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*Research Article*

# Surface Acidity and Solid-State Compatibility of Excipients with an Acid-Sensitive API: Case Study of Atorvastatin Calcium

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***Abstract.*** The objectives of this study were to measure the apparent surface acidity of common excipients and to correlate the acidity with the chemical stability of an acid-sensitive active pharmaceutical ingredient (API) in binary API-excipient powder mixtures. The acidity of 26 solid excipients was determined by two methods, (i) by measuring the pH of their suspensions or solutions and (ii) the pH equivalent ($pH_{eq}$) measured via ionization of probe molecules deposited on the surface of the excipients. The chemical stability of an API, atorvastatin calcium (AC), in mixtures with the excipients was evaluated by monitoring the appearance of an acid-induced degradant, atorvastatin lactone, under accelerated storage conditions. The extent of lactone formation in AC-excipient mixtures was presented as a function of either solution/suspension pH or $pH_{eq}$. No lactone formation was observed in mixtures with excipients having $pH_{eq} > 6$, while the lactone levels were pronounced (> 0.6% after 6 weeks at 50°C/20% RH) with excipients exhibiting $pH_{eq} < 3$. The three $pH_{eq}$ regions (> 6, 3–6, and < 3) were consistent with the reported solution pH-stability profile of AC. In contrast to the $pH_{eq}$ scale, lactone formation did not show any clear trend when plotted as a function of the suspension/solution pH. Two mechanisms to explain the discrepancy between the suspension/solution pH and the chemical stability data were discussed. Acidic excipients, which are expected to be incompatible with an acid-sensitive API, were identified based on $pH_{eq}$ measurements. The incompatibility prediction was confirmed in the chemical stability tests using AC as an example of an acid-sensitive API.

**KEY WORDS:** acidity; atorvastatin; excipients; pH indicators; solid-state stability.

## INTRODUCTION

Excipients can have a major impact on the chemical stability of an active pharmaceutical ingredient (API) and hence the shelf life of solid dosage forms. In particular, an understanding of the acidic-basic nature of excipients, combined with studies of pH-solubility and pH-stability profiles of APIs, is essential in designing excipient compatibility experiments (1). There are two common methodologies to characterize the "acidity" of solid pharmaceutical excipients. Traditionally, an aqueous solution or suspension of an excipient is prepared and the pH of the aqueous phase is measured (2). Alternatively, measurements are performed with solid materials, in which acid-base properties of the material are evaluated by monitoring protonation-dependent properties of various probe molecules with a corresponding detection method. Detection methods depend on the nature of a probe molecule and include NMR (2), fluorescence (3), attenuated total reflectance Fourier transform infrared spectroscopy (4), evanescent wave cavity ring-down spectroscopy (5), electron spin resonance (6), inverse gas chromatography (7), and diffuse reflectance visible spectroscopy (9–11). The last method usually utilizes common pH indicators (i.e., sulfonephthalein probe molecules) and represents the most common approach for pharmaceutical systems. In these measurements, the acidity of the solids has been expressed either as pH equivalent ($pH_{eq}$) (8–10) or Hammett acidity function, $H_{2-}$ (11), where, by convention, the subscript, 2−, refers to the charge of the basic form of indicator. The $pH_{eq}$ of the solid surface is defined as the pH of an aqueous solution in which the ratio of the peak absorbance signals of the ionized to the unionized forms of the indicator is the same as in the given solid sample. If the ratio of the extinction coefficients of the ionized and unionized species is similar in an aqueous solution and in the solid sample, as was shown for several sulfonephthalein indicators (11), the $pH_{eq}$ value closely approximates the $H_{2-}$ (9).

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The ultimate pharmaceutical application of these measurements is in the prediction of chemical compatibility of excipients with acid- or base-sensitive APIs in solid dosage forms. Limitations of both the approaches to measure apparent acidity for pharmaceutical solids have been discussed earlier (9,11,12). However, this is not a problem unique to solids; many liquid systems, such as mixed solvents and aqueous solutions with high salt or acid concentrations, do not have an established, thermodynamically rigorous, proton activity scale (13). In such liquid systems, multiple acidity scales have been used. The complications in developing a unified acidity scale for solutions has been elegantly articulated by Paul and Long who wrote: "…there is no single, unique good measure of acidity. There are a variety of them, and any preference depends on such things as ease of measurement and ultimate application" (14). This is exactly the situation in the case of solid surface acidity measurements, where both the ease of measurements and ultimate application, often dictate the various ways of measuring and expressing acidity of excipients in solid dosage forms.

Applying the "ease of measurement" criterion to the two methods described above, there is no doubt that the suspension/solution pH measurements provide a more convenient and consistent way to generate numerical values. The probe indicator method is more difficult from the measurement perspective and also has more experimental variables. These issues were addressed by Pudipeddi *et al* (12) and also in our earlier publications (9,11). For example, any particular probe molecule would cover only a narrow acidity range, and several indicators with different $pK_a$ values may be needed to measure acid-base properties of different excipients. In addition, $pH_{eq}$ values were dependent on the probe molecule used, when the acidity values of the same material differed by 0.1–0.5 units when measured using different indicators (11).

A meaningful test of the applicability of various acidity scales would require comparison of the measured "acidity" with the actual chemical stability of the API in drug-excipient mixtures. For example, an excipient, which the measurements reveal as strongly acidic, would be expected to catalyze degradation of an acid-labile API. Such studies, attempting to evaluate the applicability of techniques for characterization of solid pharmaceuticals, have been reported and are briefly discussed below. Badawy *et al* (15) used slurry pH measurements to select excipients for DMP 754, an ester prodrug with maximal solution stability at ~pH 4. Addition of disodium citrate (saturated solution pH 4.6) improved solid-state stability, whereas degradation was accelerated in formulations with four other acidic excipients with lower solution pH (citric acid, fumaric acid, monobasic sodium phosphate, and monosodium citrate; pH 0.4–3.5). Similarly, Serajuddin *et al* (16) used slurry pH measurements to explain reactivity in drug-excipient compatibility studies and to select formulation components. Correlations between $pH_{eq}$ measurements and solid-state stability have also been reported. In one such example, acetylsalicylic acid was deposited on dibasic calcium phosphate granules, with surfaces modified to varying acidity. The rate of solid-state degradation of acetylsalicylic acid in the resulting mixtures changed as a function of the $pH_{eq}$. The $pH_{eq}$–solid-state stability relationship matched the pH-stability profile in solutions (17). In another example, surface properties of microcrystalline cellulose granules were modified by pretreatment with different buffer systems, and the modified surfaces were characterized by $pH_{eq}$ measurements. The $pH_{eq}$-degradation rate profile of pirenzepine dihydrochloride deposited on these granules was similar to the solution pH-stability profile of pirenzepine (18).

