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RESEARCH PAPER

# Salt Stability - Effect of Particle Size, Relative Humidity, Temperature and Composition on Salt to Free Base Conversion

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## ABSTRACT

***Purpose*** The aim of this study was to investigate how factors such as temperature, relative humidity and particle size impact the extent of disproportionation (salt to free base conversion) in powder blends of miconazole, benzocaine or sertraline mesylate salts mixed with a basic additive.

***Method*** Raman spectroscopy was used to quantitate the extent of disproportionation. The data was further analyzed by multivariate analysis with partial least squares (PLS) modeling.

***Results*** It was found that salt disproportionation was significantly influenced by % weight gain due to moisture sorption both in terms of the kinetics and the conversion extent, suggesting a solution-mediated reaction. Temperature plays an important role in impacting the value of $pH_{max}$ which in turn has a significant correlation to the amount of free base formed. The particle size and drug: additive ratio were also found to influence the extent of disproportionation.

***Conclusions*** This study shows that the extent of salt disproportionation is influenced by multiple factors and the application of PLS modeling demonstrated the feasibility of utilizing multivariate analysis to generate a predictive model for estimating the extent of conversion and thus may serve as a tool for risk assessment.

**KEY WORDS** disproportionation · multivariate analysis · Raman spectroscopy · salt · storage conditions

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## INTRODUCTION

Salt formation is a common strategy to improve the physicochemical properties of ionizable active pharmaceutical ingredients (APIs), including enhancing aqueous solubility and dissolution rate (1) as well as solid state properties (2, 3). Consequently, it is usually undesirable if the salt converts to the free form, a process often referred to in the pharmaceutical literature as disproportionation (4). Although relatively few cases of salt disproportionation have been reported, conversion of the salt to the free form can have serious ramifications on product performance (5–9), and thus it is important to understand the fundamental factors underlying this phenomenon.

The $pH_{max}$ is the most critical parameter as it defines the pH which must be exceeded (for the salt of a weak base) for disproportionation to occur. For a weak base that forms salts, $pH_{max}$ is given by Eqn. 1.

$$pH_{\max} = pK_a + \log\left[\frac{S_{FB}}{S_{MS}}\right] \quad (1)$$

where $S_{MS}$ is the salt solubility, $S_{FB}$ is the solubility of the free base and $pK_a$ is the acid dissociation constant for the base. The value of $pH_{max}$ indicates the pH point where solubility is maximized with an equilibrium formed between ionized and unionized drug in solution with both the crystalline base and the crystalline salt. Conversion from the salt to the free base can only occur when the pH is above the value of $pH_{max}$; therefore, this is a critical parameter to determine. From Eqn. 1 it is apparent that, for a given basic compound, a salt with a higher solubility would have a lower $pH_{max}$ value and thus be at higher risk for disproportionation relative to a less soluble salt. Thus as the pH threshold for disproportionation becomes lower, conversion to free form becomes more likely.

This outcome has been observed experimentally for different salts of the same compound (10, 11).

When comparing different compounds, and the impact of different formulation components, the situation becomes more complex. For example, in a recent study probing the excipient-induced disproportionation behavior of benzocaine and miconazole mesylate salts, it was found that the two salts underwent different extents of disproportionation when mixed with a given excipient, even though the salts had very similar $pH_{max}$ values (10). Merritt *et al.* studied disproportionation of a number of different salts in various formulations. Qualitative agreement was obtained between experimental outcomes and model predictions for a model based on $pH_{max}$ values and excipient slurry pH values, but it was concluded that additional factors need to be considered in order to improve the model (11). John *et al.* (12) found that the slurry pH of the excipient was a poor indicator of the disproportion-inducing tendency of a given excipient and proposed that the excipient proton accepting and buffering capacity were important factors. Thus disproportionation reactions in blends are clearly complex and are still not completely understood.

While the significance of $pH_{max}$ has been recognized (4, 6, 9–14), the impact of different storage conditions (such as temperature and relative humidity) and formulation aspects such as particle size and drug to excipient ratio on the extent of disproportionation has not been widely reported. A study by Merritt *et al.* showed that storage at higher relative humidities increased the amount of free base formation (11) while another study by Christensen *et al.* suggested that higher temperature and relative humidity promoted the conversion of atorvastatin calcium to free acid (15). The goal of the current study was thus to explore the relative impact of the aforementioned factors on the disproportionation of three mesylate salt forms (benzocaine, miconazole and sertraline) blended in powder form with a basic compound. Disproportionation of the mesylate salts of each of these compounds have been studied previously (9, 10). While benzocaine and miconazole mesylate salts underwent disproportionation when mixed with several basic compounds, sertraline mesylate was only observed convert to the free form in the presence of tribasic sodium phosphate dodecahydrate (9, 10). Therefore tribasic sodium phosphate dodecahydrate was selected as the model base for this study. Multivariate analysis was used to help deconvolute the impact of the various factors on the extent of disproportionation; multivariate analysis has been found to be useful in understanding the properties of salts (16–18). For this study, partial least squares (PLS) modeling was employed to assess the importance of each variable and to derive a prediction model describing the relationships between the variables (properties/descriptors) and the extent of disproportionation.

## MATERIALS AND METHODS

### Materials

Miconazole, benzocaine, magnesium chloride hexahydrate, and magnesium nitrate hexahydrate were purchased from Spectrum Chemical (Gardena, CA). Sertraline HCl was a gift from Pfizer Inc (Groton, CT). Sertraline free base was prepared by dissolving sertraline HCl in a 1/1v/v methanol/water mixture, followed by titrating the solution to a pH above 11.5 with 0.5N NaOH. Tribasic sodium phosphate dodecahydrate (TSPd), sodium bromide, sodium chloride and potassium iodide were obtained from Mallinckrodt Chemical (Phillipsburgh, NJ). Potassium carbonate and cobalt chloride hexahydrate were purchased from VWR international (Radnor, PA).

### Salt Formation Procedure

The method of Guerrieri and Taylor was used to prepare benzocaine and miconazole mesylate salts (10). Sertraline mesylate was formed by adding an equal molar amount of 2M solution of methanesulfonic acid in water to an acetonitrile solution containing sertraline free base, followed by stirring overnight and harvesting the solids using suction filtration. The remaining solids were dried under vacuum at 40°C overnight to remove residual solvents. Thermogravimetric analysis was performed on the salts to determine the existence of hydrate or solvates using a Seiko TGA220 (Seiko instruments, Inc., Japan) with a heating rate of 10°C/min from 25°C to 250°C.

