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RESEARCH PAPER

Formulating Weakly Basic HCl Salts: Relative Ability of Common Excipients to Induce Disproportionation and the Unique Deleterious Effects of Magnesium Stearate

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ABSTRACT

Purpose Nine common excipients were examined to determine their ability to cause disproportionation of the HCl salt of a a weakly basic compound. The goal was to determine which excipients were problematic and correlate the results to known properties such as surface pH, slurry pH, or molecular structure. Such a correlation enables a general, simple excipient selection process.

Methods Binary compacts and "pseudo formulations" are studied after stressing at 40°C/75%RH and 40°C/35% RH for up to 28 days. Near-Infrared (NIR) and X-Ray powder diffraction (XRPD) measurements monitored the conversion of the HCl salt to the free base.

Results The excipients which induced measureable disproportionation were magnesium stearate, sodium croscarmellose, and sodium stearyl fumarate. Magnesium stearate induced the most extensive and rapid disproportionation at 40°C/75%RH and 40°C/35%RH. Samples containing magnesium stearate showed a unique and significant water uptake above 31%RH.

Conclusions The problematic excipients are best explained by the proton accepting capacity of excipient carboxylate groups which have pK_a's higher than the pH_{max} of the drug salt. Alternative lubricants and disintegrants are suggested and a simple excipient screening process is proposed. Magnesium stearate was the most deleterious excipient for HCl salts due to the formation of the deliquescent salt magnesium chloride.

KEY WORDS deliquescent · disproportionation · excipient induced · HCl salt · Magnesium stearate

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INTRODUCTION

In recent years, a large fraction of pharmaceutical drug candidates have had relatively poor water solubility (1–4). Strategies aimed at increasing the bioavailability of such drug substances have thus been more widely used and explored (5–13). One simple but effective means is formation of a salt form of the active pharmaceutical ingredient (API), which increases the solubility and improves dissolution properties (14,15). These solubility demands have also expanded the pK_a range of salt forms considered acceptable for development. Currently about two-thirds of API salt forms being developed are considered salts of weak bases or weak acids (14). In the more common case, a salt of a weak base, the weakly basic site on the drug is protonated and accompanied by an acceptable counter ion such as chloride, phosphate, sulfate, besylate and mesylate (14). The developmental risk associated with weakly basic salts is that upon long term stability, the API salt may revert back to the free base form of the drug, which often has lower solubility and poorer dissolution characteristics (16). This process is more generally referred to as disproportionation. In the context of weak bases, disproportionation involves proton transfer from the protonated drug site to some other site within the excipient matrix.

Given the potential impact on the pharmaceutical product, developing a better understanding of disproportionation and how it may be impacted by excipients has received recent attention in the literature. While simple acid–base reaction mechanisms can explain the major features of such excipient effects, the concept of pH_{max} (17) has been recently reassessed by Guierrieri and Taylor (18) and Stephenson *et al.* (19) to describe disproportionation of salts in solid dosage forms. This concept implies that disproportionation is a solution mediated process, occurring in sorbed water layers at the surface of API particles. The critical

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parameter pH_{max} can be calculated, and is the pH value (of the water layers) above which the salt can potentially convert to its free base form. A problematic excipient is viewed as being able to elevate the "microevironmental" pH of the sorbed water layers above the pH_{max} value (20–26). Currently, excipients are typically judged in this context by either their slurry pH values and/or a surface pH measurement (24–26). Stephenson *et al.* reviewed four oral dosage form examples in which the disproportionation observed was generally rationalized by lower pH_{max} values compared to the "expected" tablet pH microenvironments (19). Merritt *et al.* (27) examined disproportionation of ca. 10 different salt froms with pH_{max} values less then 6.0, when formulated in 4 different formulations. Excipient slurry pH values were used to build a qualitative, empirical model of the disproportionation. The authors also concluded that additional quantitative studies were needed to understand discrepancies in binary blends of excipients containing proton accepting groups, such as sodium croscarmellose. Guerrieri and Taylor studied 50/50 binary mixtures of the mesylate and besylate salts of miconazole and benzocaine with seven basic excipients including mono, di and tribasic phosphates, sodium croscarmellose, magnesium stearate and magnesium oxide (18). In terms of excipient effects, it was concluded that excipient basicity, solubility and surface area played significant roles in the disproportionation of the salts.

The current work takes a different approach and provides formulation scientists a comparative data set on common excipients across different functional classes which are typically needed to manufacture a real pharmaceutical dosage form. Nine common excipients (shown in Table I) are chosen for this study: three diluent/fillers (lactose, avicel, mannitol), four lubricants (magnesium stearate, sodium stearyl fumarate, stearic acid, and sucrose stearate) and two disintegrants (sodium croscarmellose and crospovidone). The lubricants and disintegrants have been selected not only due to their common usage, but also to specifically provide a wide range of microenvironmental pH. The ability of these excipients to induce disproportionation of a weakly basic drug substance is investigated. An HCl salt was selected because HCl salts are the most common salt form of weakly basic drug molecules approved by the FDA from 1995 to 2006 (15), and are likely the predominant salt form of weakly basic compounds currently under development.

The results are interpreted in the context of acid–base chemistry and pH_{max}. Slurry pH and surface pH of excipients alone are found to be relatively poor predictors of disproportionation. It is suggested that the excipient selection process consider the excipients' buffer capacity and also include a simple slurry pH screening study. Magnesium stearate stands out as giving rise to the most deleterious effects. This effect was investigated, and has general implications for the use of magnesium stearate when formulating the HCl salt of a weakly basic API.

MATERIALS AND METHODS

Materials and Drug Substance Properties

The "compound A" HCl salt and neutral forms were purchased from Dr. Reddy's Laboratory (India). Compound A HCl and free base forms are non-hygroscopic, anhydrous forms and are chemically and physically stable at 40°C/75%RH for 1 month. Table II shows the chemical structure and also summarizes important compound A properties such as pK_a, water solubility of the HCl salt and free base forms and the calculated pH_{max} value. The nine

Table I Typical Functional Excipient Properties

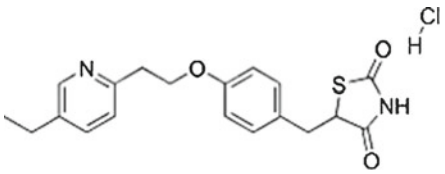
Excipient	Supplier	Application	% Carboxylate	Measured Slurry pH (10% w/v)	Surface pH (24)	Proton Acceptor/Donor
1) Magnesium Stearate	Mallinckrodt	Lubricant	14.9	8.1	5.12	Acceptor
2) Sodium Stearyl Fumarate	JRS Pharma	Lubricant	11.3	8.3	N/A	Acceptor
3) Sucrose Stearate	SE Pharm	Lubricant	0.0	8.1		Neutral
4) Stearic Acid	Cognis	Lubricant	0.0	7.9	2.04	Donor
5) Sodium Croscarmellose	FMC Biopolymers	Disintegrant	12.1†	6.2	4.79	Acceptor
6) Crospovidone	ISP Tec	Disintegrant	0.0	7.0	4.25	Neutral
7) Avicel PH-101	FMC Biopolymers	Filler	0.0	5.6	3.88	Neutral
8) Mannitol	SPI Pharma	Filler	0.0	4.6*	3.23	Neutral
9) Spray Dry Lactose Monohydrate	Foremost	Filler	0.0	3.8	3.48	Neutral

* These samples were a solution at a 10% w/v ratio

† Calculated from the sodium content typically reported in sodium croscarmellose

Table II HCl Salt Properties

A (Upper): Structure of Compound A



B (Lower): Compound A Properties

pH_{max} (Experimental)	pH_{max} (Calculated)	pK_a	HCl Salt Water Solubility (mg/mL)	Neutral Form Water Solubility (mg/mL)
2.8	3.0*	5.6	0.4	0.001

* Calculated using $pH_{max} = pK_a + \log (sol\ FB/sol\ HCl)$

excipients shown in Table I were pharmaceutical grade and used directly as obtained from the listed suppliers. Magnesium chloride hexahydrate and magnesium chloride anhydrous were purchased from Sigma Aldrich.

