Complex Effects of Drug/Silicate Ratio, Solid-State Equivalent pH, and Moisture on Chemical Stability of Amorphous Quinapril Hydrochloride Coground with Silicates

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ABSTRACT: The effects of drug/silicate ratio and moisture content on chemical stability of amorphous quinapril hydrochloride (QHCl) coground with magnesium aluminometasilicates (Neusilin US2 and Neusilin FL2) were investigated. Amorphous QHCl/Neusilin samples containing 0–95% (w/w) Neusilin were prepared by cryogrinding. All samples were found to be amorphous and remained so for the duration of the study. The chemical stability of neat amorphous QHCl and QHCl coground with various percentages of Neusilin was studied at 40°C and at various moisture contents, as dictated by varying storage relative humidity (%RH). QHCl hydrolysis, forming a dicarboxylic acid (DCA) product, slightly increased with increasing percentages of Neusilin in the coground amorphous samples. On the contrary, QHCl cyclization, forming a diketopiperazine (DKP) product, was slow at both lower (e.g., 5%) and higher (e.g., 95%) percentages of Neusilin and markedly faster at intermediate percentages (e.g., 50%) of Neusilin. This complex effect of drug/silicate ratio on cyclization of quinapril was correlated with the surface acidity of the coground amorphous systems. For neat amorphous QHCl, increasing moisture resulted in increased DKP and DCA formation, as expected. Similarly, higher DCA formation was observed in QHCl/Neusilin coground amorphous samples with increasing moisture. However, DKP formation in coground amorphous samples was high both at lower (e.g., 0% RH) and higher (e.g., 75% RH) humidity, and low at intermediate (e.g., 48% RH) humidity. This complex relationship between DKP formation and moisture content for coground amorphous samples can be explained by the competitive adsorption of drug and water molecules on Neusilin surfaces, which was confirmed by Fourier transform infrared (FTIR) spectroscopy. Therefore, drug/silicate ratio, solid-state equivalent pH (surface acidity), and moisture have significant effects on chemical stability and should be considered in formulation and packaging optimization to develop both chemically and physically stable amorphous drug formulations using silicates. © 2010 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 100:1503–1515, 2011

Keywords: Quinapril hydrochloride; amorphous; stability; chemical stability; stabilization; cogrinding; milling; silicates; Neusilin; drug/silicate ratio; moisture; relative humidity; %RH; surface acidity

INTRODUCTION

Amorphous pharmaceutical systems are being investigated to provide higher dissolution rate and bioavailability, which is particularly useful in formulation of poorly soluble drugs. However, because of their higher free energy and molecular mobility, amorphous systems are generally less stable, both physically and chemically, than the corresponding crystalline forms.[1–5] Preparation of amorphous drugs using silicates resulted in improved physical stability with corresponding enhanced dissolution rate and, in some cases, bioavailability of poorly soluble drugs.[6–9] However, silicates may have detrimental effects on chemical stability of amorphous drugs.[10–13] For instance, in our previous study, pH grade of silicates was identified as a major factor affecting the chemical

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stability of amorphous quinapril hydrochloride (QHCl).[13] Accordingly, the use of pH modifiers or selection of silicates with appropriate pH grades resulted in improved stability of the amorphous formulation. To further explore the effect of silicates on chemical stability and their potential application in developing stable amorphous drug formulations, the effects of drug/silicate ratio and relative humidity (%RH) are reported here.

Chemical degradation in solids is generally accelerated by residual moisture associated with the drug in the formulation. In pharmaceutical crystalline substances, water can exist as a crystal hydrate, adsorbed on the surface, or absorbed into disordered regions (defects) of an otherwise crystalline state.[14–16] On the contrary, amorphous systems can absorb relatively high amounts of moisture into the bulk. Shalaev et al.[17] described several mechanisms through which water can affect the chemical stability of amorphous drugs. Water can be involved as a reactant or a product in the reaction, influence the polarity of amorphous matrix, serve as a medium for proton transfer, and increase molecular mobility (reduce viscosity) due to its plasticizing effect.[2,14] For example, the presence of water in amorphous QHCl and spirapril hydrochloride significantly decreased the glass transition temperature and resulted in increased chemical reactivity.[2,18] Solid-state nuclear magnetic resonance (NMR) confirmed increased molecular mobility of amorphous QHCl with increasing humidity.

For amorphous drugs prepared with silicates, the effect of %RH on chemical stability is not well understood with both stabilizing and destabilizing effects being reported.[10,12] Yonemochi et al.[10] found an inverse relationship between %RH and the degradation rate of aspirin in silica, which was initially in the amorphous state. The authors suggested that this unusual observation was due to competitive adsorption of aspirin and water molecules on the silica surface, resulting in reduced catalytic activity of the silanols (Si—OH) on the silica surface at higher %RH. In addition, although the drug was shown to be amorphous initially, recrystallization during storage for stability study was not monitored, which could also explain the decreased degradation rate at higher %RH.[1] However, in the case of partially amorphous aspirin, the degradation rate increased with increasing %RH.[10] Similarly, Daniels et al.[12] reported a direct correlation between degradation rate and %RH for aspirin and propantheline adsorbed on silica. In that case, the physical state of the drugs adsorbed on silica was not examined either initially or during storage for stability study.

During the preparation of amorphous drugs using silicates, the drug/silicate ratio was found to affect the kinetics of drug conversion to the amorphous state and the physical stability of the amorphous drug during storage.[6,20] Bahl and Bogner[6] reported faster conversion of indomethacin to the amorphous state by cogrinding with Neusilin US2 at a ratio of 1:5 drug/Neusilin than at a 1:1 ratio. Kinoshita et al.[20] prepared amorphous formulations of a poorly soluble drug (TAS-301) by melt adsorption with several silicates at different drug/silicate ratios and showed improved physical stability at 60°C and 80% RH for amorphous formulations containing higher percentages of silicates.

Several authors reported the effect of drug/silicate ratio on chemical stability of drug formulations containing silicates.[10,21,22] Gore and Banker[21] found improved stability of aspirin tablets containing 1–15% silica as compared with the control aspirin tablets and determined an optimum concentration of about 3% silica for stabilization of aspirin. On the contrary, Yonemochi et al.[10] reported a high degradation rate of aspirin in controlled pore glass solid dispersions at drug concentrations below 2% with a reduction in degradation rate at concentrations above 2%. The authors proposed that at lower concentrations, drug molecules were dispersed homogenously on the silica surface in the amorphous state resulting in faster degradation rates. The slower degradation rate at higher drug concentration was attributed to the presence of some aspirin crystals and slow conversion to the amorphous state. The effect of silica level on chemical stability of drugs in suspension formulations has also been reported. Higher degradation rates with increasing silica concentrations from 0.5% to 1% were observed for the hydrolysis of propantheline in aqueous suspensions.[22] The effects of drug/silicate ratio on chemical stability of drugs are less well understood because both stabilization and degradation of drugs in the presence of silicates are reported and, therefore, deserve further investigation.

In previous studies, recrystallization during storage for chemical stability study [10] and/or the physical state of the drug (amorphous or crystalline state)[12,21] were not determined. Therefore, the chemical stability kinetics could have been confounded by the crystallization kinetics. However, in the present study, the chemical stability of drug/silicate formulations was investigated in systems that were maintained in the amorphous state. The absence of recrystallization was confirmed throughout the stability study period to avoid the confounding effect of recrystallization on degradation kinetics.