In order to differentiate between the two approaches, a side-by-side comparison was needed, in which surface acidity of the same system is expressed, using both measurement approaches and further compared with solid-state reactivity. An example of such a systematic study for a pharmaceutically relevant system was reported by Hailu and Bogner (19), in which the chemical reactivity of amorphous quinapril HCl in mixtures with silicates of different pH grades was studied. The authors measured both $pH_{eq}$ and suspension pH values of quinapril HCl–silica co-ground mixtures. The stability of quinapril in these mixtures was evaluated as a function of $pH_{eq}$ and suspension pH. The $pH_{eq}$–solid-state stability profile was similar to the solution pH-stability profile of quinapril, both reflecting minimum stability at a solution pH or $pH_{eq}$ of ~ 4 and relatively stable quinapril at solution pH (or $pH_{eq}$) > 6. On the other hand, when the same stability data were presented as a function of suspension pH, the "suspension pH-stability profile" was significantly shifted from both solution pH-stability and $pH_{eq}$ profile, with the minimal stability corresponding to suspension pH of approximately 7.5. Therefore, in this particular example of quinapril HCl/silicate co-ground mixtures, $pH_{eq}$ seemed to be a better stability predictor than suspension pH.

Overall, there is limited side-by-side comparison of the rate of acid or base-catalyzed solid-state reactions with the surface acidity measurements using *both* solution/suspension pH *and* $pH_{eq}$ scales (19,20). This scarcity of data makes it difficult to establish a meaningful conclusion on the reliability of either acidity scale in predicting incompatibility between acid-sensitive API and excipients.

*Therefore, the overall goal was to measure the acidity of common solid excipients, and evaluate the ability of these measurements to predict compatibility of an acid-sensitive API with each excipient.* The specific objectives were to (i) evaluate a wide variety of solid excipients for their acid-base properties using the two methods, (ii) using these measurements, predict the compatibility of these excipients with an acid-sensitive API, atorvastatin calcium, (iii) compare the predicted compatibility with experimentally measured stability of atorvastatin calcium in binary powder mixtures with these excipients, and (iv) discuss potential reasons for the difference between predicted compatibility (based on either acidity scale) and experimentally measured chemical instability. Note that the present study was focused on correlating properties of neat excipients and their impact on API stability in heterogeneous powder mixtures with API. The relationships between solid-state stability and acid-base milieu in single-phase API-excipient mixtures (such as amorphous freeze-dried materials) are covered elsewhere (21,22).

The model drug was atorvastatin calcium, a hydroxy acid statin, which exhibits a pH-dependent hydroxy acid to lactone conversion (23). Surface acidity of twenty-six excipients covering all major classes (i.e., binders, diluents, disintegrants, lubricants) was characterized by measurement of both $pH_{eq}$ and solution/suspension pH. Furthermore, binary API-

excipient mixtures were subjected to accelerated stability testing, and the solid-state chemical stability data are presented as a function of the measured acidity of the excipients.

In powder API-excipient mixtures, a significant (> 0.6% after 6 weeks at 50°C/20% RH) lactone formation was observed when $pH_{eq}$ of an excipient was <3, whereas lactone did not form when $pH_{eq}$ of an excipient was >6. This finding was consistent with the solution pH-stability profile (23), in which acidic conditions (pH < 3) favor formation of lactone, whereas lactone was not observed at near neutral and basic conditions (pH > 6). The results presented in this paper are relevant to early formulation development of acid-sensitive compounds, as they would allow the rational selection of excipients based on prediction of API-excipient compatibility.

## MATERIALS AND METHODS

*Materials.* The sulfonephthalein indicators, bromocresol green (BG), bromophenol blue (BB), bromocresol purple (BP), and thymol blue (TB) were obtained as monosodium salts from Sigma Chemical Company, St. Louis, MO. Chlorophenol red (CR; sodium salt) was obtained from Lancaster Synthesis, Pelham, NH. The excipients used in this study are listed in Table I. Sources of the excipients are provided in the Appendix. Amorphous atorvastatin calcium was a gift from Pfizer Inc.

*Solid-State Stability.* Eighteen binary API-excipient blends were prepared, first by mixing using a mortar and pestle, followed by powder blending in a TURBULA® mixer for 10 min. Excipient: API ratios were 75:1 (*w*/*w*) for diluents and enteric polymers, 15:1 for disintegrants and binders, 1:1 for lubricants, and 5:1 for additives to approximate the ratios expected in solid dosage forms. After the preparation of approximately 2–3 g of the individual blends, the samples were loaded into 60 cc amber glass bottles and covered with gauze. The bottled mixtures as well as the control (pure amorphous atorvastatin calcium) were placed in environmental chambers at 40°C/25% RH and 50°C/20% RH and sampled after 6 weeks. The lactone content in the samples was determined by reverse-phase high performance liquid chromatography (HPLC). The isocratic HPLC method utilized a $C_{18}$ reversed phase chromatography column (Phenomenex® Ultremex®; 250×4.6 mm; 5 uM) with a flow rate of 1.5 mL/min of ammonium citrate buffer (0.05 M; pH 4.0)/acetonitrile/tetrahydrofuran (53:27:20 *v*/*v*) over a period of 30 min. Detection was at 244 nm. Lactone concentration was reported as percent of the total peak area in the chromatogram.

### pH of Solutions/Suspensions

Solutions/suspensions of the excipients were prepared at 1:10 and 1:20 excipient/water weight ratios using deionized, freshly boiled, and cooled water. The samples were stored in sealed vials and were shaken intermittently over a period of 1–2 h before pH measurements. The pH values of these systems, as well as those of saturated solutions of selected excipients, were measured (Oakton pH 500 pH meter) at ambient temperature (25±2°C). The pH meter was calibrated using standard buffer solutions of pH 4.01, 7.00, and 10.01 (Oakton Instruments, Vernon Hills, IL).

### $pH_{eq}$ Determination

To deposit indicators onto the excipients, solutions of suitable sulfonephthalein indicators (1 mg/ml) in either methanol or water were mixed with each excipient and dried. Sufficient additional liquid (up to 1 ml per 5 g of sample) was added to permit homogeneous mixing of the indicator with the powder. Aqueous solutions of the indicator were used for the stearic acid and the HPMC acetate succinate samples, and methanolic solutions were used for all other excipients. The indicator concentrations ranged from 0.05 to 0.15 mg per gram of excipient. The ratios of the Kubelka–Munk functions, F(R), at the peaks corresponding to the ionized and unionized forms of the indicator (peak height ratios) were determined using a UV visible spectrophotometer (Cary 100 Bio) equipped with a diffuse reflectance accessory (Labsphere, model DRA-CA-30I). A $pH_{eq}$ value for each excipient was determined using the peak ratio in the solid samples and the peak ratio–solution pH relationships constructed for the corresponding indicator in buffered aqueous solutions (9).