Binary and Pseudo Formulation Compact Sample Preparation

Excipients one through six (Table I) were studied in a 90%:10% drug : excipient ratios as part of a binary compact study. The 90%:10% ratio realistically reflects a typical pharmaceutical tablet composition for the API and functional excipients. For example, a 100 mg tablet image in which lubricants and disintegrants would be present at 2–5%, with a API potency of 50 mg. A second set of pseudo formulation samples were also prepared to determine how hygroscopic excipients may impact HCl salt disproportionation. Three of these pseudo formulation samples were used to study the individual effects of the filler excipients (Table I, 7–9) in a 50%:50% drug : filler excipient ratio. The remaining six pseudo formulations studied the individual effects of excipients one through six (Table I) on compound A HCl salt disproportionation in the presence of the filler excipients. The composition of these six pseudo formulations were 45% compound A HCl salt, 25% avicel, 25% mannitol and 5% of excipient one through six (Table I).

Duplicate preparations of the API and excipient powders were gravimetrically dispensed into 1-dram glass vials using the Symyx Powdernium powder dispensing robot. The target weight of the binary mixtures and pseudo formulations were 280 mg. After the binary and pseudo formulations were dispensed, additional mixing was performed by mixing at 30% intensity for 5 min with the Resodyn Lab Ram acoustic mixer. All of the powder samples were then manually compressed into compacts using a 1/2 inch die with 2,000 lbs of force.

Temperature and Humidity Controls for Stability Testing

The duplicate preparations of binary and pseudo formulation samples were studied in 40°C stability chambers at 75%RH, 35%RH and 20%RH open dish conditions. The stability of 90:10 compound A HCl salt and magnesium stearate compacts were further studied at 40°C/31%RH. The 40°C/31%RH condition required tighter humidity controls and used a saturated $MgBr_2 \bullet 6H_2O$ salt solution and a 40°C stability chamber to produce a 40°C/31%RH environment.

NIR Spectroscopy

The loss of the HCl salt form was monitored throughout the binary and pseudo formulation studies using FT-NIR spectroscopy. The FT-NIR spectra were obtained using a Thermo Antaris II System (Thermo Electron Co. North Carolina). All sample and standard spectra were collected with a spectral resolution of 8 cm^{-1}. Spectra are the average of 64 accumulations to produce a single spectrum with a desirable signal to noise ratio. Calibration standards composed of mixtures of the HCl salt and the free base forms were scanned in triplicate and the spectra were chemometrically treated with a Savitsky-Golay 2nd derivative. The stressed sample compacts were scanned within 15 min of their removal from their respective storage chambers. Sampling of the compact was maximized by scanning each side of the compact and the two spectra were chemometrically treated with the same Savitsky-Golay 2nd derivative. The results from each compact were averaged into a single value.

Transmission XRPD

The disproportionation results from select stressed samples were confirmed using XRPD. It has a lower detection limit

for free base than NIR, making it more suited for samples with less than 5% free base. The XRPD spectra were collected on the Panalytical X'pert Pro diffractometer with Cu Ka1 radition of 1.5406 Å in the transmission mode. The samples were scanned between a two theta range of 4 and 20° at a step size of 0.0167° for one hour at ambient conditions. The tube power used was 45 kV and 40 mA. Calibration standards were scanned in duplicate. Peak areas were calculated using the X'Pert High Score Plus software.

^{13}C SSNMR Spectroscopy

Solid-state NMR was used to study the extent of disproportionation in a single stressed binary sample of compound A to ensure that the NIR and XRPD results were not confounded by potential presence of an amorphous form of the HCl salt or free base. ^{13}C CPMAS spectra were collected on a Bruker 400 WB solid state NMR spectrometer. Powders were packed in 4 mm zirconia rotors with Kel-F® endcaps and spun at the magic angle at 12 kHz. The method includes a 2.75 μs proton 90° pulse at 100 kHz, a Hartman-Hahn match at 80 kHz for 3 ms, and TPPM decoupling at 100 kHz. Referencing was performed externally by setting the chemical shift of the carboxyl carbon in glycine to 176.7 ppm. Calibration standards were gravimetrically prepared using crystalline HCl and crystalline free base salts. The level of disproportionation was quantified by fitting the selected spectral regions free of excipient peaks as a linear combination of reference spectra of the free base and the HCl salt.

Dynamic Vapor Sorption Measurements

Moisture sorption isotherms were obtained at 40°C using a Q5000SA Dynamic Vapor Sorption (DVS) (TA Instruments). The blend samples were compressed at 20 MPa to increase the contact between individual components. The compact was then ground gently into powder and an approximate 10 mg portion was analyzed. All samples were dried at 40°C at the beginning of the experiments. Three equilibrium conditions were used to generate moisture sorption data. The first used an equilibrium criterion of less than 0.01% weight change over a period of 5 min with a maximum equilibration time of 4 h at each humidity step. The second kept the samples at each humidity step for 6 h, while the third allowed 12 h at each step to enable the measurement of a slow moisture uptake process. All the moisture sorption data were analyzed using Universal Analysis software.

Excipient "Slurry" pH and pH Titration of Excipients

The slurry pH values of excipients one through nine (Table I) were measured by preparing 10% by weight of each excipient in water. The pH was measured after 60 min using a calibrated Accumet® Research AR15 pH meter. Slurry pH measurements for compound A and excipient mixtures at 90:10 or 50:50 by weight (Table IV) were carried out at 10% total solids in water. The pH after 20 min and 24 h were identical. Surface pH values were derived from the literature (24,25).

Excipients 1–9 (Table I) were "titrated" by adding 500 mg of each excipient to 100 ml HPLC water, then adding 0.05 N HCl in 1.0 ml aliquots and recording the pH values while the solution was vigorously stirred. In the case of the carboxylate containing excipients, 5–10 min was needed for the pH to stabilize. The ml of 0.05 N HCl needed to move the solution pH to below 3.0 was recorded, and compared to that obtained for the 100 ml HPLC water control (initial pH of 7.5).

Solubility

The aqueous solubility of compound A HCl salt and free base forms were determined at room temperature and used to calculate pH_{max}. The data from these experiments are summarized in Table IIB. The free base form was equilibrated in water for 24 h. The HCl salt was equilibrated in pH 2.7 HCl solution for 24 h. Free base was not detected in the residual solids of the HCl sample. The solubility of the HCl salt was calculated as the square root of the K_{sp}. Using the pK_a and solubility values of the HCl salt and free base, the pH_{max} of compound A is calculated to be 3.0.

RESULTS

Solid Form Quantitation: NIR Calibration Curves

In the NIR spectra, a region specific for monitoring the disproportionation of compound A HCl salt was observed between approximately 6,300–6,000 cm^{-1}. The untreated and Savitsky-Golay 2nd derivative NIR spectra of HCl salt (black line), free base form (red line), and a 1:1 salt mixture (blue line) are shown in Fig. 1a and b respectively. Significant differences in the raw spectra of compound A HCl and free base forms are apparent. The application of a Savitsky-Golay second 2nd derivative dramatically reduces baseline differences and enhances the spectral differences between the HCl and free base forms. This pre-treatment was used throughout.