### Solubility Measurement

The solubility of the free base and salt forms of each compound was obtained by measuring the concentration of the saturated solution, which was obtained by stirring excess powder in water for 72 hours at 10, 25 and 40°C. The supernatant was obtained by ultracentrifugation at 40,000RPM (equivalent to 274,356×G) in an Optima L-100 XP ultracentrifuge equipped with a SW41Ti rotor (Beckman Coulter, Inc., Brea, CA) followed by filtration through a 0.2 μm syringe filter (the first 3 mL of filtrate was used to pre-saturate the filters and then discarded). Concentrations were measured using a Waters Alliance 2690 high performance liquid chromatography (HPLC) with a 4.6× 100 mm Symmetry Shield RP8 3.5 μm column (Waters Chromatography, Milford, MA). The mobile phases for benzocaine, miconazole and sertraline consisted of a mixture of acetonitrile and pH 2.25 phosphate buffer with compositions of 60/40, 45/55 and 40/60 respectively. The detection wavelength was 230 nm for sertraline and miconazole and 287 nm for benzocaine. The injection volume was 100 μL and the

flow rate was 1 mL/min. Linear calibration curves were obtained by plotting the area under the curve as function of concentration with correlation coefficients ($R^2$) better than 0.999 obtained. Samples were diluted accordingly if the concentration exceeded the linearity range. Powder X-ray diffraction (PXRD) patterns were obtained for sertraline mesylate before and after stirring in water by using a Shimadzu XRD-6000 (Shimadzu Scientific Instruments, Columbia, MD) equipped with a Cu-$K_\alpha$ source and set in Bragg-Brentano geometry. The scan range was set between 5 and 35° (2θ), and the scan speed was set to 4°/min with a 0.04° step size. For benzocaine and miconazole mesylate, solubility values at 25°C have been reported in the literature (10) and are given in Table I. The solubility values at 10 and 40°C were obtained using the same method as for sertraline mesylate. The pH of the filtered saturated solution of each salt was measured using a Mettler Toledo Seven Easy pH meter (Columbus, OH).

## Sample Preparation

The powders (both salts and excipient) were sieved and two ranges of particle size (<53 μm and 53–150 μm) were selected for this study. Prior to blending of the salt and excipient, all materials were stored individually over calcium sulfate (W.A. Hammond Drierite Co. Ltd, Xenia, OH) for 10 days at 25°C. The individual salt was blended with TSPd with the same particle size range in different ratios (50/50 or 25/75 or 75/25 weight ratio) through geometric mixing using a spatula to lightly triturate the powders, in a glove box purged with dry nitrogen to achieve a relative humidity (RH) below 20% RH. The blends were then placed in pre-weighed 1 dram glass vials and stored at different conditions as shown in Table II. Samples were marked with an ID number with samples containing benzocaine mesylate marked with #1–10, miconazole mesylate marked with #11–20 and sertraline mesyalte marked with #21–30. All samples were prepared in triplicate. The experimental plan was designed to study the various effects on disproportionation and the experiments are summarized in Table II. Sample vials were taken out periodically for Raman spectroscopic analysis and the weight gain of the samples was monitored over time. For the purpose of studying the kinetics of disproportionation at 57%RH, a separate sample of a powder blend of the salt and TSPd was placed inside of a VGI2000M humidity and temperature control system equipped with $BaF_2$ window (Surface Measurement Systems Ltd, Allentown, PA) allowing Raman spectroscopic measurement simultaneously with exposure to moisture. The Raman spectra were taken automatically every 3 hours for 3 days. Similar powder blends were prepared and the kinetics of moisture sorption at 57% RH was monitored using a Q5000SA dynamic vapor sorption system (TA Instruments, New Castle, DE).

**Table I** Summary of relevant properties of free base and salts. The unit of solubility is molarity (M)

| Material | $pK_a$ (25°C) | $pK_a$[a] (40°C) | $pK_a$[a] (10°C) | Solubility (M,25°C) | Solubility (M, 40°C) | Solubility (M, 10°C) | $pH_{max}$ (25°C) | $pH_{max}$ (40°C) | $pH_{max}$ (10°C) | Salt pH at saturation (2.5°C) | Salt pH at saturation (40°C) | Salt pH at saturation (10°C) | Raman shift ($cm^{-1}$) | $R^2$ of calibration |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Benzocaine | 2.8 | 2.70 | 2.90 | $5.8 \times 10^{-3}$ [b] | $1.5 \times 10^{-2}$ | $3.8 \times 10^{-3}$ | - | - | - | - | - | - | 1681 | - |
| Benzocaine Mesylate | - | - | - | 0.188[b] | 0.579 | 0.158 | 1.30[b] | 0.85 | 1.28 | 1.12[b] | 0.70 | 1.20 | 1722 | 0.9993 |
| Miconazole | 6.9 | 6.60 | 7.20 | $2.40 \times 10^{-6}$ [c] | $2.40 \times 10^{-6}$ [c] | $2.40 \times 10^{-6}$ [c] | - | - | - | - | - | - | 1507 | - |
| Miconazole Mesylate | - | - | - | 0.688[b] | 1.57 | 0.61 | 1.44[b] | 0.78 | 1.80 | 1.47[b] | 1.01 | 2.74 | 780 | 0.9928 |
| Sertraline | 9.06[c] | 8.65 | 9.47 | $1.45 \times 10^{-5}$ | $2.61 \times 10^{-5}$ | $1.44 \times 10^{-5}$ | - | - | - | - | - | - | 2785 | - |
| Sertraline Mesylate | - | - | - | $4.07 \times 10^{-2}$ | 0.862 | $1.92 \times 10^{-2}$ | 5.68 | 4.13 | 6.35 | 5.55 | 4.04 | 5.85 | 3010 | 0.9981 |

[a] $pK_a$ values at 10 and 40°C are approximated based on the literature method described by Perrin (19)

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

[c] Value obtained from Box and Comer (40)

**Table II** Sample preparation and storage conditions

| Salt | ID# | Particle size (μm) | % drug load (w/w) | T (°C) | RH% | Saturated Salt solution | Particle size effect | Composition effect | RH effect | T effect |
|---|---|---|---|---|---|---|---|---|---|---|
| Benzocaine mesylate (ID# 1–10) or Miconazole mesylate (ID# 11–20) or Sertraline mesylate (ID# 21–30) | 1, 11, 21 | < 53 | 50 | 25 | 57 | Sodium Bromide | × | | | |
| | 2, 12, 22 | 53–150 | 50 | | 57 | | × | × | × | × |
| | 3, 13, 23 | | 75 | | 57 | | | × | | |
| | 4,14, 24 | | 25 | | 57 | | | × | | |
| | 5, 15, 25 | | 50 | | 75 | Sodium Chloride | | | × | |
| | 6,16, 26 | | | | 69 | Potassium Iodide | | | × | |
| | 7, 17, 27 | | | | 43 | Potassium Carbonate | | | × | |
| | 8, 18, 28 | | | | 33 | Magnesium Chloride | | | × | |
| | 9, 19, 29 | | | 40 | 55 | Cobalt Chloride | | | | × |
| | 10, 20, 30 | | | 10 | 57 | Magensium Nitrate | | | | × |

### Disproportionation Quantification

Raman spectroscopy was utilized to quantify the extent of disproportionation for the three mesylate salts as described in previous publications (9, 10). A RamanRxn1-785 Raman Spectrometer (Kaiser Optical Systems, Inc., Ann Arbor, MI) with a 785 nm excitation laser with 200 mW power equipped with non-contact fiber optic MR probe with spot size of 150 μm was utilized in this study. Raman spectra were obtained for the free bases and the salts and the unique Raman shift was identified for each of the material as summarized in Table I. Calibration data for each free drug/salt pair was obtained by plotting the peak intensity ratios of a unique Raman shift for the free base and mesylate salt form as function of molar ratios, and the $R^2$ value for the linear fit for each calibration curve is given in Table I. The calibration curves were then utilized to estimate the amount of disproportionation based on the peak intensity ratio calculated from Raman spectra obtained for the samples.