## RESULTS

Table I lists the lactone levels in API-excipient mixtures after 6 weeks of storage at 40°C/25% RH and 50°C/20% RH. No lactone formation was observed following storage of amorphous atorvastatin calcium alone (i.e., without excipients). The majority of the excipients destabilized atorvastatin calcium, with detectable lactone formation observed in 14 and 20 mixtures stored for 6 weeks at 40°C/25% RH and 50°C/20% RH, respectively.

The solution/suspension pH measurements were performed using samples with 1:20 and 1:10 excipient/water weight ratio. In addition, for the highly soluble excipients, the saturated solution pH values were also determined. Table I summarizes the results of the pH measurements. For further correlations, we have chosen solution/suspension pH values obtained at the highest solid concentration.

The $pH_{eq}$ was determined using four different probe molecules, thymol blue: $pK_a$=1.6 (24), bromophenol blue: $pK_a$=4.0 (25), bromocresol green: $pK_a$=4.7 (25) and bromocresol purple: $pK_a$=6.3 (25), to cover the acidity range of the excipients. Examples of visible diffuse reflectance spectra of thymol blue deposited on three different excipients are shown in Fig. 1. In the case of anhydrous DCP, peaks for both ionized and unionized (protonated) species of the indicator were observed, allowing calculation of $pH_{eq}$ as described earlier (9). For citric acid, only the protonated form of thymol blue was observed, suggesting that the $pH_{eq}$ was lower than the range over which thymol blue could be used. On the other hand, while thymol blue was completely ionized when deposited on DCP dihydrate (Fig. 1), bromophenol blue was partially ionized when deposited on its surface (spectra not shown), allowing calculation of $pH_{eq}$.

The $pH_{eq}$ values of the excipients are summarized in Table I. Overall, the four indicators allowed the measurement

**Table I.** Summary of the Results Including (i) Suspension/Solution pH and $pH_{eq}$ Value of Each Excipient and (ii) Lactone Formation in Atorvastatin Calcium-Excipient Binary Powder Mixtures

| ID no. | Excipient | Excipient type | Solution/suspension pH | | | Indicator used[b] | $pH_{eq}$[c] | Lactone formed in binary mixtures after 6 weeks (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | | 1 in 20 parts | 1 in 10 parts | Sat. soln.[a] | | | 40°C/25% RH | 50°C/20% RH |
| 1 | Magnesium stearate (vegetable sourced) | Lubricant | 9.2 | 9.1 | – | PR | 6.8 | NQ | NQ |
| 2 | Sodium citrate, anhydrous[a] | Additive | 8.6 | 8.6 | 8.5 | PR | 6.9 | NQ | NQ |
| 3 | Polyethylene oxide (POLYOX WSR)[d] | Binder | 8.9 | ND | – | PR | 7.8 | NQ | NQ |
| 4 | Sodium lauryl sulfate[a] | Additive | 9.4 | 9.5 | 10.2 | TB | 8.2 | NQ | NQ |
| 5 | Sodium saccharin[a] | Additive | 8.2 | 8.2 | 7.5 | BG | 4.0 | NQ | NQ |
| 6 | Pre-gelatinized starch (Starch 1500) | Diluent | 5.8 | 5.6 | – | BG | 4.2 | NQ | NQ |
| 7 | Lactose monohydrate[a] | Diluent | 5.9 | 6.1 | 5.6 | BG | 3.8 | NQ | 0.1 |
| 8 | Crospovidone (Polyplasdone XL)[d] | Disintegrant | 6.2 | ND | – | BP | 5.3 | NQ | 0.12 |
| 9 | Xylitol CM—50 micron | Diluent | 5.2 | 4.9 | ND | BG | 4.4 | NQ | 0.13 |
| 10 | Spray dried lactose (Lactose Fast Flo 316)[a] | Diluent | 6.9 | 6.8 | 5.8 | CR | 5.1 | NQ | 0.14 |
| 11 | Mannitol, Granular 2080[a] | Diluent | 5.0 | 4.6 | 4.3 | BG | 3.9 | NQ | 0.18 |
| 12 | Fructose | Diluent | 5.0 | 4.6 | ND | BG | 4.8 | NQ | 0.24 |
| 13 | Calcium acetate, hydrate[a] | Diluent | 7.6 | 7.5 | 7.4 | BP | 5.5 | 0.14 | 0.25 |
| 14 | Silicified microcrystalline cellulose (PROSOLV SMCC 90) | Diluent | 6.5 | 6.3 | – | BG | 4.80 | 0.22 | 0.2 |
| 15 | Lactose, anhydrous, (direct tableting grade)[a] | Diluent | 5.2 | 4.1 | 4.4 | BG | 3.4 | 0.23 | 0.49 |
| 16 | Sodium starch glycolate (EXPLOTAB)[d] | Disintegrant | 6.3 | ND | – | CR | 4.9 | 0.25 | 0.38 |
| 17 | Croscarmellose sodium (Ac-di-sol)[d] | Disintegrant | 5.4 | ND | – | BG | 4.8 | 0.18 | 0.43 |
| 18 | Glyceryl monostearate | Lubricant | 4.2 | 4.2 | – | BB | 2.6 | 0.3 | 0.75 |
| 19 | Sorbitol | Diluent | 4.6 | 4.3 | ND | BB | 2.9 | 0.43 | 0.94 |
| 20 | Stearic acid, powder | Lubricant | 5.7 | 5.7 | – | TB | 2.7 | 0.91 | 86.3 |
| 21 | HPMC acetate succinate HF | Enteric polymer | 3.8 | 3.7 | – | TB/BB | ~2.7 | 1.05 | 0.85 |
| 22 | Calcium phosphate dibasic, anhydrous, unmilled (A-TAB) | Diluent | 5.4 | 5.2 | – | TB | 2.17 | 1.11 | 0.89 |
| 23 | Citric acid anhydrous, fine, granular[a] | Diluent | 2.0 | 2.0 | 1.5 | TB | <1.6 | 1.37 | 2.43 |
| 24 | HPMC acetate succinate MF | Enteric polymer | 3.8 | 3.8 | – | TB/BB | ~2.7 | 1.73 | 1.31 |
| 25 | Calcium phosphate dibasic, dihydrate | Diluent | 7.8 | 7.7 | – | BB | 2.8 | 2.26 | 1.02 |
| 26 | HPMC acetate succinate LF | Enteric polymer | 3.8 | 3.7 | – | TB | 2.6 | 2.44 | 1.94 |

*NQ* not quantifiable (<0.1%), *ND* not determined

[a] When the solubility of the excipient exceeded 1 part of solid in 10 parts of water, saturated solution pH was also determined. For each excipient, the pH measured at the highest solid concentration was used for further comparative evaluation (Figs. 2, 3)

[b] *BG* bromocresol green, *BB* bromophenol blue, *BP* bromocresol purple, *TB* thymol blue, *PR* phenol red

[c] Reproducibility in $pH_{eq}$ measurements was ±0.02 or better

[d] In excipients that formed highly viscous mixtures at lower solid concentration (one part solid in 20 parts of water), higher concentrations were not evaluated for suspension pH

of $pH_{eq}$ of the majority of excipients—the exceptions were the two grades of hydroxypropyl methylcellulose acetate succinate (HPMCAS) and citric acid. The indicator thymol blue with the lowest $pK_a$ was completely unionized in the solid sample of anhydrous citric acid; therefore, $pH_{eq}$ is reported as < 1.6. For HPMCAS (MF and HF grades), while thymol blue ($pK_a$=1.6) was predominantly ionized, and bromophenol blue ($pK_a$=4.0) was predominantly unionized. The calculated $pH_{eq}$ values were beyond the working range for both indicators, and hence, a $pH_{eq}$ of ~2.7 was assigned for both grades. Note that the $pH_{eq}$ of the LF grade of HPMCAS was determined to be 2.6, which was similar to the estimated values for the MF and HF grades.