Three factor NIR calibration models were built for the compound A binary and pseudo formulation samples. Both models used the spectral region from 6280 – 6040 cm^{-1} but the pseudo formulation model also utilized a 2nd region from 4100 – 4017 cm^{-1}. The compound A binary compact

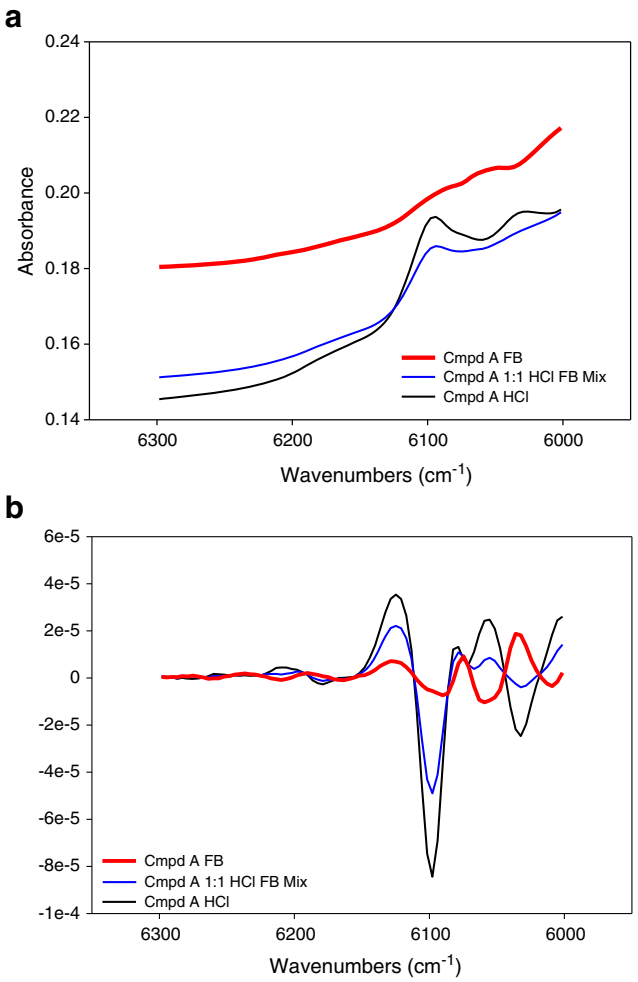


Fig. 1 (**a**) Untreated NIR spectra of compound A calibration standards, (**b**) Savitsky-Golay 2nd derivative spectra of compound A calibration standards.

NIR model was created by gravimetrically preparing eleven different standard mixtures of the HCl salt and the free base form. Excipients were not included in the binary calibration model due to the lack of spectral interference at a 10% weight concentration. The calibration standards were prepared in 10% increments and ranged from 100%HCl (0% free base) to 0% HCl (100% free base). Each standard was scanned in triplicate and the resultant 33 spectra were used to develop a partial least squares (PLS) calibration. In the case of the pseudo formulations, the three factor pseudo formulation NIR calibration model was created by re-preparing the eleven calibration standards and performing a 1:1 dilution with the 50:50 avicel:mannitol filler. In both cases, linearity was excellent (R^2=0.99) and the standard error of prediction was 2.5%.

Solid Form Quantitation: XRPD Calibration Curves

In the XRPD pattern, the 2-theta range between 7.0° and 11.0° can be used to quantify the level of compound A HCl and free base forms. In this region, the compound A crystalline free base form has three specific peaks at 7.8°, 9.1°, and 10.3° 2-theta while the HCl form has a doublet peak centered at 8.6° 2-theta. As shown in Fig. 2, when gravimetric mixtures of the free base and HCl standards are measured, the intensity of the free base and HCl peaks concomitantly change with respect to their concentrations. The XRPD LOD was determined to be approximately 2% free base and the excipients did not show significant interference in this region.

Gravimetric mixtures of HCl salt and free base were prepared as calibration standards and transferred to a 96 well plate for analysis. The compound A binary system calibration curve was developed by calculating the peak area ratio of the free base peaks (at 9.1°, and 10.3° 2-theta) to the HCl doublet peak (at 8.6° and 8.7° 2-theta). The calculated FB/HCl peak ratios were correlated to the percent free base in the standards (from 0–40% free base) and fit with a linear equation (R^2 = 0.99). The regression equation was then used to quantitate the amount of free base present in the compound A binary and pseudo formulation samples.

Quantitation of Disproportionation in Compound A 90:10 Binary Compacts

Compacts containing compound A HCl salt and excipients one through six (from Table I) were prepared in a 90:10 weight ratio and stressed at 40°C/75%RH for 5 days. The levels of HCl salt remaining in these samples were quantified by NIR (1, 3, 5 days) and XRPD (3 and 5 days) and are shown in Fig. 3. The NIR and XRPD results for the sucrose stearate, crospovidone, and stearic acid compacts did not show any detectable HCl salt disproportionation. In contrast, the NIR data indicates that the compacts containing sodium croscarmellose (solid diamond, solid line), sodium stearyl fumarate (solid square, solid line) and magnesium stearate (solid circles, solid line) rapidly lost approximately 8%, 10%, and 30% of the original compound A HCl salt

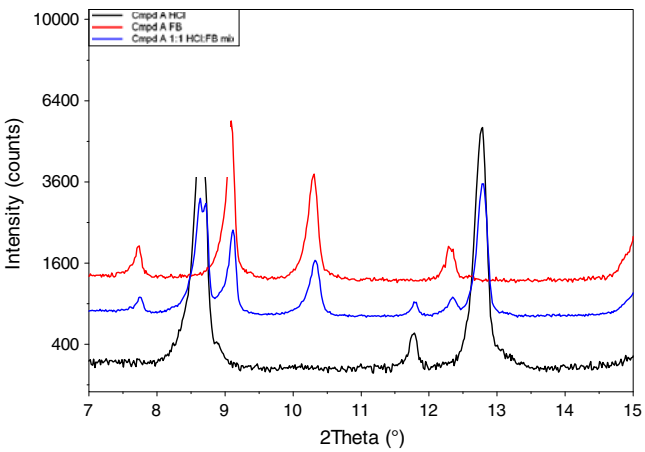


Fig. 2 X-Ray powder diffraction of compound A HCl/FB standards.

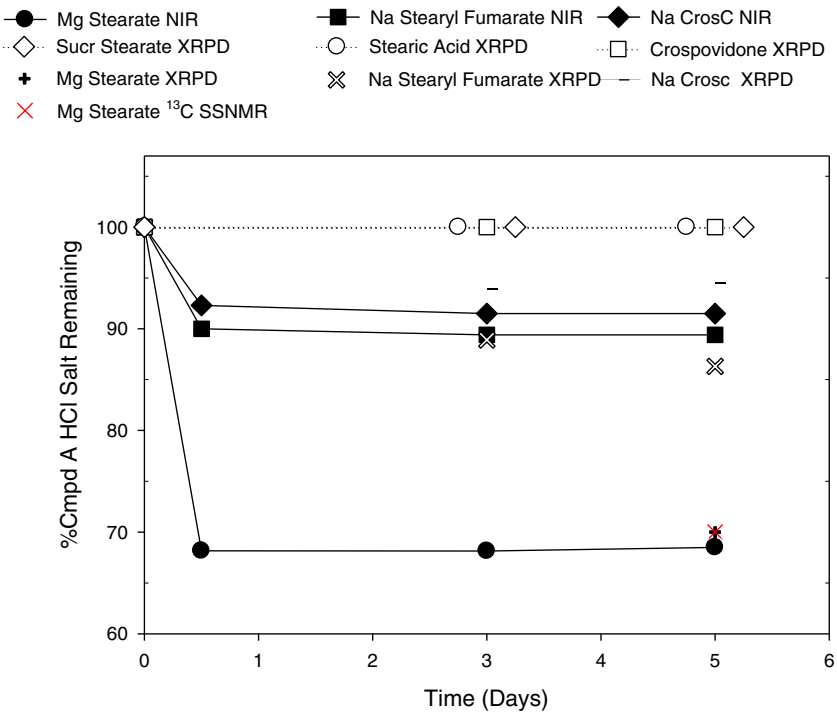


Fig. 3 Percent of HCl salt form remaining for 90:10 binary compacts of compound A HCl salt/excipients after exposure to 40°C/75%RH for 5 days.

