Pharmaceutical Research, Vol. 26, No. 8, August 2009 (© 2009)
DOI: 10.1007/s11095-009-9918-y

Research Paper

Role of Salt and Excipient Properties on Disproportionation in the Solid-State

Peter Guerrieri[1] and Lynne S. Taylor[1,2]

Received March 30 2009; accepted May 27 2009; published online June 9, 2009

Purpose. Approximately 50% of active pharmaceutical ingredients (APIs) are manufactured and formulated as salts, due to their enhanced dissolution rates or improved solid state properties. It is essential to maintain the appropriate solid state form of the drug during processing and over the lifetime of the product. The aim of this study was to investigate the contributing factors in the process of disproportionation, whereby the salt converts back to the free form of the drug.
Methods. Infrared and Raman spectroscopy were used to detect and quantify the formation of free base in physical mixtures with excipients. The pH-solubility relationships were determined based on measured salt solubilities and properties of the free form.
Results. The mesylate salts of two model pharmaceutical compounds were found to disproportionate to the free base form when physically mixed with certain common basic excipients and exposed to moderate relative humidities. In contrast, the napsylate salts were much more resistant to disproportionation. The napsylate salts had solubilities more than 3 orders of magnitude lower than the respective mesylate salts, and showed little to no detectable formation of free base. The mesylate salts with higher solubilities showed significant levels of conversion to the free base.
Conclusions. It appears that both the solubility and pH_{max} (the pH of a solution where there is saturation of both ionized and unionized species) of the salts, as well as the base solubility, play important roles in determining the susceptibility of salts to disproportionate. The extent of conversion was also affected by excipient properties, including basicity, solubility, physical state and surface area.

KEY WORDS: disproportionation; pharmaceutical salts; pH-solubility; microenvironmental pH; Raman spectroscopy.

INTRODUCTION

One of the most frequent approaches to improving the physicochemical properties of an ionizable compound, particularly properties such as solubility and dissolution rate, is to form a salt. Disproportionation, i.e. reversion of the salt to the unionized form, is extremely undesirable since it will potentially not only change the dissolution rate, but also influence solid-state properties resulting in a physical form with suboptimal chemical or physical stability.

Several examples of the detrimental effects of disproportionation have been reported in the literature. In one case, a decrease in the extent of *in-vitro* dissolution of a tablet formulation containing delavirdine mesylate following storage at accelerated stability conditions was correlated to the formation of the less soluble free base (1). Similarly, a significant loss in potency of tablets containing the maleate salt of a basic drug following stability testing was attributed to conversion of the salt to the free base (2), which had a significantly lower melting point and was shown to volatilize under the storage conditions. Increases in tablet hardness and disintegration times were noted for tablets subjected to accelerated stability testing conditions (3), coinciding with formation of the amorphous free base form of a crystalline hydrochloride salt.

In the amorphous state, the generally lower glass transition temperature of the free form relative to the salt (4) may also provide higher mobility and thus enhanced reactivity. In studies of the chemical stability of amorphous quinapril hydrochloride (5), it was concluded that lyophilization in the absence of pH control produced a mixture of the amorphous salt and free base forms due to volatilization of small amounts of HCl. Reactivity of the API was significantly enhanced in these preparations relative to those adjusted to lower pH values before lyophilization.

For disproportionation of the salt of a weak base to the free form to occur, loss of a proton is necessary, via hydration and possibly transfer to another component. The presence of at least some amount of water is generally unavoidable in pharmaceutical solid formulations, and very minimal amounts of residual water from processing or sorption from the environment are capable of providing a medium for proton transfer. The ability of formulation components to influence disproportionation of a salt to the free form by affecting microenvironmental pH is also well documented. An excellent definition of the term "microenvironmental pH" applicable to its use in this study has been reported (6): 'Although the concept of pH does not apply to solids, the term "microenvironment pH" has been loosely used

[1] Department of Industrial and Physical Pharmacy, School of Pharmacy, Purdue University, West Lafayette, Indiana 47907, USA.
[2] To whom correspondence should be addressed. (e-mail: lstaylor@purdue.edu)

to describe hydrogen ion activity in noncrystalline regions such as adsorbed water layers or water-plasticized amorphous domains'. Microenvironmental pH within sorbed moisture located at surfaces of the salt would be expected to be influenced by excipients possessing acidic/basic functionalities that are in intimate contact.

By performing a study excluding one of each of the formulation components, Rohrs *et al* (1) determined that croscarmellose sodium was responsible for free base formation in the previously mentioned case of delavirdine mesylate. Spectral evidence indicated protonation of the carboxyl groups of croscarmellose sodium, and a direct relationship between moisture content and extent of free base formation was observed. For the case of the maleate salt, Zannou *et al* (2) determined the slurry pH of various formulations susceptible to disproportionation of the API to be greater than the pH_{max} of the salt. Since the active was a weak base, the formulation 'pH' was assumed to have been sufficiently high to cause conversion to the free form. The goal of this study was to investigate the tendency of the mesylate and napsylate salts of miconazole and benzocaine to convert to the free base when blended with a number of basic excipients and stored at moderate relative humidities (RH). Infrared and Raman spectroscopy were used to detect disproportionation of the model pharmaceutical salts in the powder blends.

EXPERIMENTAL MATERIALS AND METHODS

Materials

Miconazole, benzocaine, 2-napthalene sulfonic acid, magnesium stearate, magnesium oxide, tribasic calcium phosphate (TCP) and anhydrous dibasic calcium phosphate (aDCP) were purchased from Spectrum Chemicals (New Brunswick, NJ). Methanesulfonic acid was supplied by Sigma-Aldrich Chemical Co. (St Louis, MO). Anhydrous dibasic sodium phosphate (aDSP), tribasic sodium phosphate dodecahydrate (TSPd), tetrahydrofuran, ethyl acetate and ethanol were obtained from Mallinckrodt Chemical (Phillipsburg, NJ). Croscarmellose sodium (Crosc Na) was obtained from Hercules Inc. (Wilmington, DE). Inorganic salts (magnesium chloride and sodium bromide), were obtained from Mallinckrodt AR (Paris, KY, USA).

Methods

Salt Preparation

The crystalline mesylate and napsylate salts of miconazole and benzocaine were prepared via crystallization from organic solvent solutions. Salts were formed by addition of the appropriate solution of counterion in ethanol to a solution of free base in tetrahydrofuran. The acid solutions were added dropwise to form final acid:base solutions with slight excess acid (~2% molar) relative to the equimolar concentration. Crystallization either occurred immediately or was induced by cooling to 5ºC and/or evaporation. Salts were dried via suction filtration and washed thoroughly with an organic solvent to remove any residual free base, followed by drying in a vacuum oven and subsequent storage over phosphorus pentoxide. Formation of the monosalt was confirmed by quantitative HPLC analysis.

Raman Spectroscopy

FT-Raman spectroscopy was used to obtain reference spectra of the salts, free bases and excipients and to quantify the formation of free base in binary mixtures of salts with basic excipients. Raman spectra were obtained using a Perkin Elmer Spectrum System 2000 (PerkinElmer Co., Shelton, CT). All spectra were collected at 1.0 cm^{-1} intervals with a spectral resolution of 4 cm^{-1}. Sample excitation was performed using a diode pumped near IR Nd:YAG 1,064 nm laser with a power of 1,000 mW. Spectra are the average of 128 accumulations to produce spectra with desirable signal to noise ratio. Spectra of the salt-excipient blends were collected at selected timepoints. All samples were placed in glass NMR tubes and positioned in the laser path. In order to increase the sample volume and reduce the risk of sample heating, samples were rotated in the instrument by means of an electric motor. Calibration samples were prepared in triplicate by geometric mixing of the salt and base. Binary mixtures of the base with benzocaine mesylate were used to generate a spectral data set, with approximate base to salt compositions (mol%) of 20:80, 40:60, 50:50, 60:40 and 80:20. A similar set of data was obtained for miconazole and its mesylate salt.