### Multivariate Analysis

Statistical analysis was conducted using the multivariate analysis software SIMCA-P+12.0 (Umetrics AB, Umeå, Sweden). The X variables in the dataset (the descriptors) include $pH_{max}$, salt solubility, particle size, composition (% drug load), temperature and % weight gain, while the Y variable is the percent conversion (the extent of disproportionation). All variables were auto scaled by unit variance prior to statistical operations. The quantitative relationship between the descriptors and extent of disproportionation was established using partial least squares (PLS) modeling. The analysis was performed separately on benzocaine mesylate (sample ID#1–10), miconazole mesylate (#11–20) and sertraline mesylate (#21–30).

## RESULTS

All salts are anhydrous based on themogravimetric analysis and crystalline based on PXRD data. The solubility values for the free bases and salt forms are summarized in Table I. The exact solubility of miconazole free base could not be determined due to the inherently low UV response of miconazole as well as its low aqueous solubility. Saturated miconazole solutions at all three temperatures exhibited similar HPLC response in terms of the area under the curve and it is thus assumed that there is no significant difference in the intrinsic solubility of miconazole at the different temperatures selected for this study. The acid dissociation constants ($pK_a$) at 10°C and 40°C were approximated based on publication by Perrin (19). The $pH_{max}$ values were then calculated based on the values of $pK_a$, free base solubility and salt solubility at the temperature of interest (Table I) using Eqn. 1. As seen from Table I, miconazole free base was the least soluble while benzocaine was the most soluble free form. However, miconazole mesylate is more soluble than benzocaine mesylate, while sertraline mesylate is the least soluble salt. Benzocaine is the weakest base while sertraline is the strongest. The interplay of these factors leads to miconazole and benzocaine having similar and low $pH_{max}$ values around pH 1, while sertraline has a much higher value around pH 5.

Throughout the duration of the storage period at the different relative humidity and temperature conditions, no deliquescence was observed. Thus the abrupt increase in weight gain characteristic of the deliquescence phenomenon was absent in the moisture sorption profiles and the samples remained as free flowing powders. The disproportionation kinetics of benzocaine mesylate in the presence of TSPd (50/50 w/w) at 57% RH and 25°C over a 3 day period is shown in Fig. 1 whereby the corresponding moisture sorption profile has been overlaid in the same plot. It is clear that the disproportionation process is quite rapid under these experimental conditions whereby the

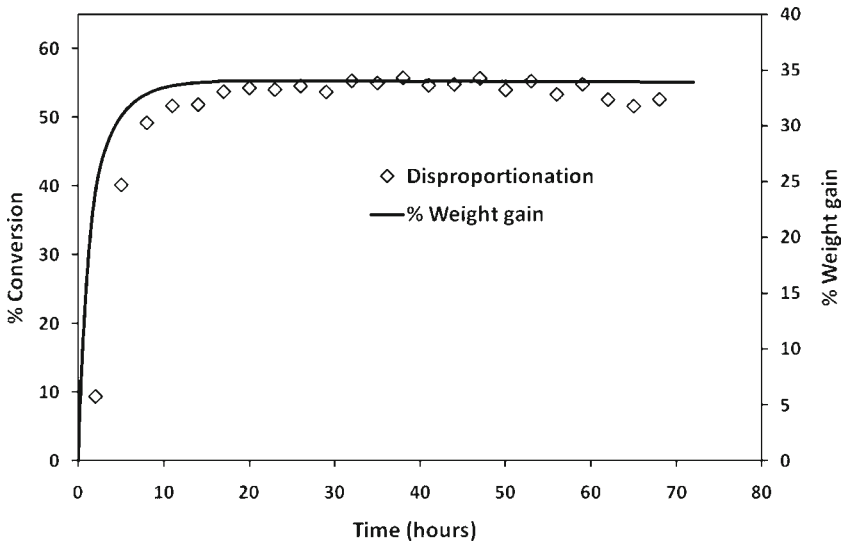


**Fig. 1** Disproportionation kinetics of benzocaine mesylate in the presence of TSPd (both particle sizes <53 $\mu$m) at 57% RH and 25°C.

extent of disproportionation reached a plateau within less than 1 day. Interestingly, the moisture sorption profile approximately mirrors the disproportionation kinetics suggesting that the sorption of moisture plays a key role in the disproportionation process. It should be noted that the large amount of water sorbed can be mainly attributed to the rehydration of TSPd which was desiccated prior to blending.

In order to study the impact of the various factors summarized in Table II on the extent of the disproportionation reaction, the amount of free base was quantified over time periods of up to 14 days as shown in Fig. 2(a) for benzocaine mesylate samples. For all the conditions tested, equilibration was fast and a plateau was reached within 4 days. The corresponding weight gain due to moisture sorption, shown in Fig. 2(b), also showed the attainment of a plateau value within this timeframe. Similar profiles (data not shown) were observed (equilibrium for both weight gain and disproportionation was reached in less than 4 days) for miconazole mesylate and sertraline mesylate samples.

The plateau disproportionation values at 14 days storage were used to evaluate the impact of the various factors under investigation on the extent of free base formation. Figure 3 shows the relationship between % conversion to the free base and % relative humidity (%RH) or the amount of moisture gained by the system as a result of storage at a controlled relative humidity/temperature condition for the three salts (ID# 2, 5–8 for benzocaine mesylate, 12, 15–18 for miconazole mesylate and 22, 25–18 for sertraline mesylate). The extent of disproportionation increased as a function of % RH or % weight gain and the relationships appeared to be linear for benzocaine and miconazole mesylate. No conversion was observed for sertraline mesylate in the presence of TSPd at 33% and 43% RH; above these RHs, the trend appears to be linear although there are only three data points to base this inference on.