form respectively. XRPD data at the 3 and 5 day time points agrees well with the NIR results (legend above Fig. 3). ^{13}C SSNMR data was also obtained for the magnesium stearate compact at 5 days. The observed SSNMR spectra were fit very well using only a linear combination of the crystalline free base and HCl signals, suggesting no significant amorphous material was present. This is consistent with our own failed efforts to isolate either amorphous free base or amorphous HCl compound A materials, both of which rapidly crystallized. The SSNMR data (red X data point in Fig. 3) is in excellent quantitative agreement with both the XRPD and NIR results.

The excipients in Fig. 3 capable of inducing disproportionation were similarly examined at the lower humidity condition of 40C/35%RH for several weeks. The disproportionation results are shown in Fig. 4. Although the disproportionation kinetics were slower at 40°C/35%RH than at 40°C/75%RH, the HCl salt form again decreased by approximately 30% in the magnesium stearate compact (solid circle, solid lines). The HCl salt decreased by 5% and 8% respectively for the sodium stearyl fumarate (solid lines, solid squares) and sodium croscarmellose compact (solid lines, solid diamonds).

Quantitation of Disproportionation in Compound A Pseudo Formulations

The pseudo formulations were stressed at 40°C/75%RH for ten days and the NIR and XRPD disproportionation data are shown in Fig. 5. The NIR data for the pseudo formulations containing sodium stearyl fumarate (solid square, Fig. 5) or sodium croscarmellose (solid diamond, Fig. 5) detected a rapid 10-15% loss of the HCl salt. The magnesium stearate pseudo formulation showed an approximate 30% decrease in the HCl salt form (solid circles, solid lines, Fig. 5) under the same conditions. XRPD data at the five day timepoints confirmed NIR data as shown in Fig. 5. However, the more sensitive XRPD method could not detect any disproportionation in the pseudo formulation samples containing sucrose stearate, stearic acid or crospovidone (open symbols). Similarly, XRPD did not detect any disproportionation in the 50:50 filler compacts (open blue symbols with dots).

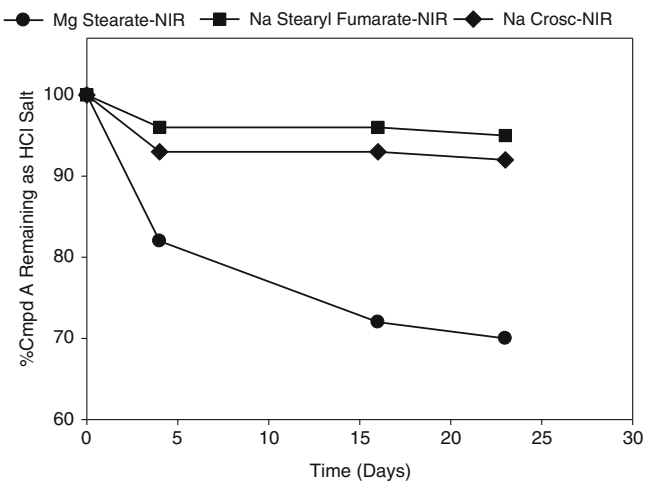


Fig. 4 Percent of HCl salt form remaining for 90:10 binary compacts of compound A HCl salt/excipients after exposure to 40°C/35%RH for 24 days.

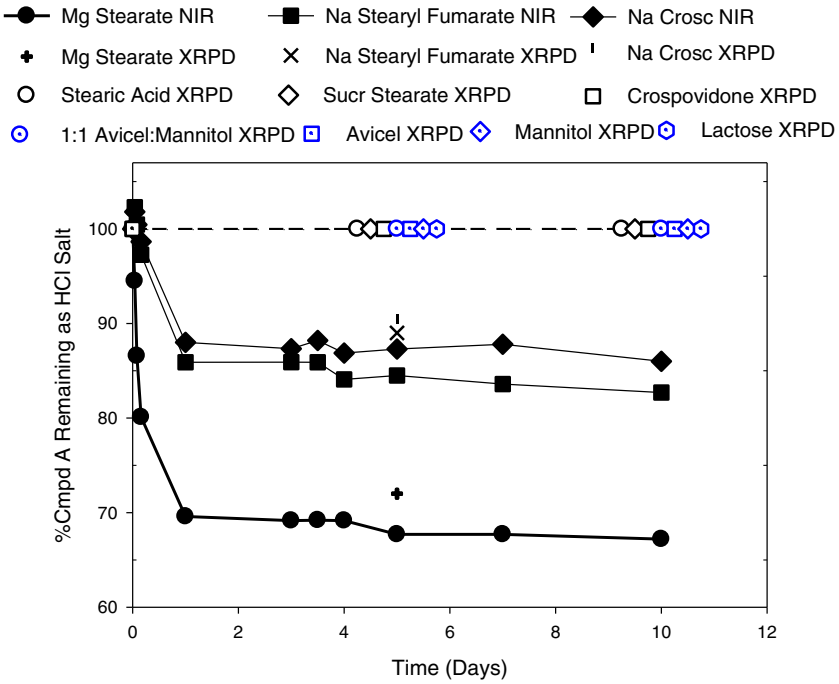


Fig. 5 Percent of HCl form remaining for 50% : 45% : 5% (avicel & mannitol : compound A HCl salt : excipient) pseudo formulation samples after exposure to 40°C/75%RH for 10 days; dotted lines are used to differentiate the neutral filler excipients from other neutral excipients, while solid lines are used to differentiate the proton accepting excipients.

The three pseudo formulation compositions showing significant disproportionation in Fig. 5 were also studied at 40°C/35% RH by NIR and the results are shown in Fig. 6. The disproportionation kinetics seen in Fig. 6 are slower than that observed at 40°C/75%RH in Fig. 5. Note the rate of disproportionation was fastest with magnesium stearate, followed by sodium croscarmellose while sodium stearyl fumarate was the slowest.

Unique Moisture Uptake of HCl Salt Compacts with Magnesium Stearate

The moisture uptake of 90:10 binary compacts at 40°C/75%RH was assessed gravimetrically. The compacts were not dried prior to exposure at 40°C/75%RH. The percent water gains observed in the approximately 280 mg binary compacts after 24 h are summarized in the upper row of Table III. A significant uptake of water (15 mg, or 5.3% of the initial compact weight) is only observed in the compact containing compound A HCl salt and magnesium stearate. To explore this further, the lower half of Table III compares the water uptake of pure magnesium stearate, pure compound A HCl salt, pure compound A free base, and finally a 90:10 compound A free base : magnesium stearate compact. None showed any significant water gain over the same 24 h period at 40°C/75%RH condition.