[1] For example, a reduction in the degradation rate of amorphous indomethacin at higher %RH (≥56%) has been reported, which was due to recrystallization of the drug to a chemically stable trihydrate crystalline form.[19]

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MATERIALS AND METHODS

Materials

Quinapril hydrochloride (3-isoquinolinecarboxylic acid, 2-[2-[[1-(ethoxycarbonyl)-3-phenylpropyl]-amino]-1-oxopropyl]-1,2,3,4-tetrahydro-, monohydrochloride, [3S-[2[R*(R*)],3R*]]), was purchased from Farmhispania, S.A. (Barcelona, Spain). Reference standards of the two major degradation products of QHCl, quinapril diketopiperazine (ethyl-[3S-[2(R*),3α,11αβ]]-1,3,4,6,11,11α-hexahydro-3-methyl-1,4-dioxo-α-(2-phenylethyl)-2H-pyrazino[1,2-b]isoquinoline-2-acetate) and quinapril dicarboxylic acid (3-isoquinolinecarboxylic acid, 2-[2-[(1-carboxy-3-phenylpropyl)amino]-1-oxopropyl]-1,2,3,4-tetrahydro-,[3S-[2[R*(R*)],3R*]]), were obtained from United States Pharmacopeia (USP, Rockville, Maryland). Magnesium aluminometasilicates (Neusilin) were obtained from Fuji Chemicals (Inglewood, New Jersey). The pH grades of Neusilin along with surface area specifications are listed in Table 1. Several pH indicators (thymol blue, bromophenol blue, bromocresol green, and phenol red) were received as monosodium salts from Sigma–Aldrich (St. Louis, Missouri). Acetonitrile (optima liquid chromatography–mass spectrometry grade), methanol [high-performance liquid chromatography (HPLC) grade], sodium hydroxide solution (1N), hydrochloric acid (1N), acetic acid (2N), and formic acid (88%) were obtained from Fisher Scientific (Atlanta, Georgia). Phosphorus pentoxide, lithium chloride, magnesium chloride hexahydrate, magnesium nitrate hexahydrate, sodium chloride, sodium acetate trihydrate, monobasic potassium phosphate, potassium chloride, and potassium biphthalate, all Certified American Chemical Society grades, were also obtained from Fisher Scientific.

Preparation and Characterization of Amorphous Samples

Neat amorphous QHCl and QHCl/Neusilin coground amorphous samples were prepared using a cryo-mill (6750 Freezer/Mill®; SPEX SamplePrep, Metuchen, New Jersey) under the optimized cryogrinding conditions reported previously.[13] QHCl/Neusilin coground amorphous samples containing 5%, 25%, 50%, 75%, and 95% (w/w) of either Neusilin US2 or Neusilin FL2 were prepared. Coground amorphous samples were characterized by X-ray diffractometry (Scintag XDS 2000 Diffractometer; Scintag, Inc., Sunnyvale, California) using CuKα radiation at 45 kV and 40 mA. Powder X-ray diffraction (PXRD) data were collected at an interval of 0.02° with a scanning rate of 2°/min over a 2θ range of 5–40°. All amorphous samples stored at specified conditions were periodically examined by PXRD throughout the stability study period to monitor any recrystallization. Polarized light microscopy was also used to confirm the amorphous state of samples as indicated by the absence of birefringence.

Table 1. Magnesium Aluminometasilicates (Neusilin) Used in This Study

		Product Specification[b]	
Neusilin Type	Abbreviation[a]	Nominal pH[c]	Surface area (m^2/g)
Neusilin US2	NUS2	6.0–8.0	300
Neusilin FL2	NFL2	8.5–10.0	150

[a] Used in this paper for convenience.
[b] From supplier.
[c] pH of 4% (w/v) suspension in water.

Chemical Stability Study of Amorphous Samples

QHCl/Neusilin coground amorphous samples containing 0%, 5%, 25%, 50%, 75%, and 95% (w/w) Neusilin were stored at 40°C/0% RH and 40°C/48% RH in open vials. Additionally, QHCl/Neusilin coground amorphous samples containing 75% Neusilin were stored at 40°C and 0%, 11.5%, 31.6%, 48%, and 75% RH in open vials. As a control, neat amorphous QHCl was also stored at 40°C and 0%, 11.5%, 31.6%, and 48% RH. Because the glass transition temperature of the neat amorphous QHCl is 51°C at 48% RH and below 40°C at 75% RH,[13] its stability was investigated at 40°C only up to 48% RH, that is, below the glass transition temperature (T_g). In contrast to the neat amorphous drug, QHCl/Neusilin coground amorphous samples remained amorphous powders even at 40°C/75% RH and, therefore, stability of the coground samples was investigated up to 75% RH. Phosphorus pentoxide powder and saturated solutions of lithium chloride, magnesium chloride hexahydrate, magnesium nitrate hexahydrate, and sodium chloride were employed to maintain 0%, 11.5%, 31.6%, 48%, and 75% RH, respectively, at 40°C.

The amounts of QHCl remaining and major degradation products, diketopiperazine (DKP) and dicarboxylic acid (DCA), formed (Fig. 1) during storage were periodically assayed using HPLC/ultraviolet (UV) (HP Series 1100, Agilent Technologies, Santa Clara, California), as reported previously.[13] HPLC/UV calibration curves were developed using pure QHCl and USP reference standards of the two major degradation products.[13]

Surface Acidity Measurement of Amorphous Samples

Solid-state surface acidity of QHCl/Neusilin amorphous samples prepared by cryogrinding with pH indicators (0.05%, w/w) was measured using diffuse reflectance spectroscopy as previously described.[23–26] Surface acidity of amorphous samples containing 0%,

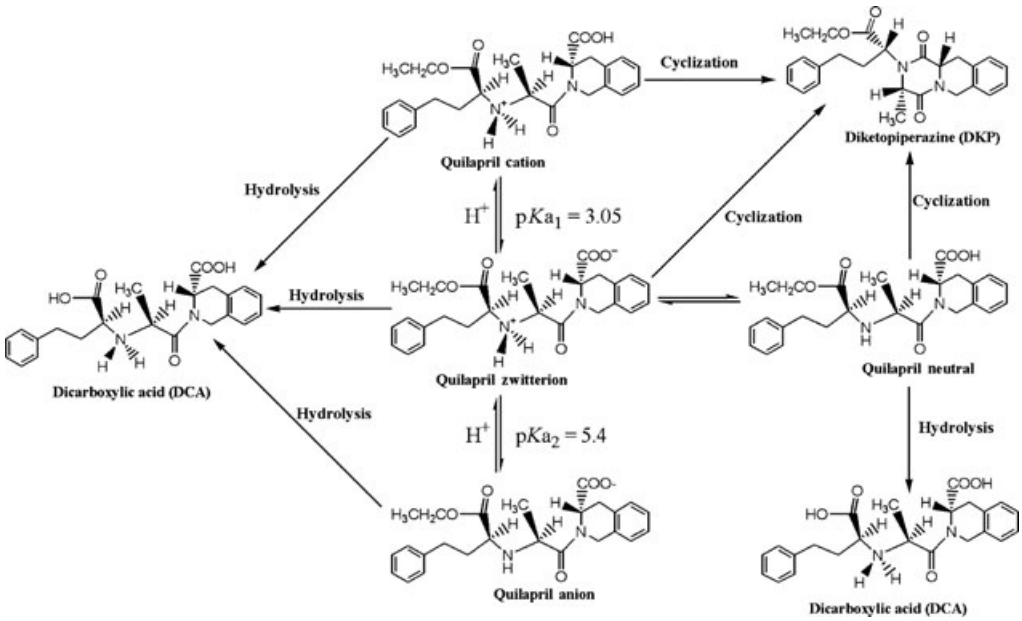

Figure 1. Ionization states and major degradation pathways of quinapril (see, References 2, 13, 18, and 29 for detailed reaction steps of degradation mechanisms).