The effect of particle size (sample ID# 1–2, 11–12 and 21–22) on disproportionation is shown in Fig. 4 with the % weight gain also plotted using a secondary y-axis. Unsurprisingly, samples with a smaller particle size range were found to undergo a greater extent of disproportionation as well as a higher % weight gain, in all cases, which may be attributed to their higher surface area per unit mass relative to powders containing larger particles. This leads to a greater area of contact with both water and TSPd and is with consistent with disproportionation occurring at the surface of the salt particles. For miconazole and sertraline salts, the smaller particle size fraction has approximately twice the extent of conversion to the free base, while the impact of particle size is even more pronounced for benzocaine. The composition (% drug loading) effect is illustrated in Fig. 5 (samples ID # 2–4, 12–14, 22–24) with Fig. 5(a) showing the extent of conversion as a function of % drug load while the relationship between % weight gain and extent of disproportionation is demonstrated in Fig. 5(b). Higher conversion was observed for samples containing a larger amount of excipient, and this was attributed to higher exposure of the salt surface to the surface of the excipient, as well as enhanced moisture sorption with increasing excipient.

The impact of temperature (sample ID# 2, 9–10 for benzocaine mesylate, #12, 19–20 for miconazole mesylate, #22, 29–30 for sertraline mesylate), is summarized in Fig. 6 where the % conversion is plotted in turn against temperature, % weight gain and $pH_{max}$ since the latter two factors are influenced by temperature. Figure 6(a) shows a general trend that the samples exposed to lower temperatures have a lesser extent of disproportionation, although, for benzocaine mesylate, the extent of conversion at 10°C was found to be similar to that at 25°C. The extent of conversion plotted as function of weight gain is presented in Fig. 6(b). The samples with the lowest weight gain, those samples at 40°C, showed the greatest

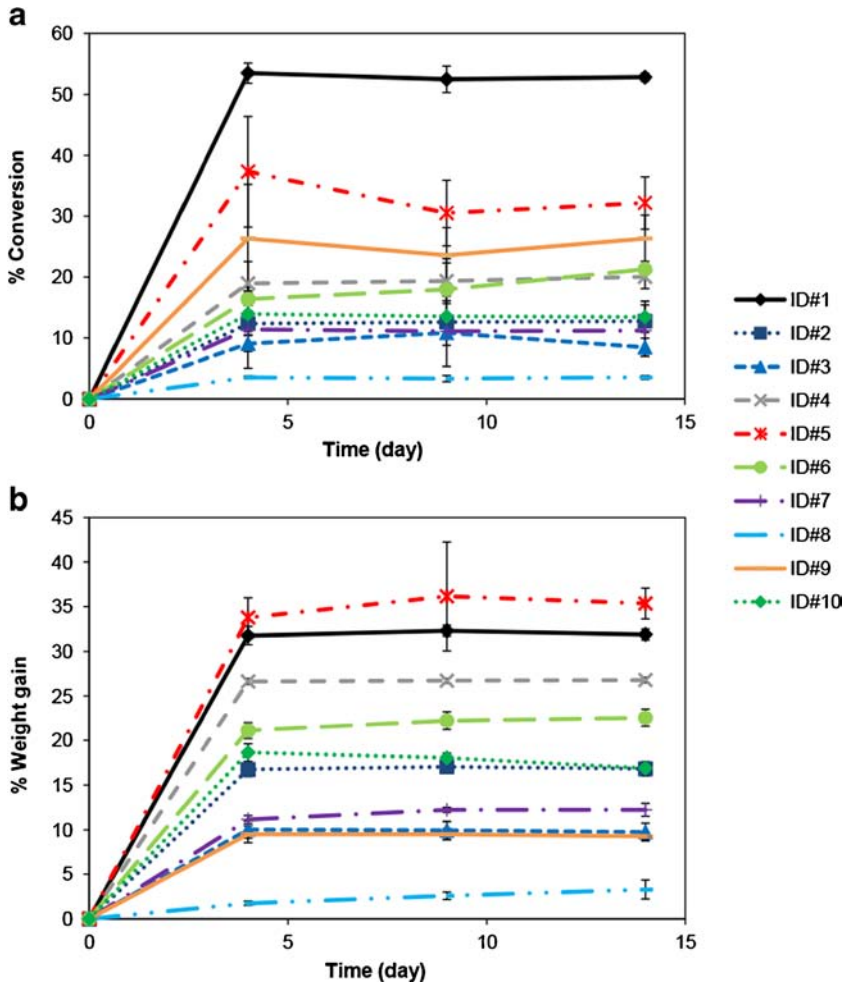


**Fig. 2** Extent of disproportionation (% conversion) (**a**) and % weight gain (**b**) as function of time for samples containing benzocaine mesylate (sample preparation and conditions are as described in Table I).

extent of disproportionation, therefore temperature effects cannot be correlated to increased moisture sorption, as expected since moisture sorption is an exothermic process. In addition, although miconazole mesylate blends at 25 and 10°C had a similar weight gain, they were found to undergo different extents of conversion. Better correlations for the three salts were obtained by plotting disproportionation extent as function of $pH_{max}$, calculated from the temperature dependence of the solubility values for the salt and the base and $pK_a$ (Fig. 6(c) and (d)).

The results of the multivariate analysis on each of the sample sets are summarized in Figs. 7–8 and in Table III. The observed *versus* predicted plot for the extent of disproportionation in miconazole mesylate systems is shown in Fig. 7. The miconazole mesylate PLS model consisted of three components with a $R^2$ of 0.97 and $Q^2$ of 0.90; for benzocaine mesylate and setraline mesylate, acceptable models were also generated and model parameters for all systems are summarized in Table III. $R^2$ is the percent of variation of the training set that is explained by the model and indicates how well the model fits the data whereby an $R^2$ value close to 1 indicates a good measure of fit, whereas $Q^2$ is the percent of variation predicted by the model based on cross validation and $Q^2$ with values greater than 0.5 suggesting good predictivity (20). The root mean square error of the estimation (RMSEE) was acceptable for all systems, ranging from 2 to 10% which is comparable for other solid state transformations modeled using PLS (21–23). The significance of each descriptor is demonstrated in VIP plot (variable importance in the projection) (Fig. 8).