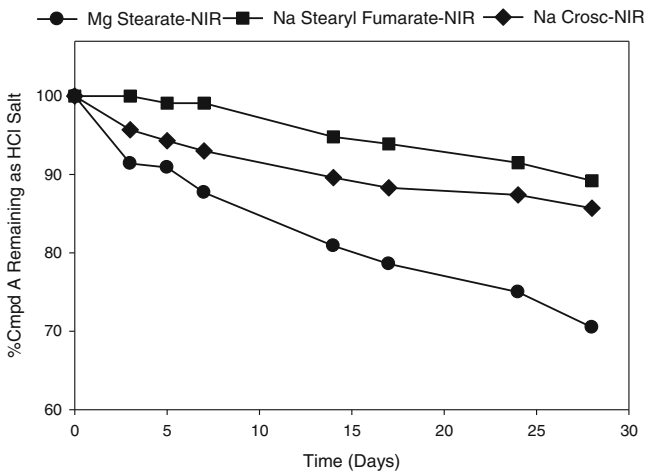


Fig. 6 Percent of HCl form remaining for 50% : 45% : 5% (avicel & mannitol : compound A HCl salt : excipient) pseudo formulation samples after exposure to 40°C/35%RH for 28 days.

The water uptake was further examined as a function of relative humidity (RH) using DVS. Figure 7 (upper) shows the moisture sorption curve of pure compound A HCl (diamonds) and pure magnesium stearate (X) at 40°C. Magnesium stearate can exist as amorphous or crystalline anhydrous, dihydrate, trihydrate forms (28). The X-ray powder pattern and the moisture content of the magnesium stearate used in this study suggests that it is mostly a dihydrate. At 40°C, magnesium stearate lost about 0.5% moisture upon drying (data not shown in Fig. 7) and gained about 0.7% moisture at 40%RH and 0.9% at 75%RH. Compound A HCl salt is not hygroscopic between 5 and 90%RH. For a mixture of 90:10 Compound A HCl salt and magnesium stearate, the water gain between 5 and 75%RH is expected to be less than 0.1% if there is no interaction between the two substances. However the 90:10 mixture (red solid triangles, lower portion of Fig. 7) showed a significantly higher amount of water uptake above 55% RH. In this data set, examination of the water uptake above 55%RH showed that the weight change did not reach equilibrium within the maximum four hour equilibration window.

Table III Compact Water Weight Gains (mg) of Various Mixtures and Pure Components and After 24 h Storage at 40°C/75%RH Open Dish

90:10 Binary Compacts of Cmpd A HCl : Excipients						
Compact Name	Mg Stearate	NaCrosc	Crospovidone	Sucr Stearate	Stearic Acid	Na Stearyl Fumarate
% Gain 1 day	5.3% (15 mg)	0.3%	0.4%	0.1%	0.1%	0.1%
Additional Compacts for Comparison						
Compact Name	Mg Stearate "neat"	Cmpd A HCl "neat"	Cmpd A FB "neat"	90:10 Cmpd A FB : MgSt		
% Gain 1 day	0.0%	0.1%	0.2%	0.2%		

Thus, two additional moisture sorption isotherms were collected with 6 and 12 h dwell times as described in the Materials and Methods section. Figure 7 (lower) shows the onset of water uptake progressively shifts lower to approximately 35%RH.

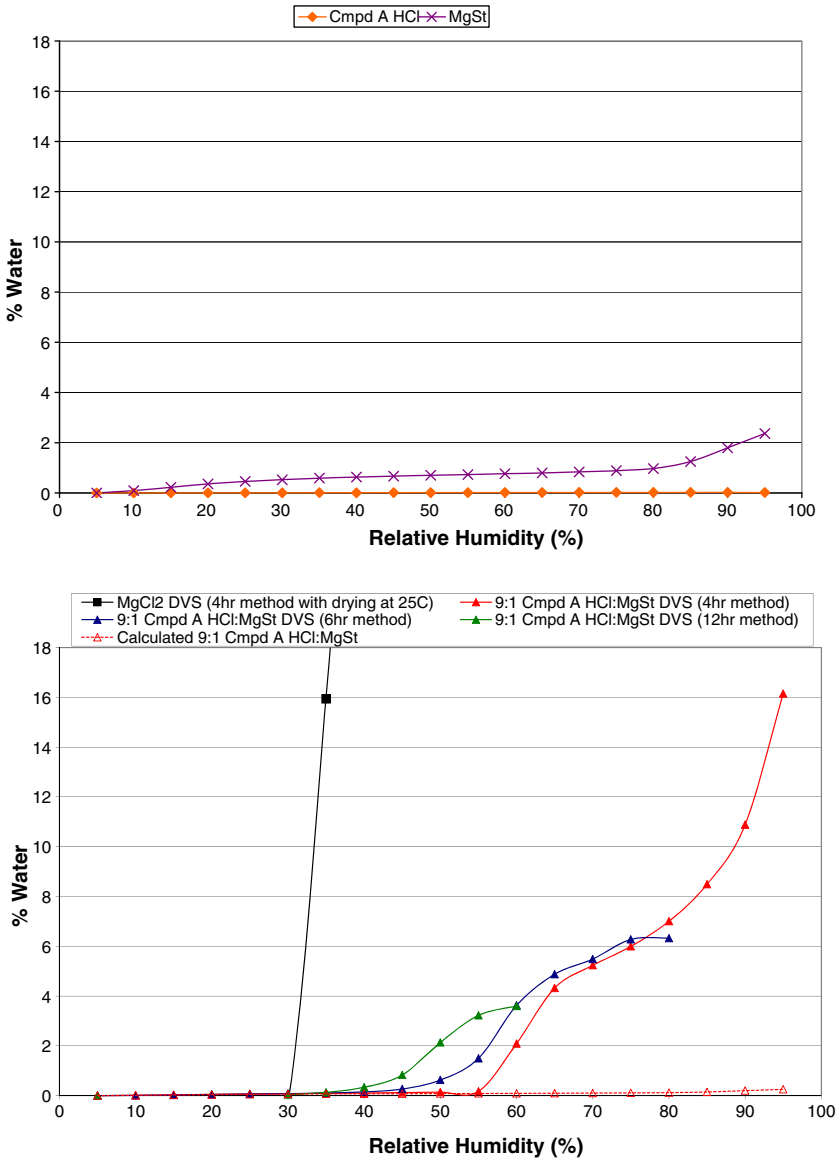


Fig. 7 Upper, moisture absorption profiles of compound A (*orange data points*) and magnesium stearate (*purple data points*). Lower, moisture absorption profile of 90:10 binary mixtures of compound A HCl salt and magnesium stearate collected with different dwell times at 40°C. Note the *arrows* highlight the observed shift in onset RH.

Finally, the spatial relationship between water uptake and regions of physical mixing of magnesium stearate and compound A HCl salt was probed. A 90:10 binary compact was made in which the magnesium stearate and the HCl salt were intentionally not mixed. A compact die base was filled with the compound A HCl salt. The center portion of the HCl salt powder bed was removed and replaced by magnesium stearate powder. The powder was then compressed into a compact and the water and magnesium stearate spatial images were obtained using NIR imaging spectroscopy (data not shown). The compact was then stressed for 3 days at 40°C/75%RH and a second set of images were obtained. The images showed that the largest water uptake had occurred at the interfacial regions, where the two components are in physical contact with one another.

Critical % RH for Magnesium Stearate Induced Disproportionation

The role of humidity in the disproportionation of 90:10 compound A HCl salt and magnesium stearate compacts was further investigated by stressing samples at 40°C and 20%, 31%, 35% and 75% relative humidities for 15 days. The loss of compound A HCl salt was monitored by NIR and XRPD and water uptake data was also measured at 5 and 15 days. Figure 8 shows that compound A HCl disproportionation rate dramatically increases above 31%RH and is accompanied by a sharp increase in water uptake. This critical % RH response for disproportionation and water uptake is well correlated to the deliquescence of magnesium chloride hexahydrate, ($MgCl_2 \cdot 6H_2O$) shown in the lower portion of Fig. 7 (solid black data points).