The acidity space of the excipients is shown in Fig. 2, which compares the two empirical acidity scales. While there is a certain degree of agreement between the two scales, significant differences were also obvious, which are discussed below.

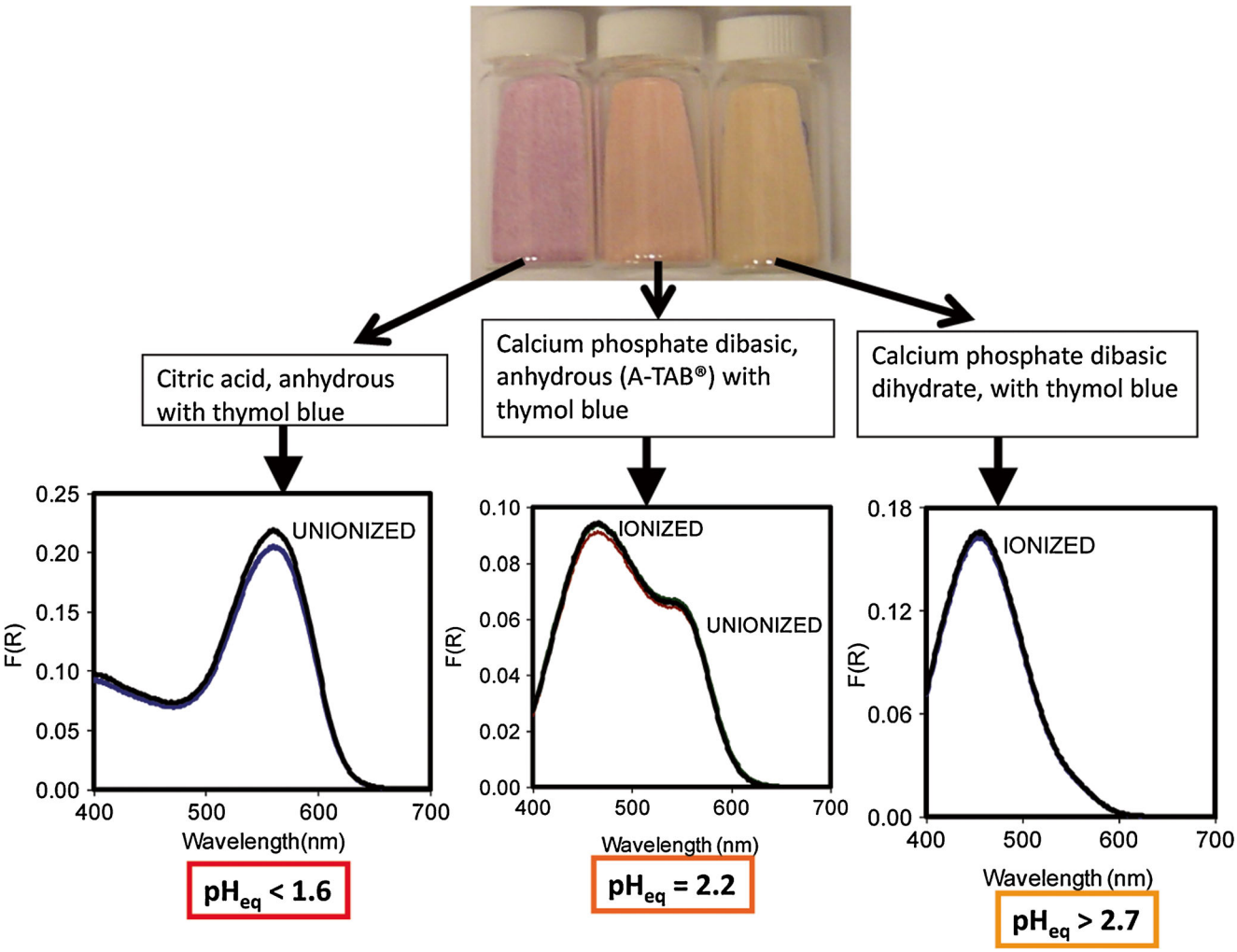



**Fig. 1.** Photographs and corresponding visible diffuse reflectance spectra of representative excipients containing thymol blue (TB)

## DISCUSSION

Atorvastatin exhibits a lactone–hydroxy acid equilibrium, as shown in Scheme 1. Both forward (lactone hydrolysis) and reverse (lactone formation) reactions are specific acids catalyzed at neutral and acidic pH. The pH dependence of the equilibrium constant, $K_{eq}$, was measured in solution and shows three regions (23). At pH values > 6, lactone is not formed ($K_{eq}$ approaches zero). $K_{eq}$ increases with decrease in pH from 6 to 3, and the extent of lactone formation depends on the time and temperature. At pH < 3, $K_{eq}$ reaches the maximum value and is fairly independent of pH, and the equilibrium is shifted toward lactone formation. Therefore, strongly acidic excipients (with the solution/suspension pH or $pH_{eq}$ < 3) would be expected to cause lactone formation and are likely to be incompatible with atorvastatin calcium, whereas near neutral/alkaline (the solution/suspension pH or $pH_{eq}$ > 6) are expected to be compatible, as demarcated in Fig. 2. Excipients that are expected to be compatible with atorvastatin calcium based on $pH_{eq}$ are located above the horizontal solid red line, and those likely to be compatible based on solution/suspension pH are located on the right side of the vertical solid black line. Furthermore, the acidic (incompatible) excipients were divided into two subgroups: (i) highly acidic excipients, which should cause generation of higher levels of lactone in AC-excipient blends and (ii) excipients of moderate acidity. The borders between high- and intermediate acidity excipients are shown as the vertical (solution/suspension pH scale) and horizontal ($pH_{eq}$ scale) broken lines. Figure 2 illustrates that the two acidity scales give different predictions, with solution/suspension pH predicting ten compatible (on the right from the solid vertical line) and one incompatible (on the left of dashed vertical line) excipients, whereas the $pH_{eq}$ scale identified four compatible (above horizontal solid line) and nine incompatible (below dashed horizontal line) excipients.