5%, 25%, 50%, 75%, and 95% (w/w) of Neusilin was measured to determine the change in surface acidity with changes in the QHCl/Neusilin ratio. Amorphous samples were equilibrated at 40°C and specified %RH in open vials for 24 h prior to surface acidity measurement.

Calibration curves of pH indicators were developed in buffer solutions of different pH as described previously.[23] The absorption spectra of pH indicators (20 μg/ml) in solution were measured using a UV-visible (UV-Vis) spectrophotometer (Cary 100 Bio; Varian, Palo Alto, California). Buffer solutions without pH indicators were used as blanks for baseline correction. The calibration curves developed for pH indicators along with the types of buffer used[27] and the pH ranges within which the calibration curves were constructed are given in Table 2.

Diffuse reflectance spectra of amorphous powders were recorded using the same UV-Vis spectrophotometer equipped with integrating sphere diffuse reflectance accessory (DRA-CA-30I; Labsphere, North Sutton, New Hampshire). The diffuse reflectance spectra were recorded relative to the spectralon® standard (Labsphere). The corresponding amorphous samples without pH indicators were used as blanks for baseline correction. Both solid and solution spectra were recorded in the wavelength range of 200–800 nm in a double-beam mode with 1 nm data collection interval, 600 nm/min scan rate, and 4 nm slit width. The solid-state equivalent pH (pHeq) was determined from the diffuse reflectance spectra using the calibration curves of pH indicators as described previously.[23]

Moisture Sorption Analysis

The moisture weight gain of neat amorphous QHCl and QHCl/Neusilin coground amorphous samples at 40°C and different %RH was determined relative to the weight of the corresponding sample equilibrated at 40°C and 0% RH using a dynamic vapor sorption (DVS) analyzer (Q5000; TA Instruments, New Castle, Delaware). About 7 mg of each amorphous sample was equilibrated at 40°C and 0%, 11.5%, 31.6%, 48%, and 75% RH for 6 h at each %RH. The sample weight at each RH was recorded as a function of time. The DVS analysis was performed under the same conditions as

Table 2. Calibration Curves for pH Indicators in Buffer Solutions of Specified pH Range

pH Indicator	p*K*a	Buffer	Calibration Curve	R^2	pH Range
Thymol blue-acidic	1.6[a]	HCl	$Y = 0.708X-1.321$	0.996	1.2–3.2
Bromophenol blue	4.1[b]	Acetate	$Y = 0.974X-3.549$	0.998	2.1–4.9
Bromocresol green	4.7[b]	Phthalate	$Y = 0.899X-3.976$	0.996	3.3–5.4
Phenol red	7.9[b]	Phosphate	$Y = 0.970X-7.061$	0.999	5.8–8.0

[a] First p*K*a value.
[b] Second p*K*a value.

the stability storage conditions. All samples remained amorphous for 6 months during stability study, as confirmed by PXRD and polarized light microscopy. Thus, samples after DVS analysis would also remain amorphous because DVS analysis was performed under the same conditions for shorter period of time.

Fourier Transform Infrared Spectroscopy

Spectra of neat amorphous QHCl and QHCl/Neusilin coground amorphous samples were collected using an Fourier transform infrared (FTIR) spectrometer (Magna IR 560; Nicolet/Thermo, Madison, Wisconsin). About 2 mg amorphous sample was mixed with 200 mg KBr and pressed at 10,000 psi for about 2 min to make a pellet using a Carver press (Carver Inc., Wabash, Indiana). Each transmission spectrum consisted of 128 scans. All spectra were baseline corrected for ambient moisture and reported without further processing.

RESULTS AND DISCUSSION

The effects of drug/silicate ratio and moisture on chemical stability of amorphous drugs prepared with silicates are complex and not unambiguously understood with both stabilization and degradation of the drug being reported.[10–13,21] In this study, the effects of drug/silicate ratio and moisture on chemical stability were investigated using amorphous QHCl prepared with magnesium aluminometasilicates (Table 1). The degradation of QHCl mainly involves ester hydrolysis and intramolecular cyclization reactions (Fig. 1). The solid-state surface acidity and moisture weight gain at different %RH were measured for amorphous formulations containing different percentages of silicates and their correlation with the chemical stability of the drug is described. The competitive adsorption of drug and water molecules on silicate surfaces is discussed as a possible explanation for the complex effect of moisture on chemical stability of the amorphous formulation.

Effect of Drug/Silicate Ratio on Chemical Stability of Coground Amorphous QHCl

The chemical stabilities of QHCl/Neusilin coground amorphous samples containing 0%, 5%, 25%, 50%, 75%, and 95% (w/w) of Neusilin US2 or Neusilin FL2 were investigated at 40°C and 48% RH to determine the effect of drug/silicate ratio. PXRD and polarized light microscopic analysis confirmed the amorphous state of all samples after cryogrinding. Moreover, both neat amorphous and coground amorphous samples stored for 6 months at 40°C and 48% RH remained in the amorphous state. Therefore, all chemical stability results were obtained for samples in the amorphous state. Because there was no recrystallization upon storage, the chemical stability kinetics was not confounded by crystallization kinetics.

The degradation kinetics of amorphous systems is nonexponential due to multiple heterogenous states (substates) in the system. The various states in the amorphous system degrade at different rates with the more reactive states degrading faster leaving the less reactive states and as a result the overall degradation kinetics is nonexponential. In general, the square root of time ($t^{1/2}$) kinetics is shown to fit the degradation kinetics of amorphous systems.[28] Similarly, in this study, the $t^{1/2}$ kinetics was fitted to the chemical stability data of neat amorphous and coground amorphous QHCl to evaluate the degradation kinetics. Figure 2 shows the degradation kinetics of QHCl/Neusilin FL2 coground amorphous samples stored at 40°C and 48% RH. The $t^{1/2}$ kinetics fits well to both data of QHCl degradation (Fig. 2a) and formation of degradation products (Figs. 2b and 2c). Similarly, the $t^{1/2}$ kinetic plots were also determined for QHCl/Neusilin US2 coground amorphous samples (data not shown).

The rate constants for QHCl degradation (k_{QHCl}), DKP formation by cyclization (k_{DKP}), and DCA formation by hydrolysis (k_{DCA}) were determined from the slopes of the $t^{1/2}$ kinetic plots. Figure 3 shows the degradation rate constants as a function of Neusilin composition for QHCl/Neusilin FL2 and QHCl/Neusilin US2 coground amorphous samples. For both grades of Neusilin, lower degradation rates of the drug were observed at both low and high percentages of Neusilin, with the highest degradation rates at intermediate percentages. The k_{DCA} increased slightly with increasing percentages of Neusilin. On the contrary, the k_{DKP} was less at both lower (e.g., 5%) and higher (e.g., 95%) percentages of Neusilin, and greater at intermediate percentages (e.g., 25–50%) of Neusilin (Fig. 3). Overall, for the QHCl/Neusilin ratios investigated, maximum degradation of the drug was observed at 25% of Neusilin FL2 (Fig. 3a) and 50% of Neusilin US2 (Fig. 3b). As shown in Figure 3, the k_{QHCl} and k_{DKP} have qualitatively similar profile indicating that QHCl degradation is mainly due to DKP formation and relatively minor DCA formation.