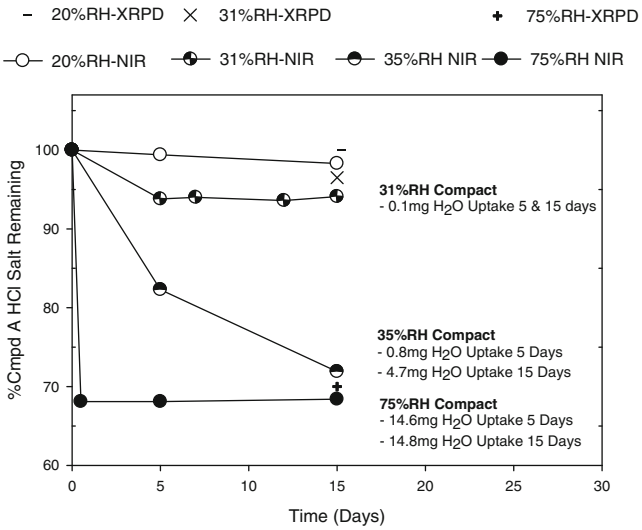


Fig. 8 Percent HCl salt form remaining for 90:10 binary compacts of compound A/magnesium stearate after exposure to 40°C and various humidities for 16 days.

DISCUSSION

Theory of Disproportionation and the pH of Maximum Solubility (pH_{max})

The general theory of disproportionation has been developed and refined numerous times (17–23,27) and will not be reviewed in great detail. Disproportionation is viewed as a solution mediated process occurring in thin films of water adsorbed to API salt particle surfaces. Given known or measured solubilities of the salt [BH+], the free base form [So], and the pKa, the critical parameter pH_{max} can be calculated from the equation below (17–23,27).

$$pH_{max} = pK_a + \log(So/[BH+]) \quad (1)$$

Disproportionation is only thermodynamically favored if the pH in the API film, or "microenvironmental" pH, is above the pH_{max} value (17–23,27). Excipients which can raise microenvironmental pH values above the drug salt pH_{max} value can promote disproportionation. There has been considerable interest in "predicting" which pharmaceutical excipients will be problematic in this context. The relative merits of excipient slurry pH and excipient surface pH measurement (26) have been discussed, with slurry pH appearing to be favored (18–23,27). Guerrieri and Taylor (18) concluded that slurry pH values had some predictive power, but noted sodium croscarmellose exhibited unique behavior, and that excipient solubility, surface area, and physical state could play a role. In Table I, the four highest slurry pH values correspond to two excipients which induced disproportionation of compound A and two which did not. Every slurry pH we measured (Table I) gave a higher pH than the compound A salt pH_{max} of 3.0, but only the "proton accepting" excipients caused disproportionation (*vide infra*).

More recently, Merritt (27) developed a qualitative model of disproportionation in which excipient effects were taken into account by using excipient slurry pH and a general excipient "solubility" to fit a pK_a value. This model qualitatively accounts for disproportionation in three of the four model formulations but significantly under predicted the disproportionation in the formulation containing 6.4% sodium croscarmellose and 1% magnesium stearate, (the remaining components were 3%HPC, 45% lactose, 38% mannitol). The authors suggested that the unique behavior of sodium croscarmellose could be due to its potential buffering capacity, which is not accounted for in their empirical modeling.

The quantitative data presented in our work highlights and confirms the importance of buffering capacity of excipients (16,27). In the studies with compound A HCl salt, every excipient containing carboxylate groups showed a differential ability to induce disproportionation compared to non-carboxylate containing excipients. The need for "significant"

excipient buffer capacity can be viewed from a congruence of two factors. The first is the very small volumes of water, 8×10^{-6}L estimated by Merrit (27), which are mediating the disproportionation reaction. Given a drug salt with a molecular weight of 400–500 g/mol and a 5 mg/ml solubility, it would take only 0.04 mg of drug salt to saturate the API water layers. This represent only a fraction of the total drug salt present in a typical tablet is needed to saturate API water layers. The saturated water layers will initially have a pH either at or below the pH_{max} value (18). Even if excipients then act to initially raise the pH above pH_{max} value, again only a very small fraction of a percent the API salt present would have dissolved to drive the pH of the water layers back down to the pH_{max} value (stopping further disproportionation). The second factor implicating excipient buffer capacity is the typical 5–10% limit of detection for free base in solid dosage formulations provided by current spectroscopic methods. Thus, in this conceptual framework, to observe "disproportionation" requires a large number of cycles of excipient pH raising (and subsequent API dissolution) to accumulate enough free base solids to be detected. In this limit, the excipients must buffer or neutralize as many protons as liberated by dissolution of the 5–10% of the API salt which has disproportionated.

Caroboxylate Groups as "Buffers" or Proton Acceptors

The pK_a of the carboxylate group containing excipients in Table I is expected to be approximately 4.5. Drug salts with pH_{max} values below pH 4.5 could thus provide protons to these carboxylate groups. The excipient slurry pH titration data in Table IV, column II shows that the water control and all non-carboxylate containing excipient slurries behaved identically, showing no buffering or proton uptake capacity. In contrast, the tritration data shows the carboxylate groups in slurries of sodium croscarmellose, magnesium stearate and sodium stearyl fumarate are readily titrated with HCl even though these excipients have very low true solubilities. Merritt (27) reported similar proton uptake for sodium croscarmellose during acid titration. The 22 mL excess HCl titrant (Table IV, compared to water control) for sodium croscarmellose and magnesium stearate corresponds to ca. 1.1×10^{-3} moles of protons that were taken up or neutralized. This is in remarkable agreement with the calculated 1.3×10^{-3} moles of carboxylate groups present in each sample, based on the approximate 12% by weight carboxylate group content from Table I. Despite these excipients being insoluble, protons can apparently be transferred through most of the excipient particle. Sodium stearyl fumarate similarly showed 7 mL's of excess HCl consumed, which corresponds to about 30% of the carboxylate groups present in the slurry. This lower value may be attributed to the particularly poor wetting of the excipient observed during the titration experiments.

Table IV Comparison of Experimental Slurry pH's and Titration Results for Pure Excipients (from Table I), Columns 3 & 4 are 9:1 Compound A : Excipient and 1:1 Compound A : Excipient Respectively

Excipient	mL of 0.05 N HCl Titrant Consumed*	9:1 Compound A : Excipient	1:1 Compound A : Excipient
1) Magnesium Stearate	**25**	2.7	**4.0**
2) Sodium Stearyl Fumarate	**10**	2.8	**3.2**
3) Sucrose Stearate	3	2.7	2.7
4) Stearic Acid	3	2.8	2.8
5) Sodium Croscarmellose	**25**	2.7	**3.4**
6) Crospovidone	3	2.7	2.8
7) Avicel PH-101	3	2.8	2.8
8) Mannitol	3	2.8	2.7
9) Spray Dry Lactose Monohydrate	3	2.8	2.8
10) DI Water (pH 7.5)	3	N/A	N/A

* Volume of 0.05 N HCl to produce a final pH of 2.9

The bold numbers are used to highlight the difference between results from these excipients and all the other excipients