## DISCUSSION

### Impact of Relative Humidity and Moisture Sorption on Disproportion

Disproportionation is a process whereby the ionization state of the molecule is changed. Because changing the ionization state involves proton transfer, water must be present to facilitate the process. No bulk moisture was observed during storage at different relative humidities in this study, which indicates that the humidity conditions were below any mutual deliquescence

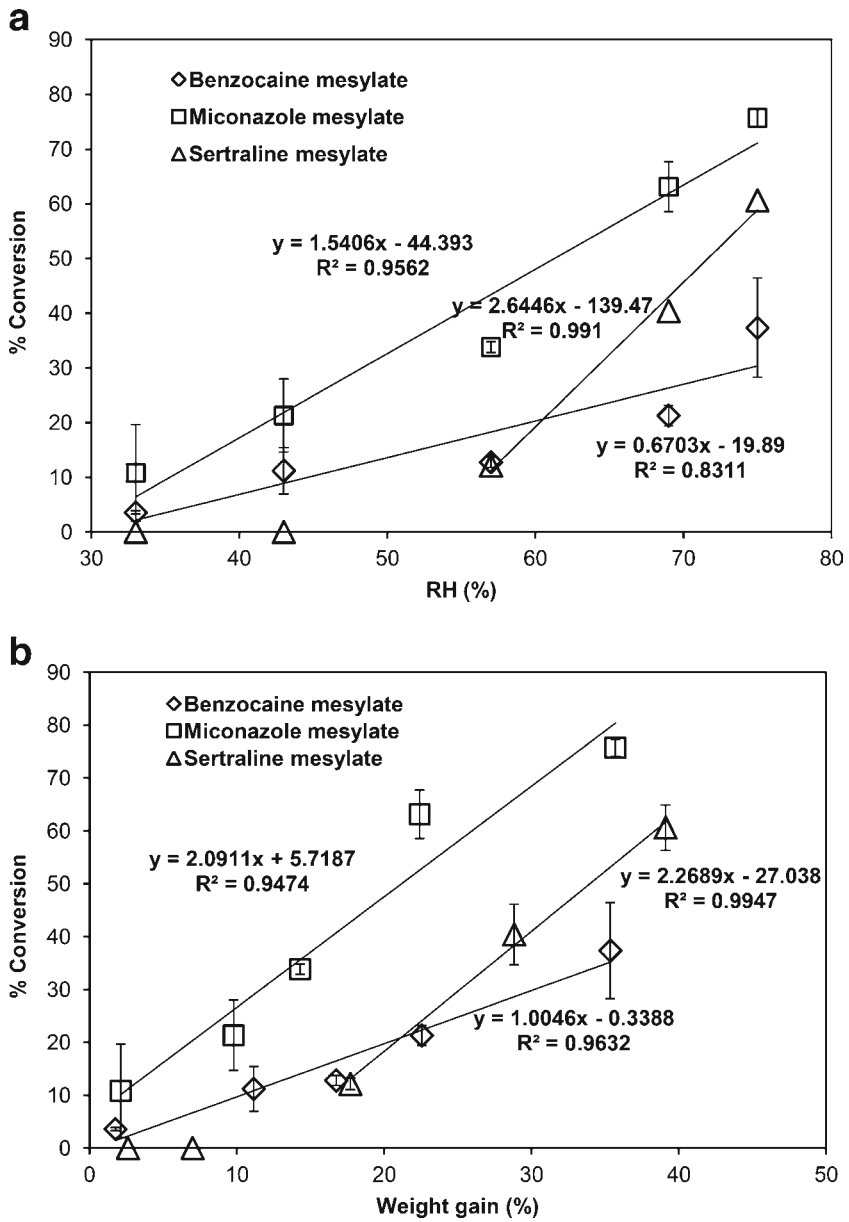


**Fig. 3** Effect of % RH (**a**) or % weight gain (**b**) due to moisture sorption on extent of disproportionation.

relative humidity (MDRH) of the salt and additive (24, 25). Therefore, it is apparent that the presence of bulk water is not necessary to facilitate the process of disproportionation. For the samples studied, moisture associated with the samples is likely to be present either as adsorbed moisture (highly crystalline salts of miconazole, benzocaine and sertraline), or as water of hydration (TSPd, which will also have adsorbed water). Even though only a small amount of water adsorbs onto the surface of the crystalline solid, the adsorbed water may form localized regions on the surface which contain mobilized species of the solid (26–29). The mobilized solid may therefore be activated and interact with other species in the water layer of an adjacent surface (30) and several studies have found that the small amount of water adsorbed in the powder system may be sufficient to promote chemical instability (31–34). The role of adsorbed water molecules is thus of great significance to the stability of solid state pharmaceutical formulations. The role of sorbed water in the disproportionation process is shown schematically in Fig. 9. The importance of moisture sorption on disproportion is exemplified by Fig. 1 which shows the relationship between the kinetics of moisture uptake and the kinetics of disproportionation for benzocaine mesylate. The kinetics of each process closely follows one another, and the slight discrepancy can be explained by the separate instrumentation and therefore slight variations in sample presentation, used to obtain the two data sets.

Further evidence for the role of water can be found in, Fig. 3(b) where it can be seen that linear regression of the data yields a y-intercept close to zero; in other words, no disproportionation is expected at zero percent RH where no

