impact on the extent of disproportionation under controlled conditions (particle size range, temperature and RH). In addition to selecting the optimal salt form, it is also important to understand how selection of different excipients may also impact disproportionation (24). Moreover, additional factors such as environmental conditions (relative humidity and temperature), and powder particle size also affect how much of the salt converts into free form, as reported in our previous work in salt stability (8).

CONCLUSION

The extent of salt disproportionation was found to be highly dependent on the value of pH_{max}. Thus, for a given compound, salt forms with higher solubility have a lower pH_{max} and subsequently a greater tendency to convert into the free base in the presence of basic excipients. In addition, the buffering capacity of the system also needs to be considered when predicting the relative disproportionation tendency of different salts. It is therefore imperative to balance disproportionation tendency with salt solubility in order to produce a robust formulation that will not be susceptible to changes in the solid state form of the API during processing and storage.

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