Examination of the literature and our own data strongly suggests that even in typical tablet formulations at 40° C/75%, carboxylate groups can take up large amounts of protons needed to convert significant quantities of HCl salt to the free base form. Rohrs *et al.* (16) studied delavirdine mesylate in a sodium croscarmellose containing formulation at 40°C/75%RH open dish. Spectroscopic data showed rapid disproportionation of about 30% of the drug salt, after which disproportionation essentially stopped. Spectroscopic evidence of significant protonation of the carboxylate groups was given, and the authors noted that the caroboxylate groups in the sodium croscarmellose appeared to be "limiting" to approximately 90% of the total carboxylate groups present in sodium croscarmellose. Merritt *et al.* (27) presented quantitative disproportionation data for a HCl salt (pH max =1.3) formulated at 6.2% drug load in a tablet that contained 6.4% sodium croscarmellose and 1% magnesium stearate. Disproportionation data was shown over ca. 500 days at%RH values ranging from 6% RH to 33%RH. The 33%RH data showed over 80% of the HCl salt had disproportionated by the last timepoint and there was still a slight upward trend. In this case, the 6.4% sodium croscarmellose corresponds to 100 mole% of the HCl salt initially present; again suggesting the very large conversion to free base was facilitated by a molar excess of carboxylate groups present. Our pseudo-formulation disproportionation data of compound A at 40°C/75%RH (Fig. 5) also demonstrates this limit. The pH_{max} value of 3.0 for compound A sits well below the pK_a's of the proton accepting carboxylate groups of sodium croscarmellose, sodium stearyl fumarate and magnesium stearate. Given the carboxylate group content of about 12% by weight (Table I) and the 90:10 weight ratio of compound A

to carboxylate containing excipients in Fig. 5, protonation of every COO^- group present would require dissolution/disproportionation of ~15% of the compound A salt present. Figure 5 shows reasonable agreement for sodium croscarmellose and sodium stearyl fumarate. It is in this context that we use the term "proton acceptors" or "proton accepting capacity", in that these excipients clearly do not act as solubilized buffers, but rather protons are able to leave the water layers and migrate deep within the excipient particles to portonate COO^- groups. Magnesium stearate seems to have additional proton accepting capacity (Fig. 5), which might derive from magnesium oxide (29) or other basic impurities. However, no additional basic equivalents were detected in the titration data in Table II. A rationale for this observation is being further studied.

Formulating Weakly Basic HCl salts

Figures 3, 4, 5 and 6 clearly show that the only excipients which induced significant disproportionation of the compound A HCl salt are the excipients classified as "proton acceptors" in the right hand side of Table I (magnesium stearate, sodium stearyl fumarate, and sodium croscarmellose). The recent results of Merritt (27) are similar to our findings and appear to be dominated by sodium croscarmellose and/or magnesium stearate in Merritt's formulations 1, 2 and 4. Similarly Rohr's work (16) also suggests that excipients with carboxylate groups, such as sodium croscarmellose, are uniquely able to induce disproportion. In-house solid state excipient compatibility studies have repeatedly flagged these excipients as uniquely able to induce disproportion. The relative amount of carboxylate containing excipient (compared to drug) can be used to estimate the worst case disproportionation that would be observed at high water activity storage conditions. Assuming API's of 400-500 amu molecular weights, the carboxylate group content of these excipients gives approximately a 1 to 1 molar ratio of COO- groups to API salt molecules at similar weights in a formulation. Thus a 50 mg potency tablet with 2.5% sodium croscarmellose could show approximately 5% disproportionation at a maximum. Although controlling water activity in final packaging can help, Merritt's data ranging of the%RH from 6%–33%RH still showed approximately 20% free base formation at 6%RH over the 500 day experiment. Thus the risks of using these carboxylate containing excipients cannot necessarily be obviated with low%RH packaging.

The data presented here offers formulation scientists alternatives of similar functional class. While sodium croscarmellose (Table I), and by analogy sodium starch glycolate based disintegrants, can induce disproportionation, crospovidone can be used as a disintegrant. Similarly, although the lubricants magnesium stearate and sodium stearyl fumarate both contain proton accepting carboxylate groups, sucrose stearate and stearic acid do not have proton accepting groups (Table I). In our view, non-carboxylate containing excipients should be given serious consideration over their functional analogs which contain carboxylate groups.

Slurry pH Values of Drug Salt and Excipient Mixtures as Risk Predictors

We attempted to develop a way to get a quicker read on understanding disproportionation risk particularly with the carboxylate containing compounds. Initially, we examined slurry pH values of compound A and each excipient together in the same 90:10 weight ratio used in our solid state studies. This procedure is similar to that suggested by Serajuddin et. al. (30) for carrying out drug excipient compatibility testing. The resulting data is shown in the third column of Table IV. In all cases the slurry pH measured was not distinguishable from the compound A pH_{max} experimental value of 2.8. However, XRD of the solids (obtained after 24 h slurry) showed that in fact, a disproportionation reaction had occurred in the slurry for the three carboxylate containing excipients in Table I. Further, the disproportionation reaction had proceeded to a similar extent as the solid state reactions shown in Figs. 5 and 6 (~10-30% with magnesium stearate being the worst case). The other 90:10 compound A : excipient slurry solids showed negligible disproportionation.

In order to explore if a more differentiating compound A salt – excipient slurry pH value could be generated, the experiment was repeated by slurrying equal moles of compound A and carboxylate groups. Thus 1 to 1 by weight compound A to excipients were slurried. The data is shown in the right hand column in Table IV highlights that in fact, at this 1:1 weight ratio the slurry pH values are clearly elevated above pH_{max} only for the three carboxylate containing compounds which gave rise to disproportionation in the solid state pseudo formulations. Magnesium stearate gave the highest slurry value. XRD analysis of the solids in these three cases showed that the majority of the remaining drug salt was in the free base form. This 1 to 1 by weight

Table V Summary of the Extent of HCl Salt Disproportionation Reached in 90:10 Binary Compacts and Pseudo Formulations with Avicel:Mannitol at 40°C/75% RH and 40°C/35% RH

90:10 Binary compacts	%HCl Lost (40°C/75%RH)	%HCl Lost (40°C/35%RH)
Na croscarmellose	8	8
Na starch fumarate	10	5
Mg stearate	32	30
Psuedo formulations		
Na Croscarmellose	14	14
Na starch fumarate	18	10
Mg stearate	32	30

slurry pH procedure can rapidly reveal (by pH value) significant proton accepting capacity as well as confirm if the pH_{max} value of the API is lower than the pK_a of the proton accepting excipients.

Water Activity in the Solid State Influences Disproportionation Rate and Extent

The rate of disproportionation in binary compacts or pseudo formulations containing the three carboxylate containing excipients appears faster at 40°C/75% RH (Figs. 3 and 5) than at 40°C/35% RH (Figs. 4 and 6). This result is consistent with the idea that sorbed water layers around different types of solid surfaces will be more developed at higher humidities (31–34), and proton diffusivity between the API water layers and excipients may be increased. In this context it is interesting to compare the % freebase observed in Figs. 4, 5 and 6. This data is further summarized in Table V and indicates that each excipient has unique behavior. In 90:10 binary compacts, both sodium croscarmellose and sodium stearyl fumarate, at both 40°C/75% RH and 40°C/35% RH conditions, show a significantly lower extent of disproportionation compared to the pseudo formulations. Sodium croscarmellose shows the same extent of disproportionation at 40°C/75% RH and 40°C/35% RH, in both binary compacts and pseudo formulations. In contrast, sodium stearyl fumarate consistently shows a ca. 50% reduction in the extent of disproportionation reached at the lower 40°C/35% RH condition. Finally, magnesium stearate shows the most unique behavior, in that the same extent of disproportionation (30–32%) is reached in binary compacts or pseudo formulations, at either humidity condition studied. It appears possible that the differential water sorption properties of avicel (in the pseudo formulations), sodium croscarmellose and sodium stearyl fumarate could influence the rate of proton transfer between compound A HCl and all the COO^- sites in each carboxylate containing excipient. We speculate that the magnesium stearate behavior may be related to its unique water uptake properties discussed in the next section.