Figure 3 gives the percent lactone formed at 40°C/25% RH and 50°C/20% RH as a function of excipient acidity, and hence, compares the compatibility predictions from the two acidity scales with the more direct measure of compatibility based on chemical stability. Excipient acidity has been represented as either solution/suspension pH (Fig. 3a, b) or $pH_{eq}$ (Fig. 3c, d). Based on a qualitative (visual) overview of the plots, mixtures with excipients having a higher $pH_{eq}$ (i.e., less

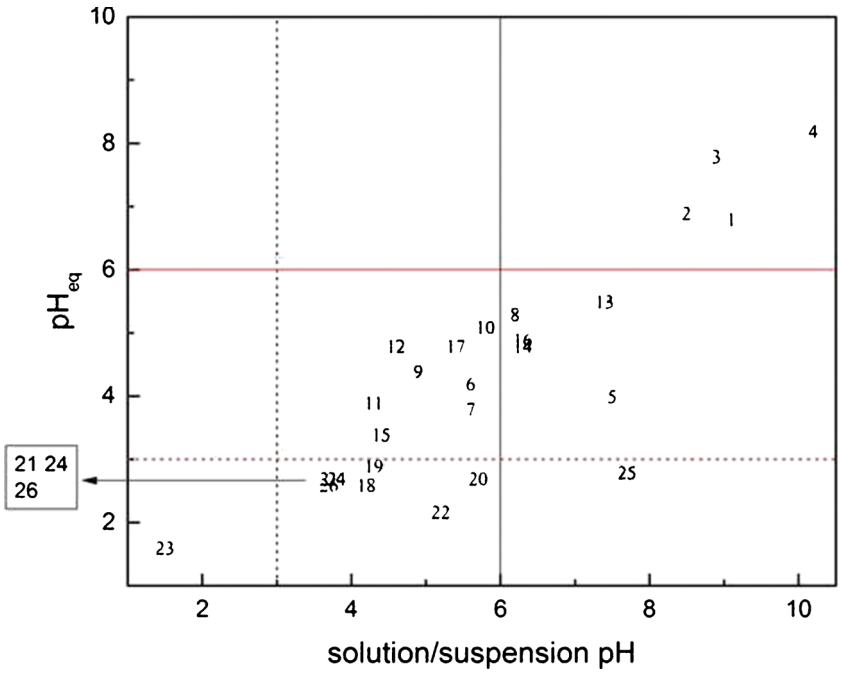
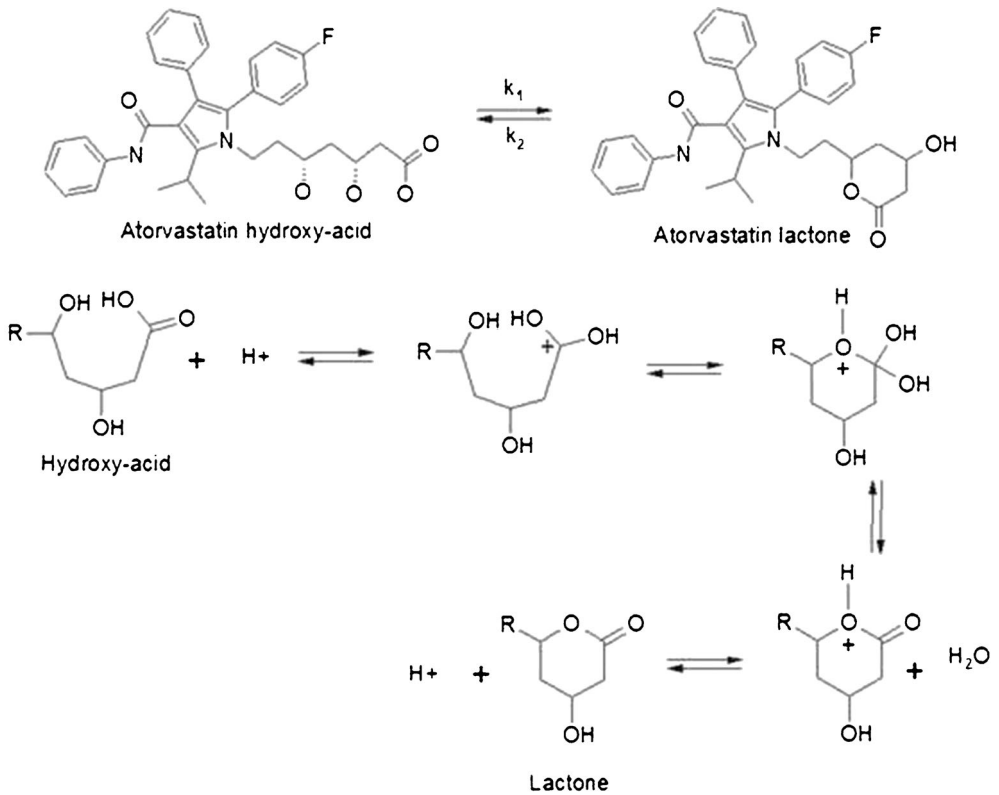



**Fig. 2.** Solid-state acidity of various excipients expressed either as pH measured in mixtures with water (at the highest solid level) or as $pH_{eq}$, based on ionization of surface deposited probes. The *numbers* correspond to ID no. in Table I

acidic) had a lower level of lactone (Fig. 3c, d), whereas no clear trend was observed when the % of lactone was plotted as a function of solution/suspension pH (Fig. 3a, b).

Nine strongly acidic excipients were identified based on the $pH_{eq}$ scale ($pH_{eq} < 3$). The lactone was formed at significant levels in binary blends of atorvastatin calcium (AC) with




**Scheme 1.** The mechanism of specific acid-catalyzed lactonization of atorvastatin hydroxy acid as proposed by Kearny *et al* (23)