Raman spectra of the powder blends with magnesium oxide were collected using a RamanRxn1-785 Raman spectrometer (Kaiser Optical Systems, Inc., Ann Arbor, MI, USA) with a 785-nm excitation laser. Total acquisition exposure time was 300 s with a laser power of 200 mW. The system is equipped with a nominal 63.5 mm working distance non-contact optics (NCO, Kaiser Optical Systems, Inc., Ann Arbor, MI) attached to an MR Probe (Kaiser Optical Systems, Inc., Ann Arbor, MI) with a spot size of 150 μm. Fiber optics are used to interface the spectrometer to the sampling device.

Infrared (IR) Spectroscopy

FT-IR spectra of the powder blends and pure materials were collected on a Bio-Rad FTS-6000 (Bio-Rad, Cambridge, MA, USA) with an attenuated total reflectance (ATR) setup (Golden Gate Mk II model single bounce diamond top-plate ATR from Specac Ltd., Cranston, RI, USA). A total of 128 scans were averaged at a resolution of 4 cm^{-1} for each sample over the wavenumber region 4000-500 cm^{-1}. The optics were purged with dry, CO_2-free air to prevent spectral interference from water vapor and CO_2.

Solubility

The aqueous solubilities of the salts were measured by stirring solutions with excess solid in a jacketed vessel at 25ºC; solutions were equilibrated for 48 h. The solids were then allowed to settle, and various aliquots were extracted with a syringe fitted with a 0.2 μm filter tip, and were then diluted and concentrations measured by high performance liquid chromatography (HPLC). For these samples, the solid remaining after equilibration in aqueous solution for 48 h was checked by Raman spectroscopy and no evidence of free

base was detected. The pH of filtered saturated solution aliquots of each salt, as prepared above, were measured using a Mettler Toledo SevenEasy pH meter equipped with an Inlab©413 probe. Solubilities of excipients were measured as described above. For the insoluble excipients, the pH of aqueous suspensions was measured during mixing after equilibration for 8 h.

Moisture Sorption and Surface Area Measurements

The specific surface areas (SSA) of the procaine salts were measured by nitrogen adsorption using the BET (Brunauer-Emmett-Teller) method with a Micromeritics ASAP 2000 (Norcross, GA). Samples (1–2 g) were degassed under vacuum (<10 mbar) at 50ºC for at least 8 h, to remove any residual or physically adsorbed water. The sample weight was adjusted for any loss during degassing, and the tube was then immersed in a liquid nitrogen dewar for measurement. The adsorption isotherm data across a range of partial pressures (0.05–0.30) were fitted to the BET model to determine the corresponding amount of adsorbate for an adsorbed monolayer, and a linearized form of the BET isotherm equation was used to determine the surface area based on the cross-sectional area of a nitrogen molecule (0.162 nm^2).

Water vapor sorption profiles of the salts and excipients used in the study were generated using an automated gravimetric analyzer (SGA-100; VT Corporation, Hialeah, FL, USA) at 25ºC. Samples (10–50 mg) were initially dried at 50ºC and 0% RH in the sorption analyzer. Equilibration at each RH step was determined to have been achieved when the weight change measured was less than 0.001% over 5 min with a maximum hold time of 90 min. For the excipients, values for the moisture sorbed as a function of RH have been normalized with respect to surface area. For the salts, estimates for moisture coverage in terms of monolayers at certain RHs were approximated from the measured moisture sorption data and measured specific surface area of the salt, using a value of 1.06×10^{-19} m^2 $molecule^{-1}$ for the surface area of a water molecule. Where applicable, the deliquescence relative humidity RH_0, the characteristic RH where a highly water soluble crystalline solid undergoes a first order phase transition to a solution (7), was measured by extrapolating the linear parts of the vapor sorption plot before and after the deliquescence event. Mixtures of deliquescent solids have been shown to deliquesce at a lower relative humidity, termed the mutual deliquescence relative humidity, or $RH_{0,mix}$. For such mixtures, $RH_{0,mix}$ can be approximated by the product of the individual component RH_0s via the Ross equation, derived with the assumption that the activity coefficient of each component in the mixture can be represented by its value in a simple solution (7).

Stability Testing

Powder blends (50/50 w/w) of each salt and excipient were prepared in 1-dram glass vials and mixed by geometric trituration with a spatula for extended periods of time to ensure homogeneous mixing. Samples were stored in desiccators over saturated salt solution at an RH of 57% (sodium bromide) at 25ºC. For the salt powder blends with sodium phosphate monobasic and sodium phosphate tribasic, a second RH of 33% (magnesium chloride) was also used. Samples were taken from the blends at time points of 3 days, 10 days, 24 days and 38 days and Raman spectra were recorded; the powder blends were remixed with light trituration using a spatula during removal of each sample. Raman spectra of the mixtures containing MgO as the excipient were taken using 785-nm excitation since severe fluorescence was observed with 1,064-nm excitation. The infrared spectra for the samples were also recorded at select time points. A separate sample of each sample mixture (total mass ~ 500 mg) was stored at identical conditions to measure the corresponding weight gain of the salts at each timepoint.

RESULTS

Properties of Salts

Miconazole, a basic imidazole antifungal agent, has a pK_a of 6.9 and is practically insoluble, with an intrinsic solubility of 2.40×10^{-6}M (8, 9). The measured solubility of miconazole mesylate and napsylate were 0.688 M and 1.93×10^{-6}M, respectively. The molar solubility of the napsylate salt is lower than the intrinsic solubility of the free base. This phenomenon has been noted for the besylate salt of ephedrine (10), and was suggested to be a combination of the higher lattice energy and weak solubilization of the anion. Benzocaine, a topical anesthetic, is a very weak base with a pK_a of 2.8 and an intrinsic solubility of 5.80×10^{-3}M (11). The solubilities of the mesylate and napsylate salts were 0.188 M and 9.65×10^{-3}M, respectively. In this case, the napsylate salt has a molar solubility slightly higher than that of the free base (see Table I). The moisture sorption profiles of the salts are shown in Fig. 1. None of the salts were particularly hygroscopic, particularly at the storage RHs employed in this study. The surface areas (m^2/g) measured for the four salts were 1.36 (miconazole mesylate), 4.13 (miconazole napsylate), 0.69 (benzocaine mesylate) and 0.52 (benzocaine napsylate). Using these values, the estimated moisture coverages at 57% RH in terms of monolayers are: 9.6 (miconazole mesylate), 0.8 (miconazole napsylate), 3.6 (benzocaine mesylate) and 0.6 (benzocaine napsylate).