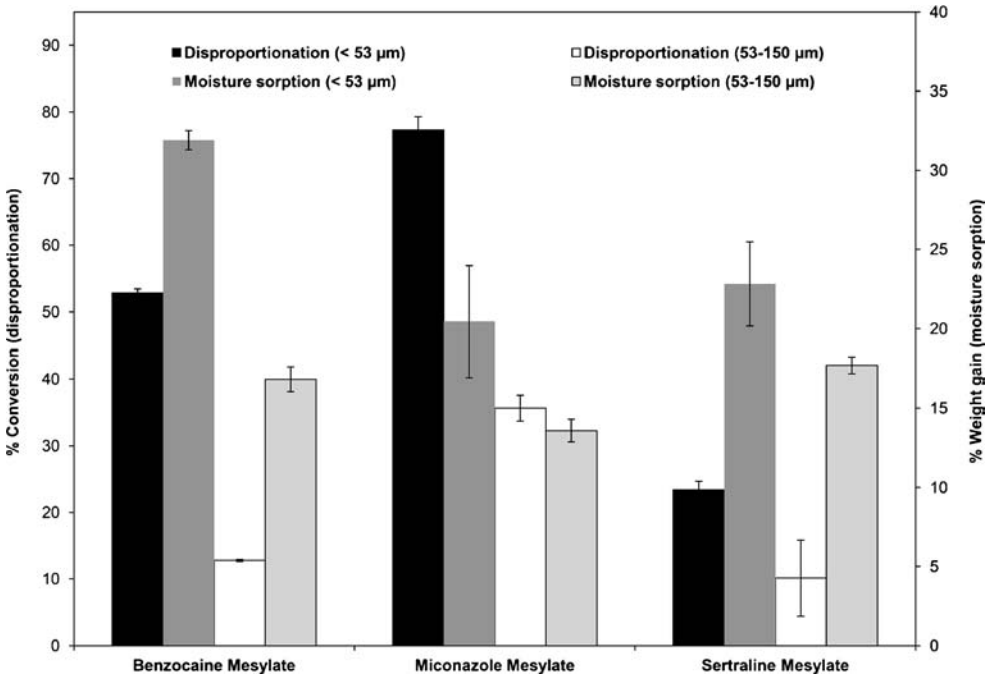


**Fig. 4** The influence of particle size and water uptake on the extent of disproportionation.

moisture is adsorbed. In the case of sertraline mesylate, no disproportionation was observed for samples at 33 or 43% RH, most likely because any disproportionation was below the limit of detection. The role of moisture-mediated surface interaction is also readily highlighted by considering the effect of particle size and blend composition (Figs. 4 and 5). The specific surface area of powders with smaller particle sizes is obviously greater, allowing more extensive interaction between the salt and excipient as well as higher extent of moisture adsorbed onto the surface of the solid, which would be expected to enhance the disproportionation process as observed experimentally. Likewise, a higher mass fraction of the basic additive in the powder blends (composition effect) also provides a higher exposure of the salt to the disproportionating agent. It is worth noting that extrapolated values for y (% conversion) for 100% drug loading based on the linear regression analysis results shown in Fig. 5(a) are close to zero for all three salts, highlighting the role of the basic additive in promoting disproportionation.

## Influence of Temperature and $pH_{max}$

It is generally accepted that temperature may influence physicochemical reactions in terms of rate and extent and that an increase in temperature often promotes the reaction process, in particular for reaction in powders, where mobility is limited, and increased temperature promotes mobility. For the disproportionation reaction, additional factors that are impacted by temperature need to be considered and deconvoluted. Having highlighted the importance of moisture, at first glance it is counterintuitive that the extent of disproportionation increases with temperature while the moisture content of the system decreases, as expected (35–37). However, if the role of water as a mediator of molecular mobility is considered, in combination with the observation that the solubility of the salts increases with temperature, it becomes easier to rationalize the results. The increase in solubility of the salt has two effects; there is more salt mobilized by surface adsorbed moisture, and based on Eqn. 1, $pH_{max}$ may be altered. According to Eqn. 1, both $pK_a$ and the solubility ratio of the free base to salt impact the value of $pH_{max}$. $pK_a$ decreases as temperature increases (see below) which reduces the value of $pH_{max}$. In addition, since the salt solubility increased more with temperature than the base solubility (Table I), the value of $pH_{max}$ is further decreased. The significant decrease in $pH_{max}$ may thus be used to rationalize the higher extent of conversion for samples at 40°C, despite having a lower extent of moisture sorption. The $pH_{max}$ values for benzocaine mesylate at 10 and 25°C are similar (1.28 and 1.30 respectively) which provides an explanation for the comparable extent of conversion observed for this system. Figure 6(c) and (d) show that there is a good correlation between $pH_{max}$ and disproportionation extent, reiterating the importance of $pH_{max}$ in impacting changes in the ionization state of a salt.

The influence of temperature can also be illustrated by considering its impact on the disproportionation equilibrium constant, $K_{eq}$, for the reaction described in Eqn. 2 and shown schematically in Fig. 9:

$$MS_{(s)} \rightleftharpoons B_{(s)} + H^+ + A^- \quad (2)$$

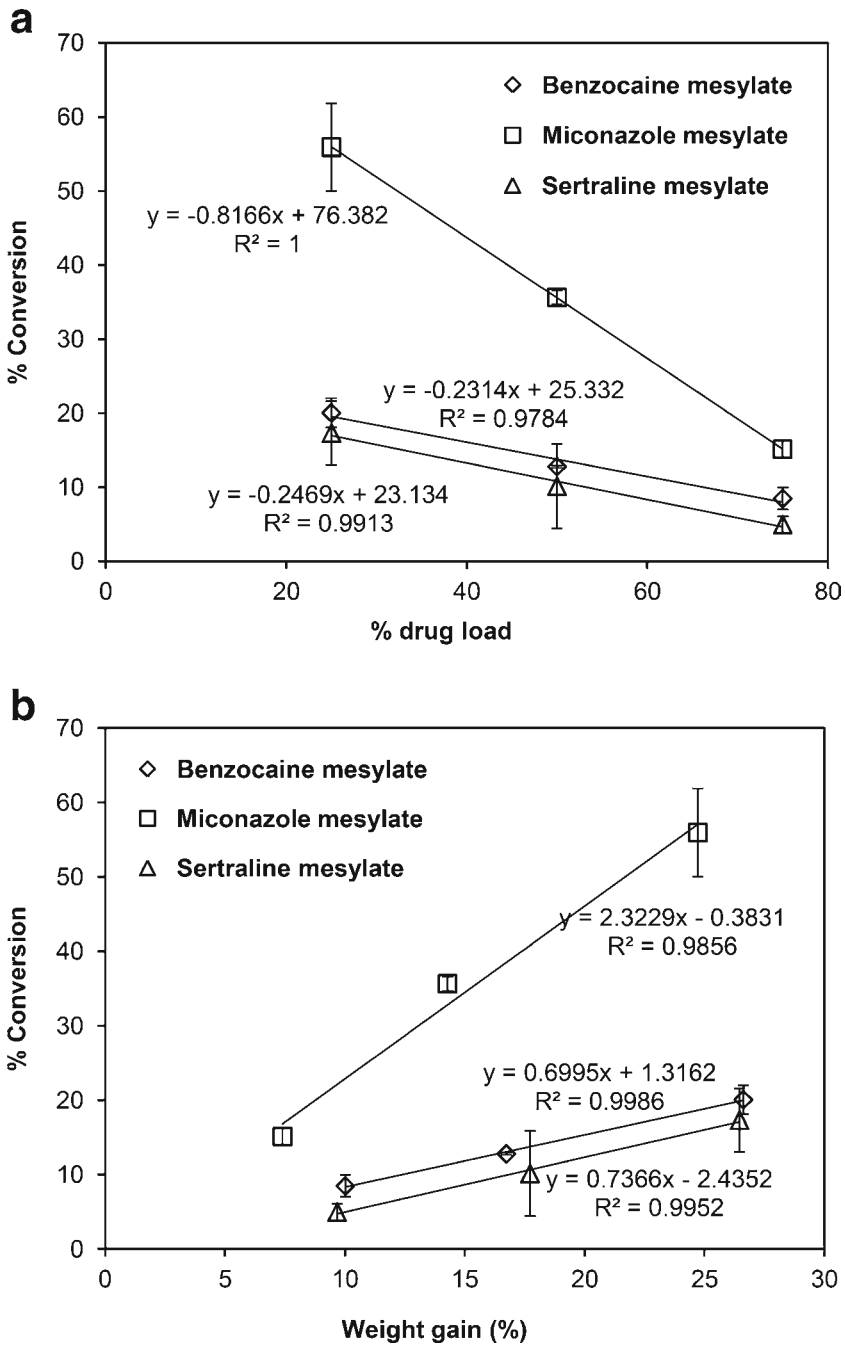


**Fig. 5** The effect of composition (% drug load) from sample ID# 2–4, 12–14, and 22–24 plotted with conversion (%) as function of **a**) composition (% drug load) and **b**) % weight gain.