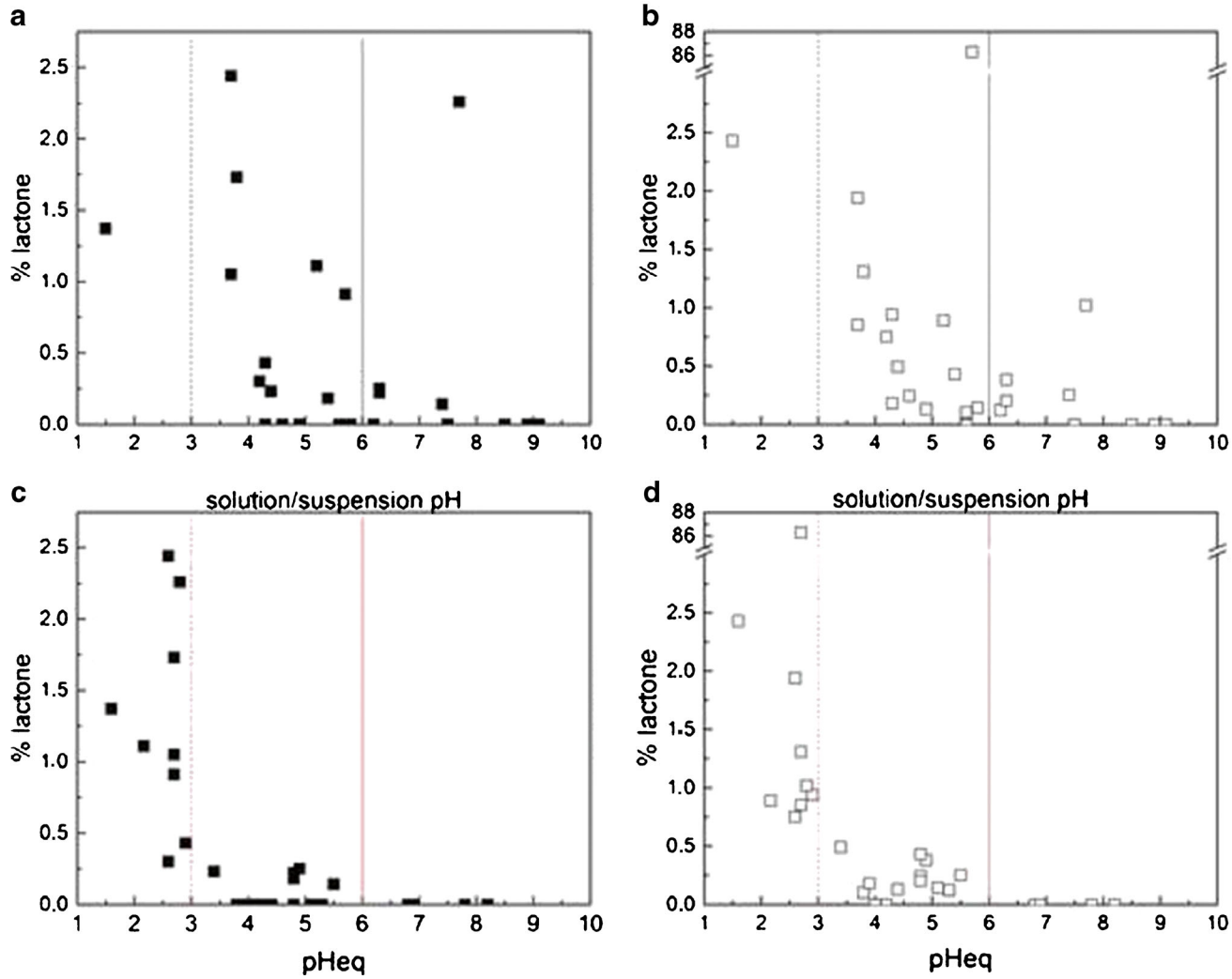



**Fig. 3.** Percent of atorvastatin lactone formed after 6 weeks at 50°C/20% RH (**b**, **d**) and 40°C/25% RH (**a**, **c**) in binary solid mixtures of amorphous atorvastatin calcium and excipients, as a function of the acidity of the excipients. In panels **a** and **b**, the acidity is expressed as the pH of an aqueous solution or suspension of the excipient (at the highest solid level available), and in panels **c** and **d**, the acidity is expressed as the $pH_{eq}$ of the solid excipient. *Vertical lines* divide three regions based on its solution stability profile (23): (i) high acidity, where atorvastatin calcium exhibits high lactone formation (pH < 3), (ii) intermediate acidity (pH 3–6), and (iii) near neutral/basic, pH > 6, where atorvastatin lactone is not formed in solution. Note that a major degradation of AC in the presence of stearic acid at 50°C is probably related to the low melting point of stearic acid reported to be between 46 and 65°C (35)

all nine excipients (Fig. 3c, d). In addition, majority of mixtures with the excipients that were classified as "moderately acidic" based on their $pH_{eq}$ ($3 < pH_{eq} < 6$) showed lactone formation, but at levels lower than that seen for the strongly acidic excipients (Fig. 3c, d). This trend is expected based on the solution pH-stability profile of atorvastatin. Note that the agreement with the solution stability profile was not perfect, as the lactone was not formed in mixtures with two of the thirteen moderately acidic excipients (i.e., sodium saccharin and pre-gelatinized starch) at 50°C/20% RH. This observation indicates that proton transfer from the excipient to the indicator in $pH_{eq}$ measurements did not correlate to proton transfer from the excipient surface to the API under the conditions of the stability study. Finally, no lactone was formed in mixtures of AC with all the near neutral/basic excipients ($pH_{eq}$ scale), which was again consistent with the solution pH-stability profile.

No clear trend in the extent of lactone formation was observed (Fig. 3a, b) when using solution/suspension pH as the measure of the excipient acidity. In particular, higher levels of lactone were observed in mixtures with several moderately acidic excipients than the "strongly acidic" ones. Moreover, lactone formation was observed in API-excipient mixtures with five of the eleven near neutral/basic excipients (Fig. 3b). Based only on solution/suspension pH, these excipients would be expected to be compatible with atorvastatin. Five excipients classified as "near neutral" by solution/suspension pH, *viz.* crospovidone, calcium acetate hydrate, silicified microcrystalline cellulose, sodium starch glycolate, and dibasic calcium phosphate dihydrate, induced various levels of lactone formation in mixtures with atorvastatin calcium. Formation of the acidic degradation product (lactone) suggests that the apparent acidity of the surface of these

five excipients was higher than the pH of the bulk solution or suspension.

While the present study could not provide definite reasons to explain the failure of solution/suspension pH to identify a number of acidic excipients, possible mechanisms can be proposed and are discussed below. The lack of agreement between the pH measured in bulk solutions and suspensions and the chemical nature of some solid excipients may be attributed to the presence of acidic impurities on the solid surface. For example, dibasic calcium phosphate dihydrate (DCPD) can undergo decomposition to yield hydroxyapatite and phosphoric acid (26,27). Indeed, forced degradation of DCPD was shown to generate acidic impurities in amounts sufficient to produce a noticeable decrease in slurry pH values (16). A small amount of phosphoric acid on the solid surface (which can be expected to form under more realistic storage conditions) is likely to have a minimal impact on the measured suspension pH of 7.7, whereas it could be expected to have a pronounced influence in the $pH_{eq}$ measured with pH indicators deposited on the surface ($pH_{eq}$ of 2.8). These surface acidic impurities can also be expected to have a disproportionate effect on the stability of an acid-labile drug in close contact with the excipient surface, as indeed was observed in the current study. Similarly, a strongly acidic surface was reported for a related excipient, anhydrous dibasic calcium phosphate (A-TAB®). This excipient, while exhibiting a moderately acidic suspension pH of 5.3, has a strongly acidic surface based on both indicator ionization ($pH_{eq}$ 2.2) and acid-catalyzed degradation of several APIs formulated with A-TAB, including bisoprolol fumarate (28), vitamin D2 (29), acetylsalicylic acid (17), and atorvastatin Ca (this study). A similar mechanism, i.e., generation of an acid during storage, could be applicable to calcium acetate hydrate, which was shown to promote acid-catalyzed degradation of the API in the present study. In addition, acidic impurities were reported in hydroxypropyl methylcellulose (up to 100 ppm), povidone (up to 1000 ppm), and sodium starch glycolate (up to 140 ppm) (30,31). Therefore, both the low $pH_{eq}$ and the incompatibility of atorvastatin calcium with Polyplasdone XL (crospovidone), PROSOLV SMCC 90 (silicified microcrystalline cellulose), EXPLOTAB® (sodium starch glycolate), observed in this study, may be attributed, at least in part, to the presence of acidic impurities on the surface of these excipients.