Properties of Excipients

The moisture sorption profiles of the excipients used in the study are shown in Fig. 2, the values of moisture uptake are normalized to the measured specific surface areas (SSA). The results for sodium phosphate tribasic dodecahydrate are not included since the material dehydrated when dried at 0%

Table I. Solubilities, Saturated Solution pH and Calculated pH_{max} of Miconazole, Benzocaine and their Salts

	solubility (M)	pH at saturation	pH_{max}
miconazole base	2.40×10^{-6}		
miconazole mesylate	0.688	1.47	1.44
miconazole napsylate	1.93×10^{-6}	4.44	6.79
benzocaine base	5.80×10^{-3}		
benzocaine mesylate	0.188	1.12	1.30
benzocaine napsylate	9.65×10^{-3}	2.32	2.70

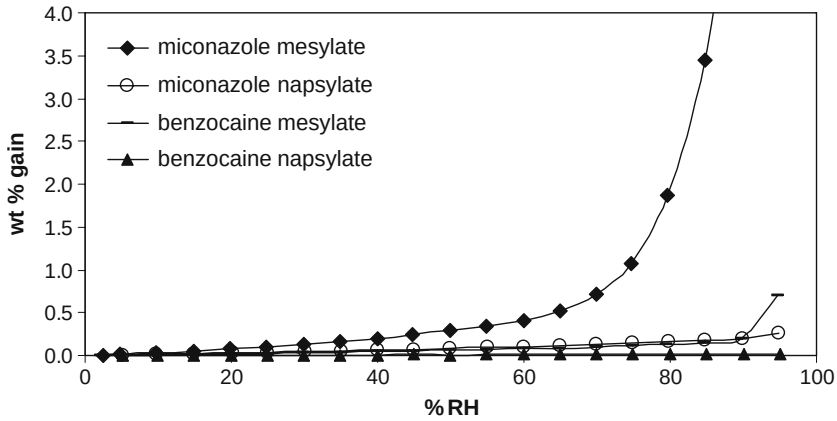

Fig. 1. Moisture sorption profiles of mesylate and napsylate salts of miconazole and benzocaine.

RH. Sodium phosphate dibasic deliquesces at approximately 55% RH (see Fig. 2). Although a number of the excipients have very low water solubilities, this does not translate into low hygroscopicities, as exemplified by magnesium oxide and croscarmellose sodium. Several of the excipients sorb more water than can be accounted for by surface adsorption by highly crystalline samples (12) suggesting that there are other mechanisms of water vapor sorption. These might include absorption into the bulk structure for disordered excipients such as croscarmallose sodium and hydrate formation in the case of magnesium stearate (13). The moisture sorption results were used to estimate the moisture uptake (% w/w) for the excipients at 57% (see Table II). The measured pH of saturated solutions and various aqueous suspensions of the excipients are also given in Table II. Sodium phosphate dibasic and tribasic, the two excipients having the highest solubilities, also had the two highest measured values of saturated solution pH. The other five excipients were fairly insoluble, and the pH of aqueous slurries ranged from 6.85 to 10.74 (see Table II).

Spectral Identification and Quantification of Base and Salt Forms

FT-Raman spectra of the mesylate and napsylate salts of benzocaine showed distinct spectral differences from the crystalline base form (Fig. 3). All spectra had numerous highly resolved peaks with various peaks exclusive to each individual material, necessary for positive identification. In order to identify the presence of base and quantify the amount present in the salt-excipient blends, the peak at 1,681 cm^{-1} was chosen because of its strong intensity and lack of interference from the mesylate and napsylate salts. The peak at 1,722 cm^{-1} arising in both the mesylate and napsylate salt was used to indicate the presence of the salt. There was minimal spectral interference from the excipients for either of these peaks. A calibration curve for the base and mesylate salt was generated by plotting the peak intensity ratio of the 1,681 cm^{-1} mode relative to the 1,722 cm^{-1} mode against molar ratio. A linear relationship was observed and linear regression analysis yielded a regression coefficient R^2 of 0.991 (see Fig. 4). For the napsylate salt, several characteristic spectral modes were evident in the 'fingerprint region' arising from stretching and deformation modes, but the mode at 1,722 cm^{-1} had the strongest intensity with only slight interference from the base spectrum. The calibration curve generated for the base/mesylate salt was used to determine the level of free base in both the benzocaine mesylate and napsylate excipient blends.

The Raman spectra of the crystalline miconazole base and salt forms again provided excellent spectral contrast for easy identification (Fig. 5). For example, close examination of

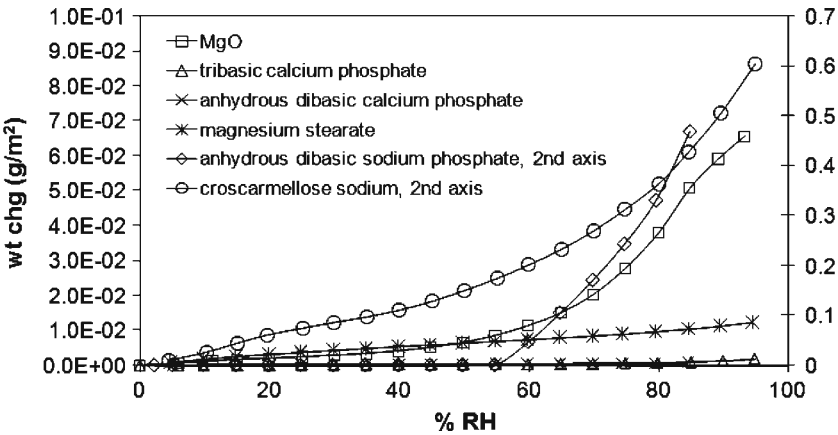

Fig. 2. Moisture sorption profiles of basic excipients, normalized to specific surface area; the secondary y axis on the right is applicable to anhydrous dibasic sodium phosphate and croscarmellose sodium.

Table II. Properties of Basic Excipients. Moisture Uptake was Predicted From Moisture Sorption Results. Included are Surface pH Values from the Literature; Values in Parentheses Represent pH of 10% wt/vol Suspensions taken from the References

	moisture uptake (wt.%) at 57% RH	measured pH in solution	literature value of surface pH	solubility*	surface area (m^2/g)
anhydrous dibasic calcium phosphate (aDCP)	0.09	7.70 (10% w/v suspension)	3.59[a] (6.92), 2.70[b] (5.5)	insoluble	1.88
tribasic calcium phosphate (TCP)	2.42	6.90 (10% w/v suspension)	–	practically insoluble	65.1
anhydrous dibasic sodium phosphate (aDSP)	0.76	8.93 (saturated)	–	1 in 8 parts water	0.39
tribasic sodium phosphate, dodecahydrate (TSPd)	4.62	12.92 (saturated)	–	1 in 5 parts water	0.43
croscarmellose sodium (Crosc Na)	19.67	6.85 (10% w/v suspension)	4.79[c]	insoluble	1.06
magnesium oxide (MgO)	2.74	10.74 (10% w/v suspension)	–	very slightly soluble	2.83
magnesium stearate (Mg stear)	2.41	8.38 (10% w/v suspension)	7.45[a] (9.57), 5.12[c]	practically insoluble	3.35

[a] Ref (25); [b] Reference(28), measured at 59% RH; [c] Ref(30)

the "fingerprint region" reveals a spectral mode at 779 cm^{-1} for the mesylate salt and at 768 cm^{-1} for the napsylate salt, which are not observed in the spectrum of the base. The peak at 1,506 cm^{-1} in the base spectrum (Fig. 6) was used for quantification, since it has sufficient intensity with little spectral interference from excipients or the salts. A mode at 3,110 cm^{-1} served as an additional marker for the base, although this region has some interference from the spectra of both salts. The peaks at 1,506 cm^{-1} and 779 cm^{-1}, exclusive to miconazole base and miconazole mesylate, respectively, were used to construct a calibration curve by plotting the ratio of the peak intensities against molar ratio, which fit a linear equation with a regression coefficient R^2 of 0.996. For the napsylate salt, a diagnostic peak was present at 768 cm^{-1}. No calibration curve was constructed for miconazole napysylate/base due to the stability of the excipient salt blends. The limits of detection, determined from the signal to noise ratio, were 0.15 mol% for the benzocaine salts and 0.87 mol% for miconazole napsylate (14).