The results in Figures 2 and 3 do not show a simple trend such as a proportional increase or decrease in drug degradation rate versus percentages of Neusilin. For instance, if Neusilin simply facilitates drug degradation, a higher degradation rate would be expected with increasing percentages of Neusilin. On the contrary, if drug/silicate interaction (e.g., by hydrogen bonding) reduces drug degradation, then lower degradation rate would be expected with increasing percentages of Neusilin. Instead, the stability profiles showed neither of these patterns. One possible explanation for the complex effect of drug/silicate ratio

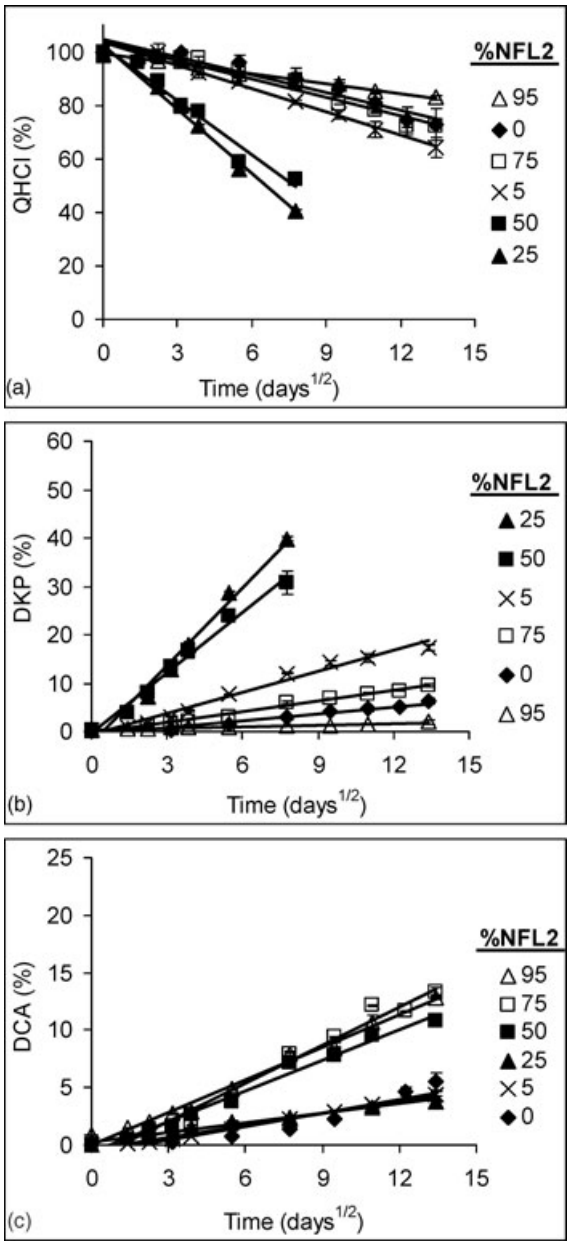

Figure 2. Degradation of amorphous quinapril hydrochloride (QHCl) coground with different percentages of Neusilin FL2 (%NFL2) stored at 40°C and 48% RH; (a) QHCl remaining, (b) diketopiperazine (DKP), and (c) dicarboxylic acid (DCA) products formed.

on chemical stability is the change in surface acidity of the formulation with changes in the percentage of Neusilin, which would influence the type of quinapril species present (i.e., the ionization state of the drug) in the formulation and hence, the chemical stability profile.

Surface Acidity and Stability Profiles of QHCl/Neusilin Amorphous Samples

For both QHCl/Neusilin FL2 and QHCl/Neusilin US2 formulations, the solid-state pHeq increased with

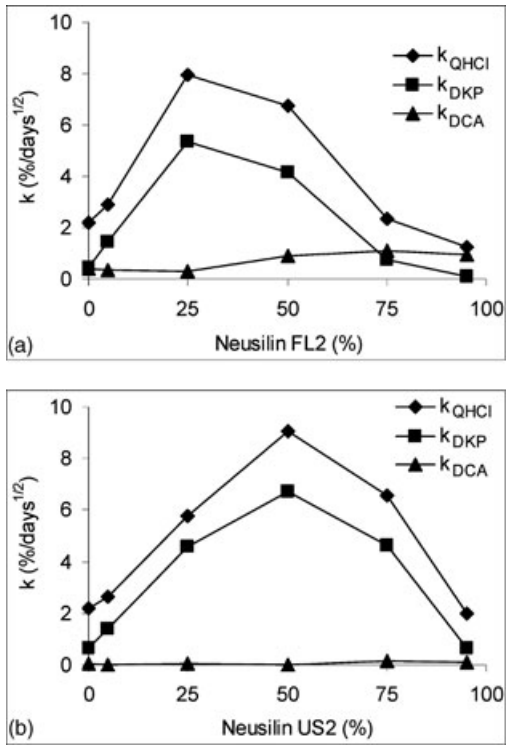

Figure 3. Degradation of quinapril hydrochloride (QHCl) in (a) QHCl/Neusilin FL2 and (b) QHCl/Neusilin US2 coground amorphous samples against percentage of Neusilin at 40°C and 48% RH; rate constants for QHCl degradation (k_{QHCl}), DKP formation (k_{DKP}), and DCA formation (k_{DCA}).

increasing percentages of Neusilin in the coground amorphous system (Table 3). For example, the pHeq of pure amorphous QHCl (0% Neusilin) was 1.2, which increased to a pHeq of 7.1 and 4.2 when coground with 95% of Neusilin FL2 and Neusilin US2, respectively. The higher pHeq for QHCl coground with Neusilin FL2 than with Neusilin US2 is consistent with the pH grade of Neusilin (Table 1).

The pH-rate profiles of QHCl/Neusilin coground amorphous samples were compared with that of the neat amorphous quinapril lyophilized from solutions of different pH adjusted with HCl or NaOH.[13] The reconstituted pH of lyophilized samples was shifted (up to 1 pH unit) for some samples as compared with the prelyophilized solution pH. Thus, the reconstituted pH, which represents the pH of lyophilized amorphous samples, was used to evaluate the pH-rate profiles of lyophilized samples.[13] Because the T_g of lyophilized neat amorphous quinapril at higher pH (4–7) is low (43–46°C)[13], both chemical stability profiles were generated at 40°C and 0% RH. The pH-rate profiles for QHCl degradation (Fig. 4a) and for DKP formation (Fig. 4b) are presented for lyophilized neat amorphous quinapril using reconstituted pH and for amorphous QHCl coground with Neusilin using pHeq. As shown in Figure 4, the pH-rate profiles for

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Table 3. Solid-State Equivalent pH of Quinapril Hydrochloride/Neusilin Coground Amorphous Samples Containing Different Percentages of Neusilin FL2 and Neusilin US2 Equilibrated at 40°C and 0% Relative Humidity for 24 h

Neusilin (%) in QHCl/Neusilin	QHCl/Neusilin FL2		QHCl/Neusilin US2	
	pH Indicator	pHeq[a]	pH Indicator	pHeq[a]
0	Thymol blue	1.2	Thymol blue	1.2
5	Thymol blue	1.5	Thymol blue	1.5
25	Thymol blue	1.9	Thymol blue	1.7
50	Bromophenol blue	3.0	Bromophenol blue	2.9
75	Bromocresol green	3.5	Bromocresol green	3.3
95	Phenol red	7.1	Bromocresol green	4.2

[a]Standard deviation < 0.15 for $n = 3$.
QHCl, quinapril hydrochloride.