As discussed by Merritt *et al.* (11), for a solution mediated reaction in the presence of a solid phase, $K_{eq}$ can be written as:

$$K'_{eq} = [H^+][A^-] = K_a \cdot \frac{S_{MS}^2}{S_{FB}} \tag{3}$$

The acid dissociation constant for the base and the solubilities of the salt and free base are influenced by temperature and thus Eqn. 3 can be rewritten as Eqn. 4, where the temperature dependence of these terms is shown:

$$K'_{eq} = K_{eq} \times \phi \times e^{\frac{(\Delta H_{FB} - 2\Delta H_{MS})}{R}\left(\frac{1}{T} - \frac{1}{T_0}\right)} \tag{4}$$

In Eqn. 4, $\varphi$ denotes a constant influencing the $K_a$, and $\Delta H_{MS}$ and $\Delta H_{FB}$ represent the change in enthalpy for dissolving the salt form and free base respectively. For a temperature change of 15 K or less, the constant $\varphi$ can be approximated for monovalent bases by Eqn. 5, assuming a linear relationship between $pK_a$ and temperature (19).

$$\phi = 10^{\left(\frac{pK_a - 0.9}{T}\right)\Delta T} \tag{5}$$

It is evident that $\varphi$ is larger than 1 for a positive change in temperature (correspondingly, $\varphi$ <1 for a negative

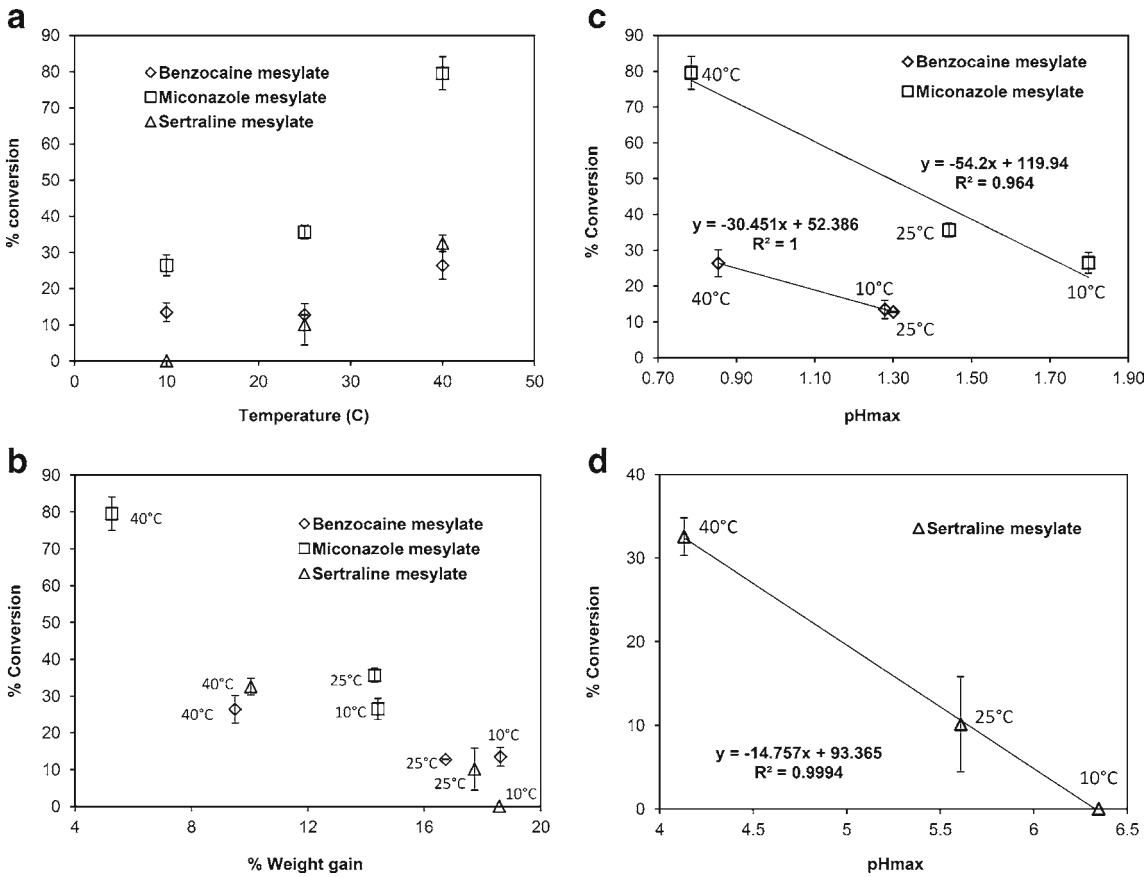


**Fig. 6** Comparison of disproportionation extent for samples stored at 40, 25 and 10°C (sample ID# 2, 9–10 for benzocaine mesylate, sample ID# 12, 19–20 for miconazole mesylate, and sample ID# 22, 29–30 for sertraline mesylate). The relationship between % conversion and temperature or % weight gain are plotted in a) and b) respectively. Figures c and d express the relationship between % conversion and $pH_{max}$ for benzocaine/miconazole mesylate and sertraline mesylate respectively.

change in temperature), which means that $K'_{eq.}$ increases with an increase in temperature due to the temperature dependence of the acid dissociation constant. Furthermore, assuming $(\Delta H_{FB} - 2\Delta H_{MS})$ is negative, the third term in Eqn. 4 also becomes greater than 1 as the temperature increases. The compounding influence of the temperature