Analysis of the FT-IR spectra (data not shown) of the benzocaine base and salt forms revealed multiple bands in the N-H stretching region exclusive to the base. For detection of

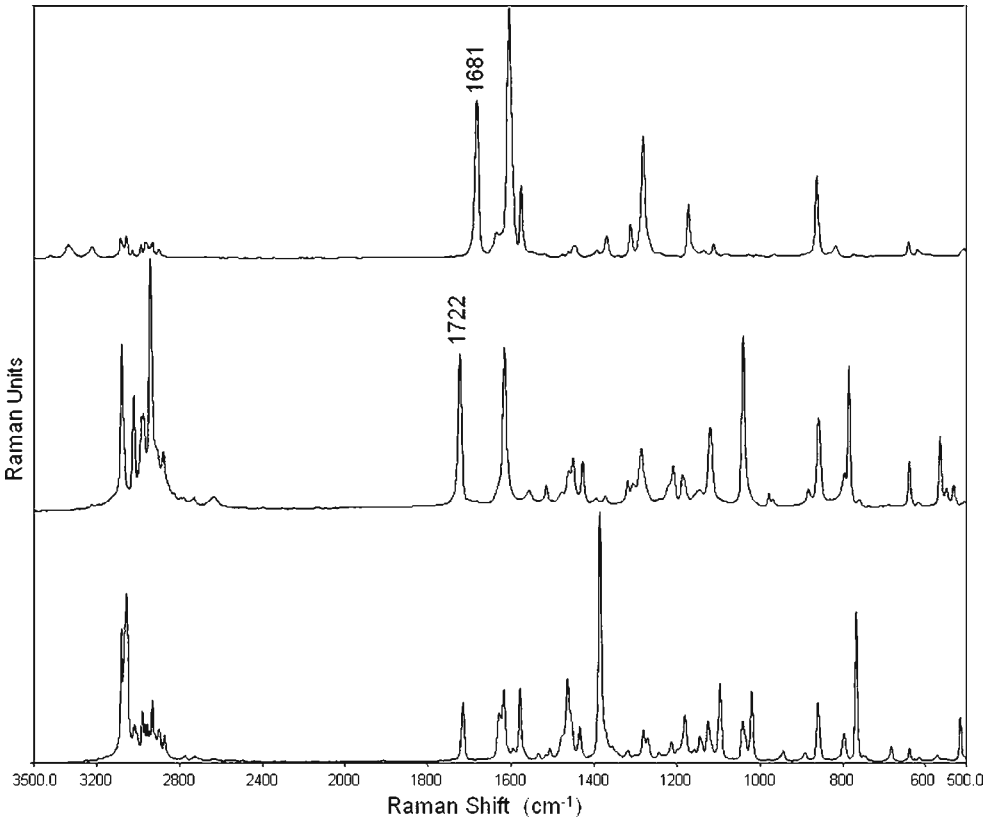

Fig. 3. FT-Raman spectra of benzocaine (*top*), benzocaine mesylate (*center*) and benzocaine napsylate (*bottom*). The peaks used for identification are marked.

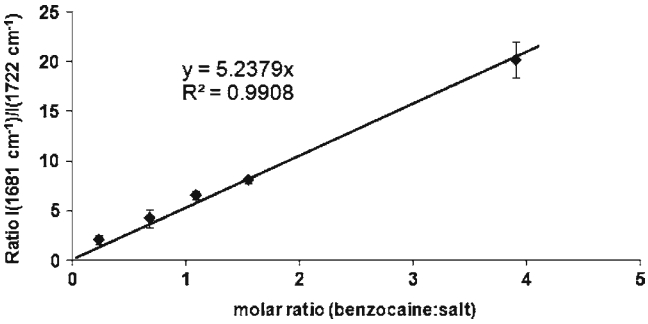

Fig. 4. Calibration curve for the quantification of benzocaine base in the presence of the salt form (error bars show standard deviation where n=3).

miconazole base in the presence of its salts, a band at 1,510 cm^{-1} observed exclusively in the miconazole base spectrum was used. Due to the surface specificity of the ATR technique as well some minor spectral interferences from the salt and excipients, the infrared spectra were used qualitatively as additional confirmation for the presence of the free base in the salt-excipient powder blends.

Free Base Formation in the Presence of Excipients and Moisture

After 3 days of storage at 25ºC/57% RH, all seven basic excipients induced some conversion of benzocaine mesylate to the free form, as detected by the presence of the 1,681 cm^{-1} peak in the Raman spectra of the stability samples. Quantification of the free base was possible, since there was no noticeable interference in the spectra from the excipients for the free base and salt marker peaks (Fig. 7). In most cases the extent of disproportionation was significant; one notable exception was aDCP. The two excipients with both the two highest solubilities and highest measured values of solution pH, aDSP and TSPd, showed the largest levels of disproportionation throughout the study (see Fig. 8). The storage RH of 57% is slightly above the measured RH_0 of aDSP; hence a saturated solution state of this excipient is thermodynamically favored. Interestingly, even at a storage RH of 33% which is below any single component RH_0 or the mixture deliquescence point $RH_{0,mix}$ as estimated by the Ross equation (15), large amounts of free base were detected for the blends with aDSP. The formation of the free base was supported by the presence of peaks exclusive to the free base in the infrared spectra, as well as the presence of characteristic peaks for the free base in other regions of the Raman spectra. The excipient blends with benzocaine napsylate showed much smaller amounts of disproportionation with only certain excipients, and in the case of aDSP, only at the final time point of 38 days (Table III).

Again, for the miconazole mesylate/excipient blends, quantification of the free base was possible, since there was no noticeable interference in the spectra from the excipients for the free base and salt marker peaks identified earlier. Miconazole mesylate was particularly susceptible to disproportionation in the presence of TSPd and aDSP (see Table III and Fig. 9); nearly two-thirds of the salt converted to free base in the presence of TSPd and approximately 45%

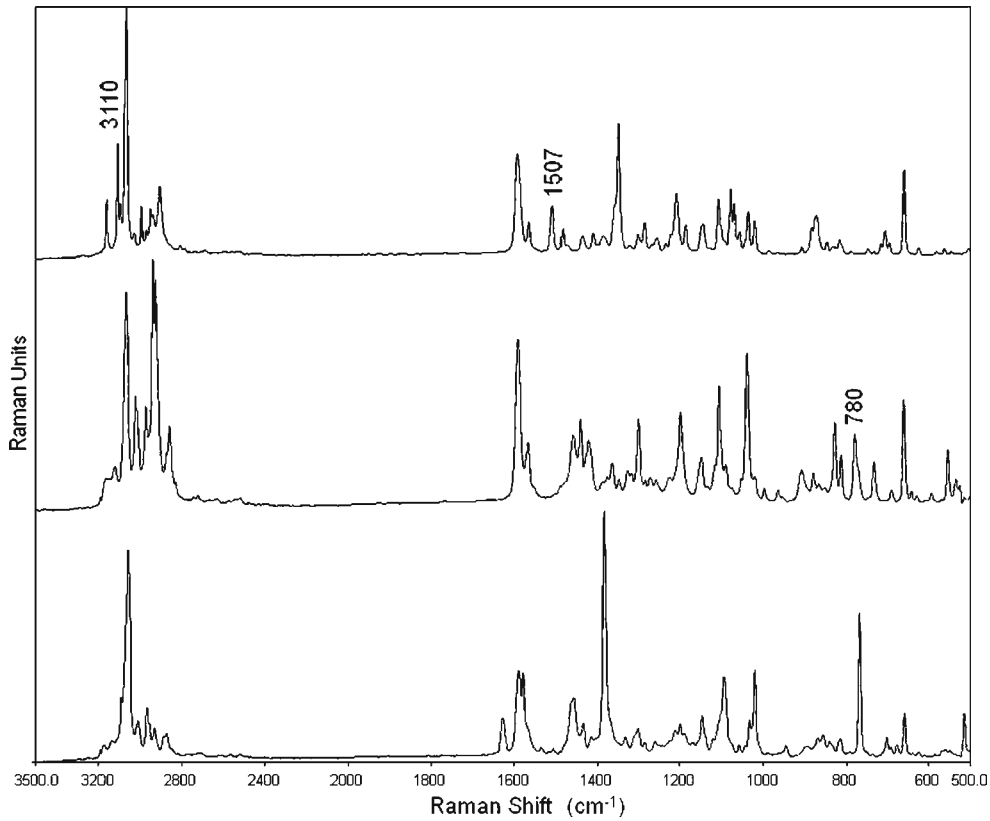

Fig. 5. FT-Raman spectra of miconazole (*top*), miconazole mesylate (*center*) and miconazole napsylate (*bottom*). The peaks used for identification are marked.