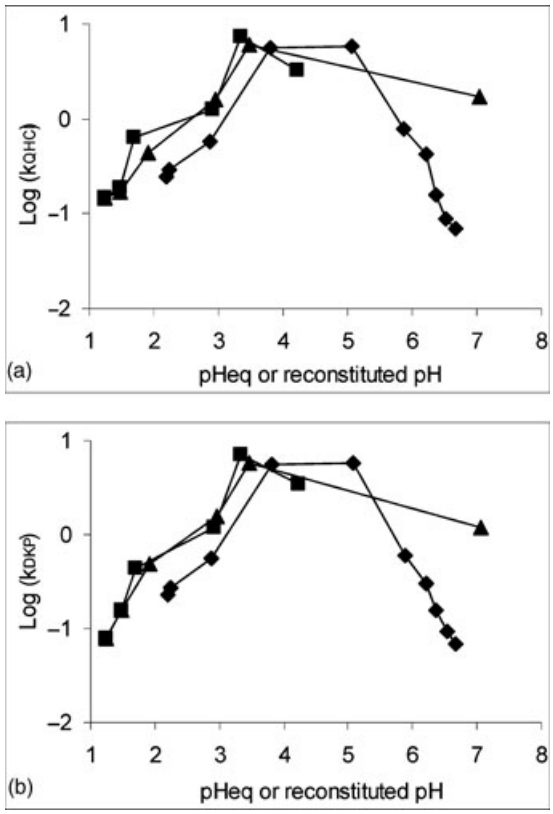

Figure 4. pH-rate profiles of amorphous quinapril hydrochloride (QHCl) at 40°C and 0% RH; (a) QHCl degradation (k_{QHCl}) and (b) DKP formation (k_{DKP}). Reconstituted pH-rate profile for lyophilized quinapril (♦), and equivalent pH (pHeq)-rate profiles for QHCl coground with different percentages of Neusilin FL2 (▲) and Neusilin US2 (■), see, Table 3 for pHeq values.

k_{QHCl} and k_{DKP} are qualitatively similar, indicating that QHCl degradation is mainly due to DKP formation. The pH-rate profile for DCA formation was not included in Figure 4 because the DCA formation by hydrolysis at 0% RH was not significant (<1.5% in 6 months).

The pHeq-rate profiles of QHCl/Neusilin coground amorphous samples were qualitatively similar to the reconstituted pH-rate profile of lyophilized quinapril (Fig. 4). This suggests that the dominant factor affecting the chemical stability of coground amorphous samples is the change in solid-state surface acidity with changes in composition (Table 3). QHCl has two acid dissociation constants, that is, $pKa_1 = 3.0$ (carboxylic acid group, $-COOH$) and $pKa_2 = 5.4$ (ammonium group $=NH_2^+$). Depending on the acidity of the amorphous system, quinapril can exist as a cation, a zwitterion in equilibrium with a neutral form (zwitterion/neutral), or as an anion.[13,29] The mechanism of quinapril cyclization, particularly from the zwitterion/neutral form, in the amorphous state has been reported.[2,13,18,29] The major species of quinapril in neat amorphous samples of pH 3.0–5.4 (between pKa_1 and pKa_2) is the more reactive zwitterion/neutral form.[13,29] Hence, the higher rate of QHCl degradation (Fig. 4a) due to higher rate of DKP formation (Fig. 4b) for both coground and lyophilized amorphous samples around pH 4–5 is consistent with the presence of more reactive species of quinapril (zwitterion/neutral form).

The use of higher percentages of silicates in preparation of drug/silicate amorphous formulations has been shown to provide faster conversion of drugs to the amorphous state and improved physical stability of the amorphous system during storage.[6,20] However, as shown here, the surface acidity of the amorphous formulation changes with percentages of silicates. As a result, the use of higher percentages of silicates may have detrimental effect on the chemical stability of the drug, depending on its pH-stability profile. Therefore, formulation optimization must consider the percentage of silicates, the pH grade of silicates, and the resulting surface acidity of the formulation in relation to the pH-stability profile of the drug to develop both physically and chemically stable amorphous formulations. In addition, depending on the pH-stability profile of the drug, acidic or basic pH modifiers can be

used to adjust the surface acidity of the formulation for improved drug stability.[13,23]

Relative Moisture Content of QHCl/Neusilin Coground Amorphous Samples

Figure 5 shows the weight gain due to moisture sorption for QHCl/Neusilin coground amorphous samples at 40°C and 48% RH relative to the sample weight at 40°C and 0% RH determined using dynamic vapor sorption (DVS) analysis.[2] For both QHCl/Neusilin FL2 (Fig. 5a) and QHCl/Neusilin US2 (Fig. 5b) coground amorphous samples, a relatively higher weight gain was observed for intermediate percentages of Neusilin and this was more notable in QHCl/Neusilin FL2 systems. These moisture sorption profiles qualitatively agreed with the chemical stability profiles (Fig. 3) with higher degradation rates observed for higher moisture content (intermediate Neusilin percentage) samples. However, the chemical stability profile of lyophilized neat amorphous quinapril at 40°C and 0% RH (Fig. 4) showed maximum degradation only around pH 4–5, despite the same water content (about 0.5% at 0% RH) for all lyophilized samples (pH 2–7). This suggests that the chemical stability profile of amorphous quinapril is mainly influenced by the pH of the formulation (i.e., ionization state of the drug), as described before.

The moisture weight gain (W) of QHCl/Neusilin coground amorphous samples was also calculated from the weight gains (w_1 and w_2) of individual amorphous components based on the weight fractions (x_1 and x_2) in the coground amorphous sample, that is, $W = (w_1 \times x_1 + w_2 \times x_2)$, where the subscripts 1 and 2 refer to QHCl and Neusilin, respectively. For both QHCl/Neusilin FL2 (Fig. 5a) and QHCl/Neusilin US2 (Fig. 5b) coground amorphous samples, the measured moisture contents were higher than the moisture contents calculated based on ideal mixtures (weight fractions).

Deviations between measured and calculated moisture contents have been reported for other amorphous formulations. For example, for drug/Polyvinylpyrrolidone (PVP) amorphous formulations, lower experimental water uptake values were observed as compared with the values predicted by using weight fractions, which was attributed to the intermolecular interactions between drug and PVP molecules.[30] For drug/silicate amorphous systems, the interaction of drug molecules with silicates (e.g., by hydrogen bonding) is also evident from FTIR analysis. However, unlike the drug/PVP amorphous systems,[30] a higher moisture uptake than calculated was observed in this study for the QHCl/Neusilin coground amorphous samples and could not be explained by drug/silicate interactions. Instead, the deviations between measured and calculated moisture contents suggest a different change in the physicochemical properties of the components in the coground amorphous samples as compared with the individual amorphous components. For example, the ionization state of the drug in pure amorphous QHCl may be different from the coground amorphous QHCl due to changes in the pHeq of the formulation. Depending on the type of quinapril species (based on ionization state), the moisture sorption and other physicochemical properties may change, resulting in deviations between calculated and measured moisture contents at 48% RH. Indeed, lower T_g and higher degradation rate have been observed for the zwitterion/neutral form than the cationic form of quinapril in the amorphous state.[13,29,31]