Unique Behavior of Magnesium Stearate: *In Situ* Formation of Magnesium Chloride

Throughout the work described here, magnesium stearate shows unique effects compared to the other two carboxylate group containing excipients sodium croscarmellose and sodium stearyl fumarate. Binary compacts and pseudo formulations (Figs. 3, 4, 5 and 6) with magnesium stearate all show markedly more rapid and greater extent of disproportionation than the other carboxylate containing excipients (Table V). Table III highlights that only the magnesium stearate binary compacts absorbed unusually high amounts of water. The DVS data in Fig. 7 shows that this unique water sorption only occurs when magnesium stearate and the compound A HCl salt are mixed together. These observations indicate that a new chemical species is formed in the binary compact and that it is hygroscopic. These data are readily explained by simply considering the full charge balanced disproportionation equation at hand:

Table VI Comparison of Equilibrium Water Weight Gains (mg) of Dried $MgCl_2 \bullet 6H_2O$ *vs.* Various 90:10 Compound A HCl Salt : Magnesium Stearate After Storage at 40°C and Various Percent Relative Humidities

Sample	Moles H_2O/Moles of Mg^{+2}
75% RH Open Dish	
$MgCl_2 \bullet 6H_2O$- 10 Days$^{+\dagger}$	21
90:10 75%RH-5, 15 Days, †	19*
35% RH Open Dish	
$MgCl_2 \bullet 6H_2O$-20 Days$^{+\dagger}$	10
90:10-15Days	7*
90:10–28 Days†	12*

$^{+}$ $MgCl_2 \bullet 6H_2O$ was dried at 60°C for 3 weeks then KF was taken and confirmed the hexahydrate stoichiometry. The weight gain was assumed to be solely attributed to water and was used to calculate the water to Mg^{+2} ratio

† Samples were weighed until a constant mass was obtained and are considered to be at equilibrium

* The magnesium stearate contained 3.2% water or approximately one additional mole of water per mole of Mg^{+2}. The additional mole of water was included in the total moles of water to moles of Mg^{+2} calculation for 90:10 binary compacts

$$\underset{\text{drug HCl salt}}{(2)D{-}H^{+}Cl^{-}} + \underset{\text{(mag.stearate)}}{R{-}COO^{-}Mg^{+2-}OOC{-}R} \longrightarrow \underset{\text{stearic acid}}{(2)R{-}COOH} + \underset{\text{magnesium chloride}}{MgCl_2} + \underset{\text{drug free base}}{(2)\,D} \quad (2)$$

Equation (2) is a reminder that in order to maintain charge neutrality, proton transfer from the weakly acidic drug to the carboxylate groups must be accompanied by the formation of magnesium chloride, $MgCl_2$. We have noted that the water weight gains observed in our 90:10 compound A: magnesium stearate binary compacts (Table III, Fig. 8) appear to correspond to that expected for the equivalent amount of $MgCl_2 \cdot 6H_2O$ under the same humidity conditions. This data is shown and described in Table VI. When dry $MgCl_2$ solid is placed at 40°C/75% RH and allowed to come to equilibrium, the solid deliquesces and the molar ratio of water to Mg^{+2} ion is ~21. The water to Mg^{+2} ratio in the 90:10 compacts at the same 40°C/75% RH condition is ~19. This remarkable result

argues that the 5.3% water weight gain in the compact corresponds to almost complete conversion of all the magnesium ions present in the magnesium stearate to $MgCl_2$ as shown in Eq. (2). The signal for $MgCl_2$ in the 90:10 compound A : magnesium stearate was too weak for detection by XRPD. If a 1:1 compact of compound A HCl salt and magnesium stearate is stored at 40°C/75%RH and subsequently dried, we are able to identify weak but unique XRPD signals of crystalline magnesium chloride near 33 and 34 2-theta (data not shown). The critical % RH dependence observed in Fig. 8 (just above 31% RH), as well as the DVS data in the lower portion of Fig. 7 is consistent with the formation of $MgCl_2$ and the weak signal observed in XRPD. The critical RH dependence corresponds to the deliquescent RH (DRH) for $MgCl_2$ of ~32.5% RH near 40°C (35). These data suggest that disproportionation rates are increased above 33%RH (at 40C) in the binary compacts and pseudo formulations containing magnesium stearate due to $MgCl_2$ formation and deliquescence. The formation of $MgCl_2$ is likely a general effect for low pH_{max} HCl salts and magnesium stearate containing formulations.

It is worthwhile to briefly consider Eq. (2) in the context of potential formation and deliquescence of sodium chloride in the sodium croscarmellose or sodium stearyl fumarate containing samples. The DRH of NaCl is reported to be approximately 75%RH at 25–40°C (35, 36). When pure NaCl salt was exposed to our 40°C/75%RH stability chamber for 5 days, deliquescence was not observed. This was consistent with the report by Cantrell, *et al.* (37) that NaCl crystals do not deliquesce until slightly above 75%RH. Thus in our 90:10 binary compacts of compound A HCl and either croscramellose sodium or sodium stearyl fumarate, we do not expect to observe NaCl deliquesence; and no unusal water weight gains were observed (Table III). However, if the NaCl is mixed with a highly soluble excipient such as lactose or mannitol the DRH is lowered to 72% RH (38). While NaCl deliquescence could be possible in formulations containing soluble excipients such as lactose and mannitol, the DRH would still be near 72%RH and is much higher than that of $MgCl_2$. Thus $MgCl_2$ deliquescence poses a unique threat to facilitate disproportionation rates in the more realistic long-term packaging %RH humidity range above 35%RH.

CONCLUSIONS

Salts of a weak base with low pH_{max} values pose significant formulation challenges associated with excipient induced disproportionation. Nine common excipients including three fillers, four lubricants and two disintegrants have been examined with regard to their ability to induce such disproportionation. Only two lubricants, sodium stearyl fumarate and magnesium stearate, and one disintegrant, sodium croscarmellose, caused disproportionation. Alternative lubricants and disintegrants are demonstrated. The problematic excipients all contain high densities of proton accepting carboxylate groups which have pK_a values above that of the pH_{max} of the drug salt. The extent of disproportionation observed was correlated to almost complete protonation of all the carboxylate groups present. Neither excipient slurry pH or excipient surface pH was found to be a selective predictor of whether or not an excipient would induce significant disproportionation. This result is rationalized by realizing a pH measurement does not reveal the proton accepting (buffering) capacity of the system being measured. An excipient screening procedure is suggested in which the drug salt and the excipient are slurried together in a 1 to 1 weight or 1 to 1 molar proton acceptor - proton donor ratio, and the pH compared to the drug salt pH_{max} value. This procedure can more selectively reveal "high risk" excipients. Consideration of the anticipated relative abundance of the drug salt and the excipient in the formulated dosage form then frames this risk more appropriately. Magnesium stearate was found to have unique behavior and was the most problematic excipient for HCl salts, largely due to the *in-situ* formation of $MgCl_2$, which is deliquescent above ~32.5%RH. This disproportionation product draws in water at low percent relative humidity values which further enhances disproportionation rates. The use of carboxylate group containing excipients should be considered carefully when developing a solid dosage form for an HCl salt of a weak base. The selection of excipients should not only take the proton accepting capacity of the excipient into consideration, but also the hygroscopicity of all the disproportionation products.

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