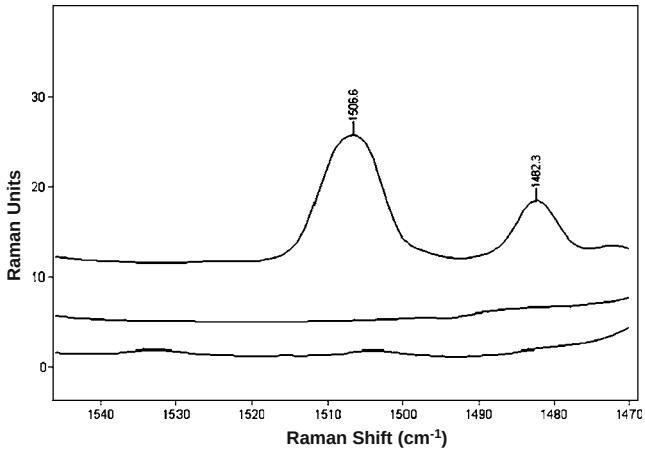

Fig. 6. Expanded view of the FT-Raman spectra of miconazole base (*top*) and its mesylate (center) and napsylate (bottom) salts showing the characteristic base peak at 1507 $cm^{-1}$and the lack of interference from the salts.

conversion was observed in the presence of aDSP after storage for 38 days at 25ºC/57% RH. Similar to the case of benzocaine mesylate, significant conversion to free base was detected at 33% RH, although the RH is again below the estimated $RH_{0,mix}$. The infrared and Raman spectra of the excipient blends with miconazole napsylate did not show any evidence for formation of the free base in any of the excipient blends throughout the study. The mol % conversion of salt to free base within the excipient blends stored at 57% RH are given in Table III for benzocaine mesylate, benzocaine napsylate and miconazole mesylate. Also included are the results for aDSP at 33% RH.

DISCUSSION

Theory of Disproportionation

In order to understand the conditions under which disproportionation of a salt to the free base will occur, it is necessary to consider the various equilibria that can occur between the neutral and ionized species in solution and the solid state. There is ample evidence that thin film water exists on the surface of crystals and that this water can solvate surface species (16-20). Thus disproportionation can be considered a solution mediated transformation. The transformation of the crystalline salt to the free form will depend on their relative solubilities, as well as the equilibrium between the ionized and unionized forms existing in solution in the thin film water, which in turn will be related to the microenvironmental pH. The microenviromental pH in the thin film water will be controlled by both the salt-base pair and the excipient properties.

The solubility-pH profile for a weak base/salt pair can be predicted if the pK_a, base intrinsic solubility and solubility product for the salt are known (21). The equilibrium for the dissociation of a salt of a weak base may be expressed as:

$$BH^+ + H_2O \overset{K_a}{\leftrightarrow} B + H_3O^+ \tag{1}$$

where BH^+ is the protonated base, B is the free base and K_a is the dissociation constant of BH^+ defined as:

$$K_a = \frac{[H_3O^+][B]}{[BH^+]} \tag{2}$$

The total solubility S at any pH will be the sum of the individual concentrations of the unionized (the organic base, B) and the ionized form:

$$S = [B] + [BH^+] \tag{3}$$

where the protonated species has an acid dissociation constant K_a. The maximum concentration of the base and ionized forms will of course be determined by their respective solubilities and the solubility product of the salt (K_{sp}). At low pH where the solubility of BH^+ is limiting (i.e. there is an equilibrium between the solid salt and the protonated form in solution), the following relationship holds:

$$S = \left(1 + \frac{K_a}{[H_3O^+]}\right) BH^+ \tag{4}$$

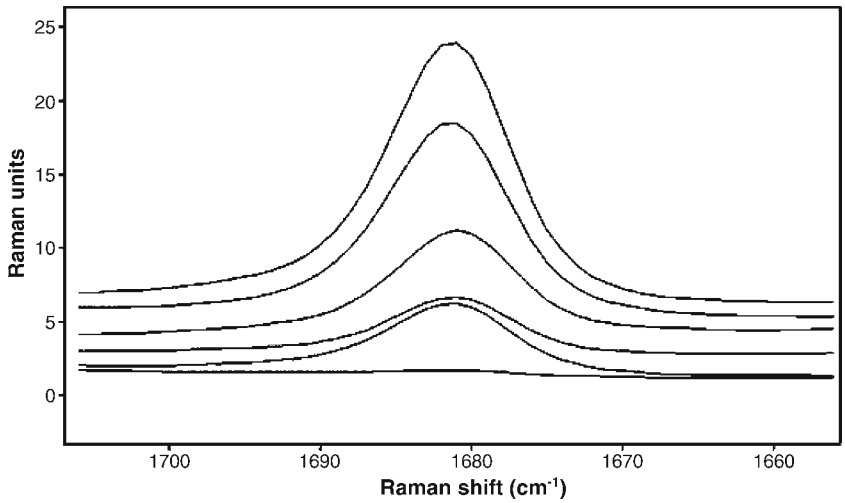

Fig. 7. FT-Raman spectra of benzocaine mesylate/excipient samples after 3 days at 25ºC/57% RH showing the appearance of the benzocaine base peak at 1681 cm^{-1}. From top to bottom, TSPD; ADSP; TCP; Mg stearate; Crosc Na; ADCP.

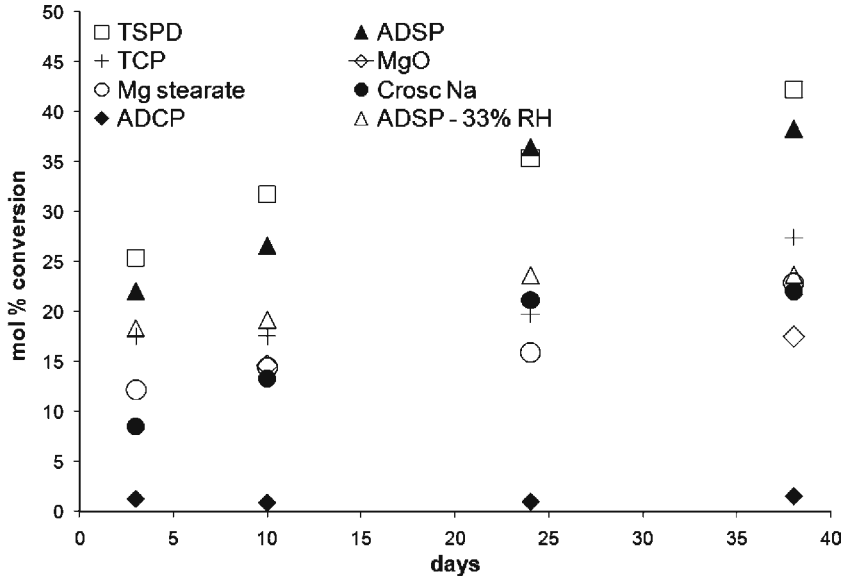

Fig. 8. Quantity of benzocaine free base as a function of time for benzocaine mesylate/basic excipient samples following storage at 25°C/57% RH; included is the data for benzocaine mesylate/ADSP at 25°C/33% RH.