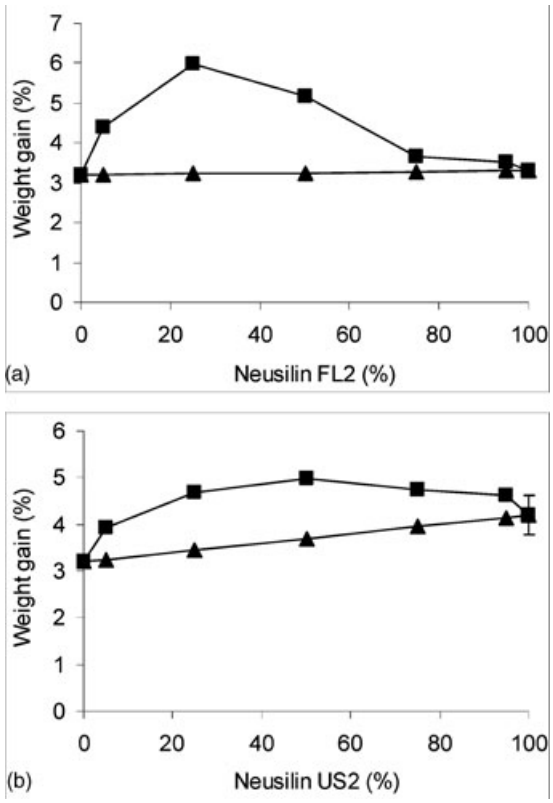

Figure 5. Moisture content (% weight gain) of (a) quinapril hydrochloride (QHCl)/Neusilin FL2 and (b) QHCl/Neusilin US2 coground amorphous samples at 40°C and 48% RH relative to the sample weight at 40°C and 0% RH; (■): measured and (▲): calculated based on weight fractions of individual components in the coground sample.

[2] dagger;Karl Fischer (KF) titration may not accurately determine the water content of drug/silicate coground amorphous samples because structural water and silanols (Si-OH) of silicates react with KF reagents. Also, Thermogravimetic analysis (TGA) could not be applied because removal of structural water of silicates (mainly by condensation of silanols) requires heating at 150–800°C, which is not applicable for drug formulations.

Effect of Moisture on Chemical Stability of Amorphous QHCl Coground with Neusilin

The chemical stability of neat amorphous QHCl and QHCl/Neusilin (1:3) coground amorphous samples was assessed at 40°C and a range of %RH. Previous studies on chemical stability of drug/silicate formulations reported both improved and decreased stability of drugs with increasing moisture.[10,12] However, the amorphous state of the drug and recrystallization during stability study, which would affect the degradation kinetics, were not reported. In this study, the chemical stability of neat amorphous QHCl and QHCl/Neusilin coground amorphous samples was investigated in the amorphous state, which was confirmed by PXRD and polarized light microscopic analysis of samples during the stability study period of 6 months. Therefore, the degradation kinetics in this study was not confounded by the recrystallization of the drug.

Figure 6 shows the degradation rate of QHCl against %RH for QHCl/Neusilin (1:3) coground amorphous samples at 40°C. For both QHCl/Neusilin FL2 (Fig. 6a) and QHCl/Neusilin US2 (Fig. 6b) coground amorphous samples, the k_{QHCl} and the k_{DKP} were faster at both lower and higher %RH, and slower at intermediate %RH. On the contrary, the k_{DCA} increased slightly with increasing %RH. For the %RH investigated, the minimum rates of QHCl degradation and DKP formation were observed at 48% RH for both QHCl/Neusilin FL2 (Fig. 6a) and QHCl/Neusilin US2 (Fig. 6b) coground amorphous samples. Again, the rate profiles of k_{QHCl} and k_{DKP} are qualitatively similar, indicating that the degradation of QHCl is mainly attributed to the DKP formation.

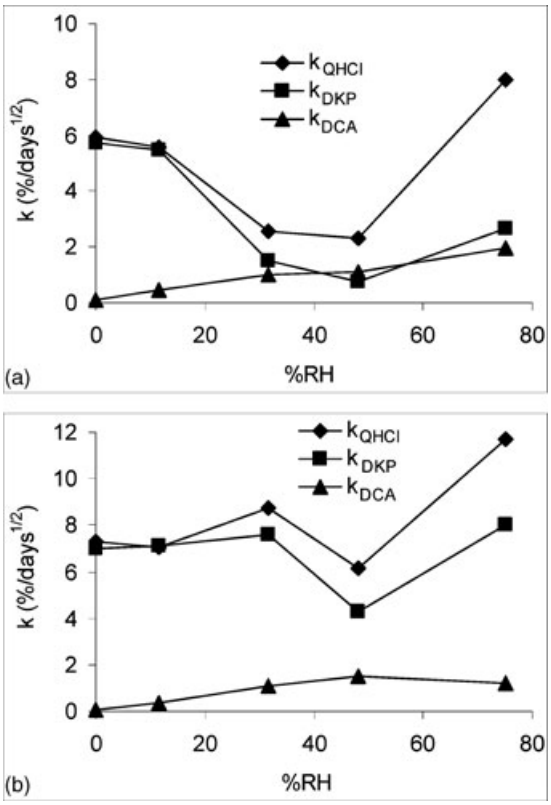

Figure 6. Degradation of quinapril hydrochloride (QHCl) in (a) QHCl/Neusilin FL2 (1:3) and (b) QHCl/Neusilin US2 (1:3) coground amorphous samples against relative humidity (%RH) stored at 40°C; rate constants for QHCl degradation (k_{QHCl}), DKP formation (k_{DKP}), and DCA formation (k_{DCA}).

For comparison, in neat amorphous QHCl, increasing %RH resulted in higher rates of both hydrolysis and cyclization of quinapril (Fig. 7), which is consistent with previous reports.[2,32] This is expected because water facilitates the hydrolysis of QHCl. Water may also serve as a medium for proton transfer and increase the rate of DKP formation by cyclization reaction.[2,13,29] For amorphous systems, in general, increasing moisture is expected to increase chemical degradation due to the plasticizing effect of water, which results in increased molecular mobility.[2,14,17,18] In addition, water can be involved in the chemical reaction (e.g., hydrolysis) or served as a medium for proton transfer and facilitate drug degradation. Therefore, the higher rates of hydrolysis and cyclization for neat amorphous QHCl, and the higher hydrolysis for QHCl/Neusilin coground amorphous samples with increasing %RH observed in this study were expected trends. However, the greater rate of cyclization of quinapril observed at both lower and higher %RH for QHCl/Neusilin coground amorphous samples suggests a more complex mechanism. Yonemochi et al.[10] reported a decreasing degradation rate of amorphous aspirin in controlled pore glass (silica) with increasing %RH. The results were attributed to the competitive adsorption of drug and water molecules on silica surface resulting in reduced catalytic effect of silica at higher %RH.

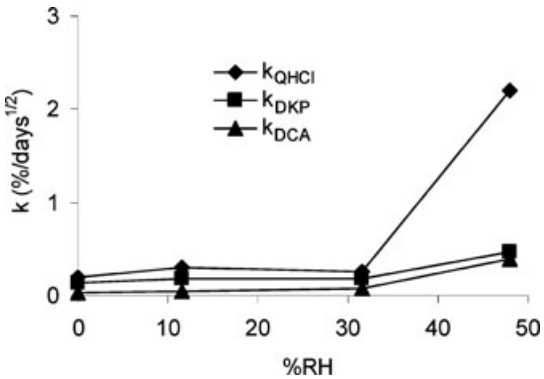

Figure 7. Degradation of neat cryoground amorphous quinapril hydrochloride (QHCl) against relative humidity (%RH) stored at 40°C; rate constants for QHCl degradation (k_{QHCl}), DKP formation (k_{DKP}), and DCA formation (k_{DCA}).

The catalytic activity of silicates to facilitate chemical reactions, such as acid–base and oxidation–reduction reactions, is attributed primarily to their surface acidity, that is, their ability to donate protons (Brønsted acid) and accept electrons (Lewis acid). The protons are mainly generated from the surface silanol (Si—OH) groups of silicates. In the presence of moisture, water molecules get adsorbed on silicate surfaces by hydrogen bonding with silanol groups. For drug/silicate systems, water and drug molecules may compete for adsorption on silanol groups of silicate surfaces. Thus, the presence of water could lower the catalytic activity of silicates due to reduction in the number of free silanols available to donate protons and/or due to competitive adsorption of water and drug molecules for silanol groups, resulting in lower drug/silicate interactions.