It should be noted that measurement of the suspension supernatant pH may not reflect the environment close to the surface of a solid. Indeed, the differences between the apparent acidity of the liquid layer in the immediate microenvironment of a solid surface and the pH of the bulk suspension have been investigated using several different approaches. Partitioning of ions and pH gradients near charged solid surfaces was studied, and the concentration of positively charged ions, including protons, was calculated based on the charge density (32). It was concluded that the apparent pH of the liquid layer near a negatively charged surface can be lower than the bulk pH by three units or more. In another study, the degradation rate of digoxin in solution at a pH of 3.5 was compared with its degradation in a clay suspension prepared at the same pH value (33). The degradation rate in the suspension, i.e., in the presence of negatively charged clay

**Table II.** Excipients Classified Based on Their Acidity as Measured both by $pH_{eq}$ and the Extent of Formation of Atorvastatin Lactone in Binary Mixtures with Atorvastatin Calcium After 6 Weeks Storage at 50°C/20% RH

| Excipient type | Classification | | |
|---|---|---|---|
| | Strongly acidic | Moderately acidic | Near neutral/basic |
| Lubricant | Glyceryl monostearate<br>Stearic acid, powder | – | Magnesium stearate (vegetable sourced) |
| Binder | – | – | Polyethylene oxide (POLYOX WSR) |
| Disintegrant | – | Crospovidone (Polyplasdone XL)<br>Sodium starch glycolate (EXPLOTAB)<br>Croscarmellose sodium (Ac-di-sol) | – |
| Additive | – | Sodium saccharin | Sodium citrate, anhydrous<br>Sodium lauryl sulfate |
| Diluent | Calcium phosphate dibasic, dihydrate<br>Calcium phosphate dibasic, anhydrous, unmilled (A-TAB)<br>Citric acid anhydrous, fine, granular Sorbitol | Pre-gelatinized starch (Starch 1500)<br>Lactose monohydrate<br>Xylitol CM—50 micron<br>Spray Dried Lactose (Lactose Fast Flo 316)<br>Mannitol, Granular 2080 (Mannogem 2080)<br>Fructose<br>Calcium acetate, hydrate<br>Silicified microcrystalline cellulose (PROSOLV SMCC 90)<br>Lactose, anhydrous (direct compression grade) | – |
| Enteric polymer | HPMC acetate succinate (HF, MF, and LF grades) | – | – |

Strongly acidic excipients: $pH_{eq} < 3$, > 0.6% lactone formed
Moderately acidic: $pH_{eq}$ 3–6; between 0.1 and 0.5% lactone formed. Two exceptions were Starch 1500 and sodium saccharin, which did not cause detectable lactone formation
Near neutral/basic: $pH_{eq} > 6$; no detectable lactone formation

surfaces, was significantly faster than that in solution. This observation was explained by the higher acidity near the surface of the clay particles (estimated to be pH 2.0) due to preferred partitioning of protons closer to the solid surface. Furthermore, using pH indicators, pronounced differences in extent of indicator ionization were observed between solid surface and suspension supernatant. For example, when phenol red was incorporated in a suspension of ground calcium carbonate (CalciPure GCC-300) in methanol, visual observation of the suspension suggested that the indicator was unionized in the methanol supernatant (yellow) but was significantly ionized (pink) when adsorbed on the solid surface of the settled calcium carbonate (9).

It should also be stressed that the impact of excipients on the stability of the API can be affected by extent of contact between particles of API and excipient, and therefore can be expected to depend on the particle size and API/excipient ratio (34). In addition, apparent acidity of solid surfaces may depend on the solid structure in some cases, and therefore can be impacted by potential structural changes during solid-state processing. For example, when the surface properties of cefditoren pivoxil, a cephalosporin antibiotic, were characterized by inverse gas chromatography using polar probes, the intact crystalline surface was found to be acidic, with a basic/acidic parameter ratio, $K_D/K_A=0.8$ (7). Milling of the crystals and resulting amorphization resulted in exposure of the electron donating carbonyl groups of the molecule, which were initially within the crystalline solid phase. Exposure of these basic groups resulted in the solid surface becoming increasingly basic as a function of decreasing crystallinity. The $K_D/K_A$ ratio for the amorphous material was ~2.0 suggesting a predominantly basic surface (7). The influence of such surface properties of excipients on the environment experienced by the API might be better characterized by probe-based techniques, provided that the $pH_{eq}$ measurements are performed with the material which was treated using a representative process. Considering these additional factors in the solid-state stability of powder mixtures, it is obvious that one can only expect semi-quantitative correlations between a test performed on individual excipients (i.e., $pH_{eq}$) and stability of API in API-excipient powder mixture. Indeed, Fig. 3c, d clearly demonstrated that, while the apparent acidity of excipients, which is expressed as $pH_{eq}$, allowed us to separate excipients into three groups based on their expected compatibility with the acid-labile AC, quantitative relationships between pHeq and stability within each of three groups are probably influenced by other factors, including the extent of API-excipient contacts and potential solid-state structural changes during powder processing.

## CONCLUSION

The current study compared two different ways to express surface acidity of solid pharmaceutical excipients, i.e., solution/suspension pH and $pH_{eq}$, with the latter based on the ionization of indicators deposited on excipients' surface. The two scales were used to predict compatibility of excipients with acid-sensitive API, atorvastatin calcium, by comparing the acidity of the excipients with the solution pH-stability profile of atorvastatin (23). In addition, compatibility was determined in accelerated stability study of binary excipient/API mixtures at typical ratios expected in solid formulations. This was assessed by measuring the growth of the acidic degradation product, atorvastatin lactone. Compatibility, predicted using $pH_{eq}$, was consistent with the results obtained in the accelerated stability study. These findings corroborated earlier reports on correlations between solid-state acidity (expressed as either $pH_{eq}$ or Hammett acidity function) and stability of aspirin and quinapril HCl (17,19). Overall, the results support use of $pH_{eq}$ as an empirical scale to represent relative acidity of different excipients in predicting solid-state incompatibility with acid-sensitive API. The agreement between $pH_{eq}$ and chemical stability of an acid-sensitive compound provided a basis for the classification of the acidic nature of the excipients, as summarized in Table II.