For solutions at pH values greater than a certain pH value termed pH_{max} where the solubility of the free base S_0 is limiting (i.e. there is an equilibrium between the solid base and the solution species), the total solubility can be expressed as:

$$S = S_0\left(1 + \frac{[H_3O^+]}{K_a}\right) \tag{5}$$

At pH_{max}, the solution is saturated with respect to both the free base and salt form (i.e, there is an equilibrium between the solution and the solid forms of both the base and the salt), and Eqs. (4, 5) simultaneously apply. By setting the two equations equal and solving for pH_{max}, Bogardus *et al.* (22) derived the following expression for a base:

$$pH_{\max} = pK_a + \log\frac{S_0}{BH^+} \tag{6}$$

For a more detailed description of the equations presented above as well as similar equations for the salts of acids, the reader is referred to the literature (23,24).

In order to determine the risk for disproportionation, it is necessary to estimate the pH-solubility profiles in order to estimate pH_{max}. pH_{max} is a critical value since at pH values above pH_{max}, the salt can potentially convert to the base. pH_{max}

Table III. Levels of Conversion (mol %) of Salts to Free Base in 50/50 w/w Excipient Blends. The Data Represent the Samples Stored at 57% RH, Except Where Noted. The Dash Marks Represent Samples Where no Evidence of Free Base was Observed From the Spectra

days	TCP	aDCP	Crosc Na	Mg stearate	MgO	aDSP	TSPd	aDSP (33% RH)
benzocaine mesylate								
3	17.6	1.30	8.5	12.2	*	22.1	25.4	18.3
10	17.6	0.94	13.4	14.5	14.7	26.6	31.8	19.2
24	19.8	1.03	21.2	16.0	*	36.5	35.4	23.6
38	27.4	1.57	22.1	22.9	17.5	38.3	42.3	23.7
benzocaine napsylate								
3	–	1.11	–	2.9	–	–	-	–
10	–	0.92	–	3.9	–	–	1.53	–
24	–	1.29	–	5.2	–	–	2.27	–
38	–	1.26	–	7.3	–	1.00	1.75	–
miconazole mesylate								
3	–	–	19.3	–	–	21.1	57.9	13.1
10	–	–	22.8	–	–	28.0	63.8	14.4
24	–	–	25.7	–	–	42.5	63.8	14.4
38	–	–	37.2	–	–	45.4	67.3	14.9
miconazole napsylate								
3	–	–	–	–	–	–	–	–
10	–	–	–	–	–	–	–	–
24	–	–	–	–	–	–	–	–
38	–	–	–	–	–	–	–	–

*Spectra were not collected

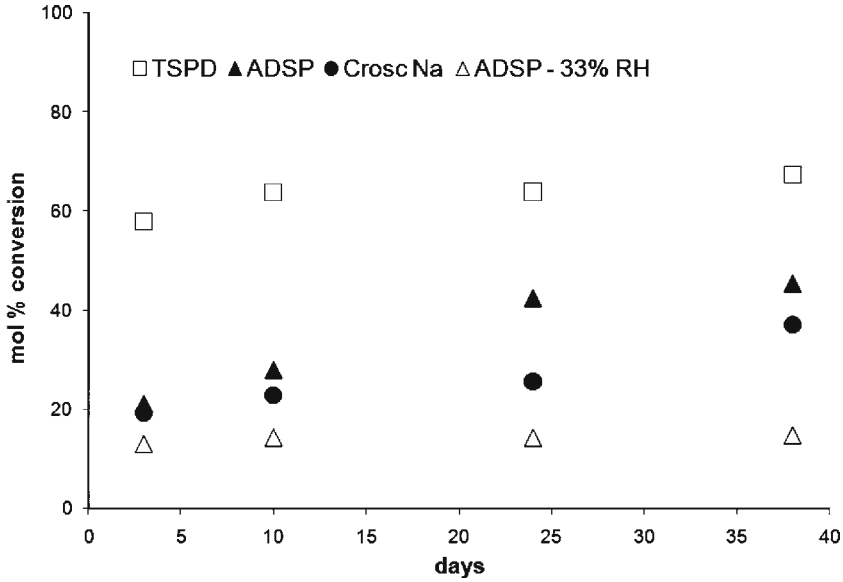

Fig. 9. Quantity of miconazole free base as a function of time for miconazole mesylate/basic excipient samples following storage at 25°C/57% RH; included are the data for miconazole mesylate/ADSP at 25°C/33% RH.

can be estimated if the solubility of the salt and base are known, in addition to the pK_a. The theoretical solubility-pH profiles, constructed as described above are shown in Fig. 10 for the mesylate salts of both miconazole and benzocaine. The pH_{max} is represented by the intersection between the two sections of the solubility curve. For a solution in equilibrium with the solid salt, if the measured pH is lower than pH_{max}, disproportionation cannot occur, no solid base should be present, and the solubility

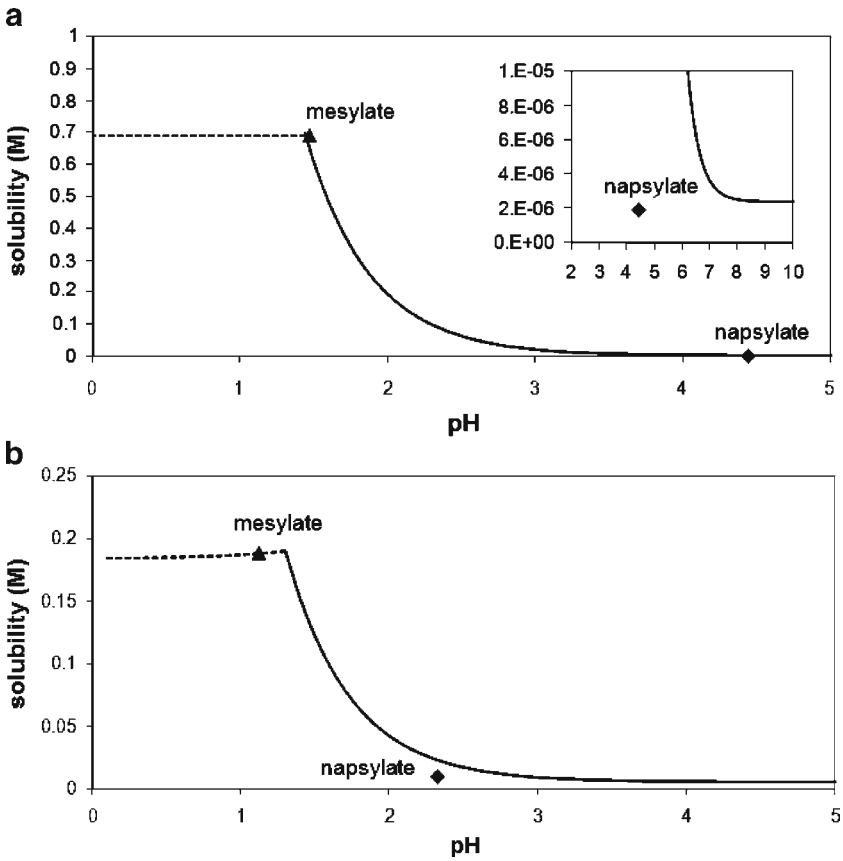

Fig. 10. pH-solubility profiles of **a**) miconazole mesylate and **b**) benzocaine mesylate. The points represent the saturation concentration and corresponding measured pH for unbuffered solutions of the salts; data for the napsylate salts are included. The inset in **a**) is an expansion of the region surrounding the napsylate solubility and pH.

product K_{sp} can be determined via Eq. (4). For the mesylate and napsylate salts, the measured pH values of the saturated solutions were either lower than pH_{max} or at pH_{max} (within experimental error) (see Table I).