In this study, the competitive adsorption of drug and water molecules for Neusilin surface was explored to explain the complex relationship between the rate of cyclization of quinapril and moisture (Fig. 6). At low %RH (e.g., 0% and 11.5%), a greater proportion of the drug molecules are expected to interact with the Neusilin surface resulting in higher DKP formation due to the catalytic effect of Neusilin surface. As the %RH increased (e.g., 48%), an increasing proportion of drug molecules at the Neusilin surface are expected to be replaced by water molecules resulting in lower DKP formation from isolated (noninteracted) drug molecules. However, at very high %RH (e.g., 75%), although a greater proportion of the drug molecules at the surface of Neusilin would be replaced by water, DKP formation even from the noninteracted drug molecules would be higher due to higher moisture content as seen in neat amorphous QHCl (Fig. 7).

Fourier transform infrared (FTIR) spectroscopic analysis of amorphous samples stored at different %RH was conducted to further explore the competitive adsorption of drug and water molecules for silicate surface. Figure 8 shows FTIR spectra of neat amorphous QHCl and QHCl/Neusilin FL2 (1:3) coground amorphous samples stored at 40°C and a range of %RH for 24 h. The wavenumbers (cm^{-1}) for the peaks in the spectra along with the assigned functional groups of quinapril are given in Table 4. The FTIR spectrum of neat amorphous QHCl shows a single peak for ester and carboxylic carbonyl (C=O) groups at 1740 cm^{-1}, and the amide carbonyl (C=O) peak at 1651 cm^{-1} (Table 4 and Fig. 8a), which are identical to the peaks reported by Guo et al.[33] Cogrinding of QHCl with Neusilin FL2 resulted in spectral shifts to lower wavenumbers. The ester and carboxylic carbonyl peak shifted from 1740 cm^{-1} to 1735 cm^{-1} and the amide carbonyl peak shifted from 1651 cm^{-1} to 1645 cm^{-1} (Table 4 and Fig. 8 b). These spectral shifts to lower wavenumbers are consistent with hydrogen bonding of the carbonyl

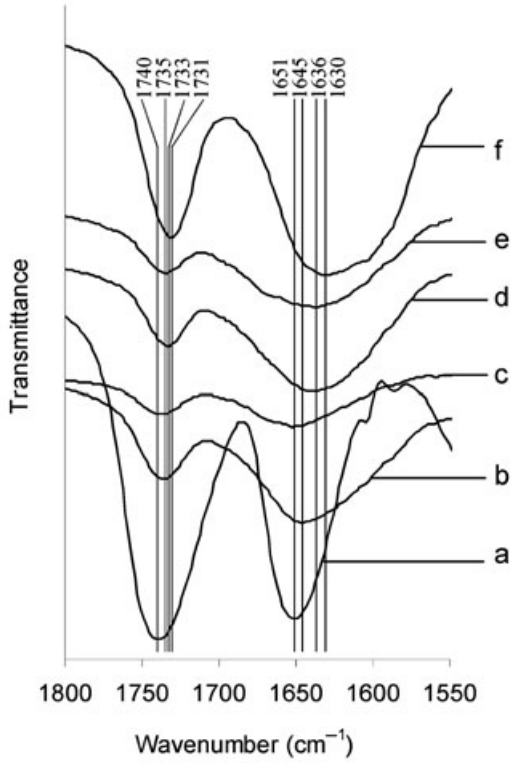

Figure 8. Fourier transform infrared spectra of amorphous samples stored at 40°C and different relative humidity (%RH) for 24 h; (a) neat amorphous quinapril hydrochloride (QHCl) at 0% RH; QHCl/Neusilin FL2 (1:3) coground amorphous samples at (b) 0%, (c) 11.5%, (d) 48%, and (e) 75% RH; and (f) lyophilized neat amorphous quinapril (pH 5.8) at 0% RH.

(C=O) groups of quinapril with the silanol (Si—OH) groups of Neusilin. Storage of QHCl/Neusilin FL2 (1:3) coground amorphous samples at 11.5% RH did not result in further spectral shift (Table. 4 and Fig. 8 c). However, storage at 48% and 75% RH resulted in spectral shifts to even lower wavenumbers. The ester and carboxylic carbonyl peak shifted from 1735 to 1733 cm^{-1} and the amide carbonyl peak shifted from 1645 to 1636 cm^{-1} (Table 4 and Fig. 8d and 8e). Similar spectral shifts were also observed for QHCl/Neusilin US2 (1:3) coground amorphous samples (data not shown).

The spectral shifts observed for QHCl/Neusilin coground amorphous samples at 48% and 75% RH are consistent with the competitive adsorption of drug and water molecules for Neusilin surface at higher %RH, that is, partial replacement of hydrogen bonded drug molecules by the water molecules at higher %RH. However, spectral shifts toward higher wavenumbers would be expected for replacement of drug molecules because the peaks for pure amorphous drug (Table 4 and Fig. 8a) are at higher wavenumbers than the coground drug (Table 4 and Fig. 8b). Instead, the results show spectral shifts toward lower

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Table 4. Fourier Transformed Infrared Spectra Peaks of Quinapril Measured from Amorphous Quinapril Hydrochloride and Quinapril Hydrochloride/Neusilin FL2 (1:3) Coground Amorphous Samples Stored at 40°C and Different Relative Humidity for 24 h

Number[a]	Amorphous sample	Storage %RH	Ester and Carboxylic C=O	Amide C=O
A	QHCl	0	1740 cm^{-1}	1651 cm^{-1}
B	QHCl:NFL2 (1:3)	0	1735 cm^{-1}	1645 cm^{-1}
C	QHCl:NFL2 (1:3)	11.5	1735 cm^{-1}	1645 cm^{-1}
D	QHCl:NFL2 (1:3)	48	1733 cm^{-1}	1636 cm^{-1}
E	QHCl:NFL2 (1:3)	75	1733 cm^{-1}	1636 cm^{-1}
F	QHCl-lyophile (pH 5.8)	0	1731 cm^{-1}	1630 cm^{-1}

[a] Refer to Figure 10, spectra a–f.
QHCl, quinapril hydrochloride; RH, relative humidity.