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## REFERENCES

1. Narang AS, Desai D, Badawy S. Impact of excipient interactions on solid dosage form stability. Pharm Res. 2012;29(10):2660–83.
2. Haw JF. Zeolite acid strength and reaction mechanisms in catalysis. Phys Chem Chem Phys. 2002;4(22):5431–41.
3. Ding AG, Schwendeman SP. Acidic microclimate pH distribution in PLGA microspheres monitored by confocal laser scanning microscopy. Pharm Res. 2008;25(9):2041–52.
4. Dowding CE, Borda MJ, Fey MV, Sparks DL. A new method for gaining insight into the chemistry of drying mineral surfaces using ATR-FTIR. J Colloid Interface Sci. 2005;292(1):148–51.
5. O'Reilly JP, Butts CP, I'Anson IA, Shaw AM. Interfacial pH at an isolated silica-water surface. J Am Chem Soc. 2005;127(6):1632–3.
6. Mader K, Gallez B, Liu KJ, Swartz HM. Non-invasive in vivo characterization of release processes in biodegradable polymers by low-frequency electron paramagnetic resonance spectroscopy. Biomaterials. 1996;17(4):457–61.
7. Ohta M, Buckton G. The use of inverse gas chromatography to assess the acid-base contributions to surface energies of cefditoren pivoxil and methacrylate copolymers and possible links to instability. Int J Pharm. 2004;272(1–2):121–8.
8. Glombitza BW, Oelkrug D, Schmidt PC. Surface acidity of solid pharmaceutical excipients. I. Determination of the surface acidity. Eur J Pharm Biopharm. 1994;40(5):289–93.
9. 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(10):2454–68.
10. Scheef CA, Oelkrug D, Schmidt PC. Surface acidity of solid pharmaceutical excipients III. Excipients for solid dosage forms. Eur J Pharm Biopharm. 1998;46(2):209–13.
11. Govindarajan R, Chatterjee K, Gatlin L, Suryanarayanan R, Shalaev EY. Impact of freeze-drying on ionization of sulfonephthalein probe molecules in trehalose-citrate systems. J Pharm Sci. 2006;95(7):1498–510.
12. Pudipeddi M, Zannou EA, Vasanthavada M, Dontabhaktuni A, Royce AE, Joshi 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(5):1831–42.

13. Bates RG. Determination of pH: theory and practice. John Wiley; 1973.
14. Paul MA, Long FA. H0 and related indicator acidity functions. Chem Rev. 1957;57(1):1–45.
15. Badawy SIF, Williams RC, Gilbert DL. Chemical stability of an ester prodrug of a glycoprotein IIb/IIIa receptor antagonist in solid dosage forms. J Pharm Sci. 1999;88(4):428–33.
16. Serajuddin ATM, Thakur AB, Ghoshal RN, Fakes MG, Ranadive SA, Morris KR, *et al*. Selection of solid dosage form composition through drug-excipient compatibility testing. J Pharm Sci. 1999;88(7):696–704.
17. Glombitza BW, Schmidt PC. Surface acidity of solid pharmaceutical excipients II. Effect of the surface acidity on the decomposition rate of acetylsalicylic acid. Eur J Pharm Biopharm. 1995;41(2):114–9.
18. Scheef CA, Schmidt PC. Influence of surface acidity of excipients on the solid state stability of pirenzepine. S T P Pharma Sci. 1998;8(2):91–7.
19. Hailu SA, Bogner RH. Solid-state surface acidity and pH-stability profiles of amorphous quinapril hydrochloride and silicate formulations. J Pharm Sci. 2010;99(6):2786–99.
20. Gana FZ, Rashid I, Badwan A, Alkhamis KA. Determination of solid-state acidity of chitin-metal silicates and their effect on the degradation of cephalosporin antibiotics. J Pharm Sci. 2012;101(7):2398–407.
21. Song Y, Schowen RL, Borchardt RT, Topp EM. Effect of "pH" on the rate of asparagine deamidation in polymeric formulations: "pH"-rate profile. J Pharm Sci. 2001;90(2):141–56.
22. Chatterjee K, Shalaev EY, Suryanarayanan R, Govindarajan R. Correlation between chemical reactivity and the Hammett acidity function in amorphous solids using inversion of sucrose as a model reaction. J Pharm Sci. 2008;97(1):274–86.
23. Kearney AS, Crawford LF, Mehta SC, Radebaugh GW. The interconversion kinetics, equilibrium, and solubilities of the lactone and hydroxyacid forms of the HMG-CoA reductase inhibitor, CI-981. Pharm Res. 1993;10(10):1461–5.
24. Balderas-Hernandez P, Ramirez MT, Rojas-Hernandez A, Gutierrez A. Determination of $pK_a$s for thymol blue in aqueous medium: evidence of dimer formation. Talanta. 1998;46(6):1439–52.
25. In: S.Budavari, editor. The Merck Index. 12th Edition ed. Merck Research Labs, Merck & Co; 1996.
26. Eyjolfsson R. Why are aqueous suspensions of the coarse grades of anhydrous calcium hydrogen phosphate acidic? Pharmazie. 2010;65(7):527.
27. Kim S, Park S. Effect of additives on the hydrolysis of dicalcium phosphate dihydrate. In: Messing G, Hirano S, Hausner H, editors. Ceramic powder science III. The American Ceramic Society: Inc; 1990. p. 201–7.
28. Dulin WA. Degradation of bisoprolol fumarate in tablets formulated with dicalcium phosphate. Drug Dev Ind Pharm. 1995;21(4):393–409.
29. Takahashi T, Yamamoto R. Studies on the stability of vitamin D2 powder preparations. II. Relationship between surface acidity of excipients and isomerization of vitamin D2. (2). Yakugaku Zasshi. 1969;89(7):914–8.
30. del Barrio MA, Hu J, Zhou P, Cauchon N. Simultaneous determination of formic acid and formaldehyde in pharmaceutical excipients using headspace GC/MS. J Pharm Biomed Anal. 2006;41(3):738–43.
31. Wu Y, Levons J, Narang AS, Raghavan K, Rao VM. Reactive impurities in excipients: profiling, identification and mitigation of drug-excipient incompatibility. AAPS PharmSciTech. 2011;12(4):1248–63.
32. Hartvig RA, Van De Weert M, Østergaard J, Jorgensen L, Jensen H. Protein adsorption at charged surfaces: the role of electrostatic interactions and interfacial charge regulation. Langmuir. 2011;27(6):2634–43.
33. White JL, Hem SL. Pharmaceutical aspects of clay-organic interactions. Ind Eng Chem Prod Res Dev. 1983;22(4):665–71.
34. Waterman KC, Gerst P, Dai Z. A generalized relation for solid-state drug stability as a function of excipient dilution: temperature-independent behavior. J Pharm Sci. 2012;101(11):4170–77.
35. Li TX, Lee J-H, Wang RZ, Kang YT. Enhancement of heat transfer for thermal energy storage application using stearic acid nanocomposite with multi-walled carbon nanotubes. Energy. 2013;55:752–61.