The pH_{max} values determined for the mesylate salts of benzocaine and miconazole and benzocaine napsylate all occur at pH's lower than 3. This result suggests that a microenvironmental pH higher than this value could lead to disproportionation. Interestingly, comparable values of pH_{max} were found for the mesylate salts of benzocaine and miconazole (1.30 and 1.44, respectively), even though the pK_a values of miconazole and benzocaine differ by 4 units. This is a consequence of the competing factors which dictate pH_{max} as shown by Eq. (6). An increase in the pK_a of the base by one unit will result in an increase in pH_{max} by one unit. However, increasing the salt solubility product by an order of magnitude (i.e. increasing the solubility of the salt) or decreasing the intrinsic base solubility by the same amount will result in a decrease in pH_{max} by one unit. Thus weaker bases (lower pK_a) or salt-base pairs where the salt-base solubility ratio is very high will have lower pH_{max} values and will be more susceptible to disproportionation. The low pH_{max} value for benzocaine arises because it is a very weak base. For miconazole, the low pH_{max} value is due to the very low intrinsic solubility of miconazole base relative to that of the mesylate salt. This result should be particularly alarming, as the aqueous solubilities of new chemical entities continue to decrease; one author estimates as many as two-thirds of new compounds under investigation have solubilities below 100 μg/mL (23). Salts that provide the greatest solubility advantage will yield lower pH_{max} values, translating to a higher susceptibility of the salt to undergo conversion across a wider range of effective 'pH' conditions.

Comparison of Disproportionation Tendency of the Different Salts

Both miconazole mesylate and benzocaine mesylate showed significant amounts of free base formation in the presence of many of the basic excipients studied, even at the earliest time point of 3 days. In the case of benzocaine mesylate, all seven basic excipients appear to result in a microenvironmental pH sufficiently above pH_{max} to facilitate a large extent of disproportionation (Table III and Fig. 8). For miconazole mesylate, disproportionation was only observed in blends with some excipients; the highly water soluble sodium phosphate salts and croscarmellose sodium (Table III and Fig. 9). Given that the two salts have very similar pH_{max} values, it is of interest to consider why miconazole mesylate is more resistant to disproportionation than benzocaine mesylate in the presence of certain excipients.

The higher solubility and pK_a and hence buffering capability of miconazole mesylate relative to its benzocaine counterpart, is the most likely explanation for the observed differences between the two salts whereby magnesium stearate, aDCP, TCP and MgO did not cause free base conversion. If thin films of water are being formed between the salt and the excipient, the microenvironmental pH will be a function of the concentration of each species which in turn will be dictated by solubility, and the acid-base properties of each component. Given the low aqueous solubilities of the ineffective excipients in the case of miconazole mesylate, it appears that sufficient API salt is able to dissolve to buffer the effects of the excipients. Benzocaine mesylate is less soluble with a lower pK_a, and thus a less efficient buffer. The surface area of the salts did not appear to play any readily ascribable role in the conversion; for instance the two benzocaine salts had very similar surface area values, while miconazole napsylate had the highest measured value. The underlying reason for the effectiveness of croscarmellose sodium at causing disproportionation of miconazole mesylate is unknown at the present time. One possibility is the well known swelling behavior of this excipient in the presence of water, with a concurrent increase in molecular mobility which may facilitate proton transfer beyond regions of surface interaction (1).

Benzocaine napsylate showed evidence of a low extent of disproportionation with a limited number of excipients while no evidence of free base was found in any of the mixtures containing miconazole napsylate and the basic excipients. The lack of disproportionation of miconazole napsylate can probably be accounted for by two factors. First, the measured solubility of miconazole napsylate is below the intrinsic solubility of the free base, as noted earlier hence there is no thermodynamic driving force for crystallization of the free base. Second, the calculated pH_{max} of miconazole napsylate is 6.79, which means that the microenvironmental pH would have to be higher than this value for disproportionation to occur. The corresponding value of pH_{max} for benzocaine napsylate is 2.70, and the napsylate salt is more soluble than the base. However, benzocaine napsylate is much less soluble than the corresponding mesylate salt (Table 1), which in conjunction with the observation that it also has a lower hygroscopicity, probably explains why a much smaller extent of disproportionation is observed.

Role of Excipient Properties

Important excipient properties that would be expected to influence the extent of disproportionation include basicity, aqueous solubility, physical state (e.g. amorphous or crystalline), and surface area. Since all seven basic excipients produced some levels of free base in the benzocaine mesylate/excipient blends, these results should provide insight into the effect of excipient basicity and other factors on the extent of conversion. Although a poor surrogate for the exact microenvironmental pH conditions at a solid surface (25-29), particularly for the less soluble/hygroscopic excipients, solution/suspension pH values for the excipients are listed in Table II. Also listed in Table II are literature values of surface pH and corresponding pH of 10% wt/vol. aqueous suspensions where available; noteworthy differences from the solution pH values can be seen, as well as disagreement between values of surface pH reported. Some correlation was observed between the extent of benzocaine mesylate disproportionation and either measure of pH; generally higher amounts of free base were observed for those excipients that generated a higher corresponding value of solution pH, although exceptions were observed. For example, aDCP produced much lower levels of free base than TCP, despite producing a higher suspension pH. This result may well be

due to the much lower surface area of aDCP, and/or a less basic microenvironmental surface pH relative to that of a dispersion (see Table II). While surface area may seem to offer some explanation for the results observed for benzocaine mesylate, the effect was opposite in the case of benzocaine napsylate, illustrating the complexity of competing factors.

A surface area effect may also be responsible for the effect of Mg stearate on benzocaine napsylate — although Mg stearate does not have a high measured surface area, it is well known that this lubricating excipient can coat the surface of particles when blended with drug substances (30). The solubility of the excipients is also clearly of relevance. The sodium phosphate salts are highly soluble and are commencing deliquescence at the storage RH of 57% RH. Disproportionation of susceptible salts was seen in all instances in powder blends with these compounds. Disproportionation with the sodium phosphate salts was also seen in the case of benzocaine mesylate, even when the storage RH was 33% RH, well below any deliquescence point. Finally we have to consider the amorphous or crystalline nature of the excipients. In the case of miconazole mesylate, none of the insoluble excipients resulted in disproportionation except croscarmellose Na which is the only hydrophilic amorphous excipient.

Pharmaceutical Relevance

Detection of the free form can easily go unnoticed using a technique such as liquid chromatography, as salt and free forms may be indistinguishable due to the nature of their equilibrium form in a particular buffer solution. However, both an understanding of the factors which may lead to conversion to the free form as well as the knowledge of techniques capable of detecting the latter form may be extremely useful in avoiding the manufacturing conditions and formulation variables capable of facilitating the conversion. Even frequently used pharmaceutical excipients such as croscarmellose sodium and magnesium stearate were able to facilitate significant amounts of conversion to free base, highlighting the importance of the pH_{max} relative to the microenvironmental pH provided by such components. The conditions used in this study were not high stress conditions, but represent moderate RH conditions which may be expected to be present in many environments relevant to both processing and long-term storage of the drug product. In addition to the effects of disproportionation on performance due to the properties of a less soluble form, liberation of the free acid/base may cause additional stability/toxicity issues within the formulation.