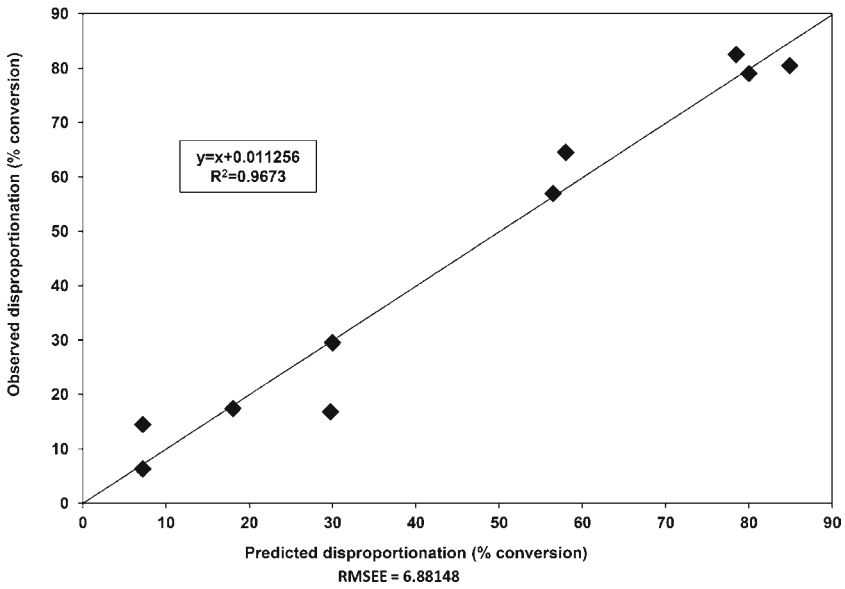


**Fig. 7** Observed *versus* predicted percent conversion of miconazole mesylate sample sets.

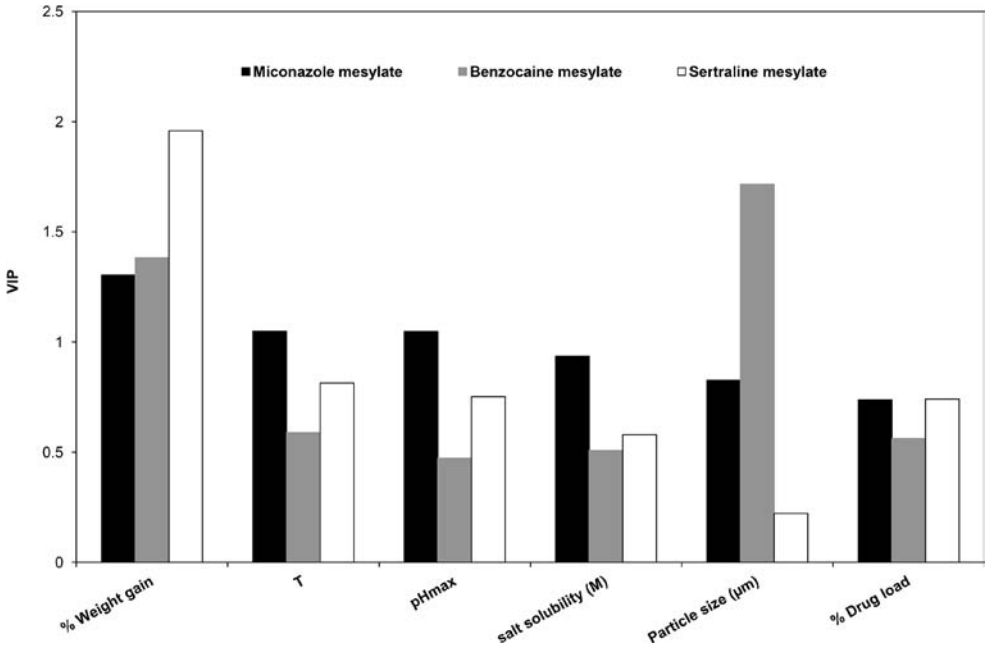


**Fig. 8** Variable of importance in the projection (VIP) plot from the PLS models of all three salts.

**Table III** Model overview and parameters describing the fit and the linear relationship between observations and predictions obtained through multivariate analysis using PLS

| Salt | Model fit overview | | | |
|---|---|---|---|---|
| | # of components | $R^2$ | $Q^2$ | RMSEE |
| Benzocaine mesylate | 3 | 0.983 | 0.768 | 2.2 |
| Miconazole mesylate | 3 | 0.967 | 0.902 | 6.9 |
| Sertraline mesylate | 3 | 0.898 | 0.558 | 10.1 |

dependence of the acid dissociation constant and the solubility on the value of $K'_{eq.}$ thus explains why the extent of disproportionation is increased with an increase in temperature.

## Multivariate Modeling of Conversion from Salt to Free Form

PLS modeling provides some insight into the relative importance of the different factors in influencing the extent of disproportionation. Figure 8 shows the VIP plot of the descriptors which depicts the level of importance of each X-variable (i.e. the various factors such as $pH_{max}$) with respect to Y (the extent of disproportionation). Descriptors having VIP higher than 0.8 are considered to be important (38); for miconazole mesylate, all terms, except for the descriptor "% drug load" which has a slightly lower value of 0.74, are of significance. It is therefore apparent the weight gain, temperature and $pH_{max}$, having VIP >1, have the most influence on the Y variable. Some variations were observed in the models developed for benzocaine mesylate and sertraline mesylate, indicating different levels of importance for each descriptor for the different salts. For benzocaine mesylate, particle size appeared to be of greatest significance in influencing the Y variable; nevertheless, for all the salts, % weight gain was a prominent factor influencing the extent of disproportionation.

## Formulation Considerations

The presence of basic excipients in a solid state formulation has been shown to induce disproportionation of the salts of weak bases and it has been observed that different excipients may induce different level of conversion (10–12). Disproportionation may be avoided by incorporating neutral or acidic excipients in the formulation of the basic salt (6, 39); however, it may not always be feasible to change formulation due to the limited selection of excipients. Furthermore, if the chosen salt form from the screening process has higher propensity to disproportionation due to its inherent properties (low $pH_{max}$ and buffering capacity), it may be unavoidable to have some

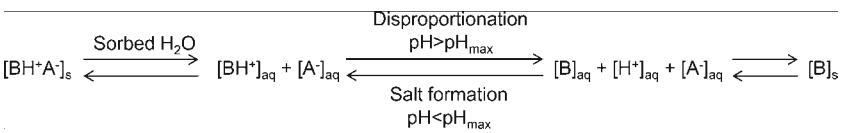


**Fig. 9** Illustration of disproportionation and salt formation processes.

extent of disproportionation occurring in the formulation; indeed there are commercial formulations that have been approved which contain a mixture of free form and salt (7). Clearly, given the role of water in mediating disproportionation, it may be expedient to avoid the use of certain unit operations that involve bulk water such as wet granulation. Furthermore, different packaging design strategies, such as a blister pack, may be considered to reduce the likelihood of disproportionation during storage. Furthermore, since it appears possible to build a predictive model for the extent of disproportionation, this approach could be used to make inferences about the likely impact of a change in storage conditions or formulation factors.

## CONCLUSIONS

The impact of various factors on the extent of disproportionation of the mesylate salts of three weak bases to the corresponding free form in powder blends with a basic additive has been elucidated in this study. Conversion of the salt to the free form is rapid in powder blends, being complete within 4 days. A linear relationship was observed between the conversion extent and the weight gain due to moisture sorption, supporting the supposition that the mechanism of disproportionation is a solution-mediated reaction occurring in the surface moisture layer. Increased temperature, through its influence on pKa and salt solubility, plays an important role in lowering the $pH_{max}$ value, which in turn increases the extent of disproportionation in spite of a lower moisture gain at higher temperatures. Particle size and drug: basic additive ratio also influenced the extent of disproportionation. This study thus provides insight into how changing storage conditions or formulation factors may lead to egregious changes in product stability.

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