wavenumbers at higher %RH (Table 4 and Fig. 8d and 8e). This can be explained by the change in the ionization state of the drug in the coground amorphous sample as compared with the pure amorphous drug. Raman or solid-state NMR analysis was not conducted to directly confirm the ionization state of the drug. However, for comparison, the FTIR spectra of lyophilized neat amorphous quinapril, which had a reconstituted pH of 5.8 (above $pKa_2 = 5.4$), is included (Table 4 and Fig. 8f). The spectra for lyophilized quinapril show the ester carbonyl peak at 1731 cm^{-1}. Because the carboxylic group exists as carboxylate ion at the higher pH (5.8), the broad peak around 1630 cm^{-1} was due to an overlap of the amide carbonyl and the carboxylate peaks. Thus, the spectra of neat amorphous quinapril of higher pH also shifted to lower wavenumbers due to changes in the ionization state of quinapril. Therefore, the spectral shift toward lower frequency observed for QHCl/Neusilin coground amorphous samples stored at higher %RH (48% and 75% RH) is due to competitive adsorption of water and quinapril molecules with a different ionization state of quinapril in the coground samples. The shift to lower frequency is due to a change in the ionization state of quinapril molecules replaced by water molecules from Neusilin surface. The change in the ionization state of quinapril is consistent with the pH-rate profiles of the coground amorphous systems (Fig. 4). However, it could also be argued that the spectral shift to lower wavenumbers observed for QHCl/Neusilin coground amorphous samples is simply due to increased extent of ionization of the drug at higher moisture. For example, the polarity of the amorphous matrix may increase with increasing moisture resulting in a greater extent of ionization of the drug. To explore this possibility, the FTIR spectra of neat amorphous QHCl were measured after storage at different %RH to determine the effect of moisture on the extent of ionization in the absence of competitive interaction, that is, no Neusilin. As shown in Figure 9, no spectral shifts were observed for neat cryoground amorphous QHCl stored at 0%, 11.5%, and 48% RH for 1 day (Fig. 9a–9c, respectively). Moreover, storage of neat amorphous QHCl at 48% RH even for 3 and 5 days did not result in any spectral shift (Fig. 9d and 9e). For all samples, the ester and carboxylic carbonyl peak remained at 1740 cm^{-1} and the amide carbonyl (C=O) peak remained at 1651 cm^{-1}, indicating that increasing moisture does not have a significant effect on the extent of ionization of the neat amorphous drug. The absence of spectral shift also indicates that the FTIR spectra of KBr pellets made with amorphous samples of different moisture contents were not affected by the difference in moisture content or by redistribution of moisture to KBr. The absence of spectral shifts for neat amorphous QHCl (Fig. 9) and the presence of spectral shifts for QHCl/Neusilin coground amorphous samples (Fig. 8) on storage at 48% RH confirms that the spectral shifts in the coground amorphous samples were mainly due to competitive adsorption. Therefore, the complex effect of moisture on cyclization rate of quinapril in QHCl/Neusilin coground amorphous samples (Fig. 6), which was explained by competitive interaction of drug and water molecules on Neusilin surface, is consistent with the FTIR results.

The solid-state pHeq of QHCl/Neusilin (1:3) coground amorphous samples was measured after equilibration at 40°C over a range of %RH to determine the change in pH of the coground amorphous samples as a function of moisture. The pHeq increased with increasing %RH for both QHCl/Neusilin FL2 and QHCl/Neusilin US2 coground amorphous samples (Table 5). However, the increase in pHeq with %RH does not explain the observed chemical stability profile of the coground amorphous samples against %RH (Fig. 6). For example, for QHCl/Neusilin FL2 (1:3) coground amorphous sample, the pHeq increased from 3.5 to 5.0 as the %RH increased from 0% to 75% RH (Table 5). The pH-rate profile of amorphous samples shows maximum degradation rate between pH 3.5 and 5.0 (Fig. 4), whereas the stability profile against %RH shows a minimum degradation rate between 0% and 75% RH (i.e., at 48% RH; Fig. 6). Therefore, the effect of %RH on chemical stability of the QHCl/Neusilin coground amorphous samples

Table 5. pHeq of Quinapril Hydrochloride/Neusilin (1:3) Coground Amorphous Samples Equilibrated at 40°C and Different Relative Humidity for 24 h; Bromocresol Green was Used as a pH Indicator

Amorphous sample	QHCl/Neusilin FL2 (1:3)				QHCl/Neusilin US2 (1:3)			
Relative humidity	0	11.5	48	75	0	11.5	48	75
pHeq[a]	3.5	3.6	4.5	5.0	3.3	3.3	3.9	4.5

[a]Standard deviation < 0.15 for $n = 3$.
QHCl, quinapril hydrochloride; pHeq, equivalent pH.

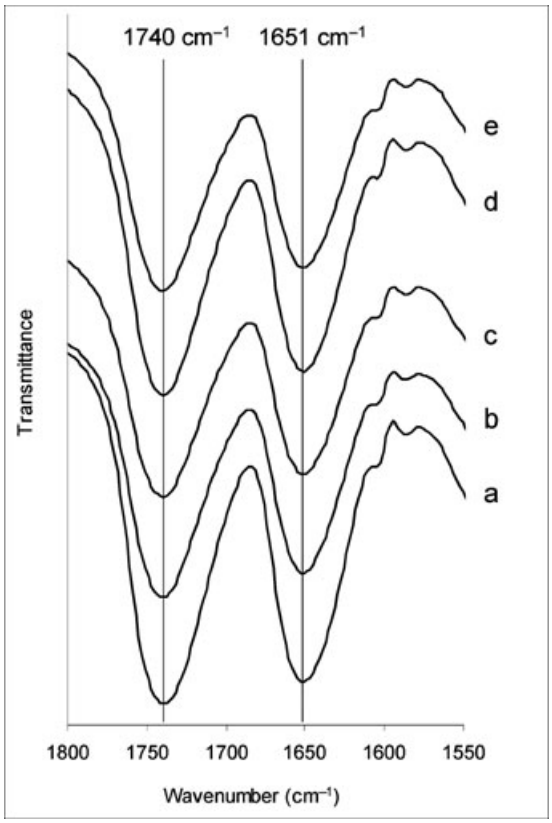

Figure 9. Fourier transform infrared spectra of neat amorphous quinapril hydrochloride (QHCl) stored at 40°C and different relative humidity (%RH); (a) 0% RH for 1 day, (b) 11.5% RH for 1day, (c) 48% RH for 1day, (d) 48% RH for 3 days, and (e) 48% RH for 5 days.

cannot be explained by the increase in pHeq with %RH, whereas the competitive adsorption, explained above, is a plausible explanation.

Pan et al.[34] reported competitive adsorption for the amorphization of indomethacin in silica gel in which greater amorphization of the drug was observed at both lower and higher %RH with a minimum at intermediate %RH. Moreover, Yonemochi et al.[10] observed a decreasing degradation rate of amorphous aspirin in silica solid dispersions with increasing %RH, which was attributed to competitive adsorption of water and aspirin molecules for silica surface. Therefore, the effect of moisture on chemical stability of QHCl/Neusilin coground amorphous samples obtained in this study and explained by competitive adsorption agrees with previous observations.[10,34] However, further study is required to understand competitive adsorption and conclusively determine the effect of moisture on chemical stability and amorphization kinetics of drug/silicate formulations. Studies involving determination of enthalpy of adsorption for drug and water molecules on silicate surfaces and quantification of adsorbed drug under different %RH, which are under investigation in our group, will provide more understanding of competitive adsorption.

CONCLUSIONS

The chemical stability of amorphous drugs prepared with silicates can be affected by drug/silicate ratio, solid-state pHeq, and moisture, as demonstrated in this study using QHCl and Neusilin. The effect of drug/silicate ratio is correlated with the surface acidity of amorphous formulations, which changes with percentages of silicates and influences the ionization state of the drug in the formulation. Although higher percentage of silicates resulted in faster drug amorphization and improved physical stability,[6,20] it may have detrimental effect on the chemical stability of the drug, depending on its pH-stability profile. Therefore, to develop both physically and chemically stable amorphous formulations, it is essential to consider the percentage and pH grade of silicates, and the resulting surface acidity of the formulation in relation to the pH-stability profile of the drug in solid state.

The effect of moisture on chemical stability of drug/silicate amorphous formulations can be explained by the competitive adsorption of drug and water molecules on silicate surface. Drug amorphization using silicates is reported to be greater at both lower and higher moisture contents.[6,34] However, the higher drug degradation rate at lower and higher moisture, and maximum stability at intermediate moisture observed in this study suggest that optimization of the moisture content is required to develop drug/silicate amorphous formulations with maximum physical and chemical stability.

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