CONCLUSIONS

The solid-state disproportionation of a four model pharmaceutical salts showed a dependence on a number of factors. Both the salt and base aqueous solubility and pH_{max} are important factors in determining the extent of conversion, as are the pH environments provided by the excipients. Insights into the factors controlling pH_{max} were presented and the significance of pH_{max} was shown using the model salts. In particular, a lower intrinsic solubility of the basic free form will yield a salt that is much more susceptible to disproportionation by producing a lower pH_{max}. A number of factors appear to be involved in the mechanism of disproportionation in the local environment of the salt as influenced by the presence of excipients. Both the solubilities of the salt and excipient were important. The effectiveness of the excipients also appears to depend on basicity, surface area, and physical state. Solution pH measurements did not fully explain the results, suggesting local effective pH is dependent on the moisture content and other factors. The results showed evidence for solvation of the salts within adsorbed moisture, and suggest the solubility and mobility of the excipients play a vital role as well. Finally, Raman spectroscopy has proven to be a useful technique for the detection and quantification of the free form in the presence of the salt and excipients.

ACKNOWLEDGEMENTS

The authors acknowledge AstraZeneca R&D Lund Sweden for funding this research. Dr. Kjell Jarring is sincerely thanked for helpful discussions. Aansh jarmarwala is thanked for his help in collecting spectra.

REFERENCES

1. Rohrs BR, Thamann TJ, Gao P, Stelzer DJ, Bergren MS, Chao RS. Tablet dissolution affected by a moisture mediated solid-state interaction between drug and disintegrant. Pharm. Res. 1999; 16:1850–56.
2. Zannou EA, Ji Q, Joshi YM, Serajuddin ATM. Stabilization of the maleate salt of a basic drug by adjustment of microenvironmental pH in solid dosage form. Int. J. Pharm. 2007;337:210–8.
3. Williams AC, Cooper VB, Thomas L, Griffith LJ, Petts CR, Booth SW. Evaluation of drug physical form during granulation, tabletting and storage. Int. J. Pharm. 2004;275:29–39.
4. Towler CS, Li TL, Wikstrom H, Remick DM, Sanchez-Felix MV, Taylor LS. An Investigation into the Influence of Counterion on the Properties of Some Amorphous Organic Salts. Mol. Pharm. 2008;5:946–55.
5. Guo YS, Byrn SR, Zografi G. Effects of lyophilization on the physical characteristics and chemical stability of amorphous quinapril hydrochloride. Pharm. Res. 2000;17:930–5.
6. Adeyeye MC and Brittain HG (eds.). Preformulation in Solid Dosage Form Development, Informa Healthcare, 2008.
7. Salameh AK, Taylor LS. Deliquescence in binary mixtures. Pharm. Res. 2005;22:318–24.
8. Box KJ, Comer JEA. Using Measured pK(a) LogP and Solubility to Investigate Supersaturation and Predict BCS Class. Curr. Drug Metab. 2008;9:869–78.
9. Piel G, Evrard B, Fillet M, Llabres G, Delattre L. Development of a non-surfactant parenteral formulation of miconazole by the use of cyclodextrins. Int. J. Pharm. 1998;169:15–22.
10. Black SN, Collier EA, Davey RJ, Roberts RJ. Structure, solubility, screening, and synthesis of molecular salts. J. Pharm. Sci. 2007;96:1053–68.
11. Avila CM, Martinez F. Thermodynamic study of the solubility of benzocaine in some organic and aqueous solvents. J. Solution Chem. 2002;31:975–85.
12. Zografi G, Hancock B. Water-Solid Interactions in Pharmaceutical Systems. In: Crommelin DJA, Midha KK, Nagai T, editors. Topics in Pharmaceutical Sciences. Stuttgart, Germany: Proceedings of International Congress on Pharmaceutical Sciences FIP; 1993. p. 405–19.
13. Sharpe SA, Celik M, Newman AW, Brittain HG. Physical characterization of the polymorphic variations of magnesium stearate and magnesium palmitate hydrate species. Struct. Chem. 1997;8(1):73–84.
14. Skoog DA, Holler FJ, Nieman TA. Principles of Instrumental Analysis. 5th ed. Philadelphia: Saunders College Publishing; 1998.

15. Ross KD. Estimation of Water Activity in Intermediate Moisture Foods. Food Technol. 1975;29:26–34.
16. Dai DJ, Peters SJ, Ewing GE. Water-Adsorption and Dissociation on Nacl Surfaces. J. Phys. Chem. 1995;99:10299–304.
17. Luna M, Rieutord F, Melman NA, Dai Q, Salmeron M. Adsorption of water on alkali halide surfaces studied by scanning polarization force microscopy. J. Phys. Chem. A. 1998;102:6793–800.
18. Shindo H, Ohashi M, Baba K, Seo A. AFM observation of monatomic step movements on NaCl(001) with the help of adsorbed water. Surf. Sci. 1996;358:111–4.
19. Shindo H, Ohashi M, Tateishi O, Seo A. Atomic force microscopic observation of step movements on NaCl(001) and NaF(001) with the help of adsorbed water. J. Chem. Soc., Faraday Trans. 1997;93:1169–74.
20. Verdaguer A, Sacha GM, Luna M, Ogletree DF and Salmeron M. Initial stages of water adsorption on NaCl (100) studied by scanning polarization force microscopy. J. Chem. Phy. 123: (2005).
21. Kramer SF and Flynn GL. Solubility of Organic Hydrochlorides. J. Pharm. Sci.. 61:1896-& (1972).
22. Bogardus JB, Blackwood RK. Solubility of Doxycycline in Aqueous-Solution. J. Pharm. Sci. 1979;68:188–94.
23. Serajuddin ATM. Salt formation to improve drug solubility. Adv. Drug Delivery Rev. 2007;59:603–16.
24. Stahl PH, Wemuth CG. Handbook of Pharmaceutical Salts. New York: Wiley-VCH; 2002.
25. Govindarajan R, Zinchuk A, Hancock B, Shalaev E, Suryanarayanan R. Ionization states in the microenvironment of solid dosage forms: Effect of formulation variables and processing. Pharm. Res. 2006;23:2454–68.
26. Pudipeddi M, Zannou EA, Vasanthavada M, Dontabhaktuni A, Royce AE, Josh YM, *et al*. Measurement of surface pH of pharmaceutical solids: A critical evaluation of indicator dye-sorption method and its comparison with slurry pH method. J. Pharm. Sci. 2008;97:1831–42.
27. Dulin WA. Degradation of bisoprolol fumarate in tablets formulated with dicalcium phosphate. Drug Dev. Ind. Pharm. 1995;21:393–409.
28. Glombitza BW, Oelkrug D, Schmidt PC. Surface-acidity of solid pharmaceutical excipients 1. Determination of the surface-acidity. Eur. J. Pharm. Biopharm. 1994;40:289–93.
29. Glombitza BW, Schmidt PC. Surface-acidity of solid pharmaceutical excipients 2. Effect of the surface-acidity on the decomposition rate of acetylsalicylic acid. Eur. J. Pharm. Biopharm. 1995;41:114–9.
30. Hussain MSH, York P, Timmins P. A study of the formation of magnesium stearate film on sodium-chloride using energy-dispersive x-ray-analysis. Int. J. Pharm. 1988;42:89–95.