Effects of Lyophilization on the Physical Characteristics and Chemical Stability of Amorphous Quinapril Hydrochloride

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Purpose. To prepare amorphous quinapril hydrochloride (QHCl) by lyophilization and to compare its physical characteristics and chemical stability as a function of the initial pH of the pre-lyophilized solution.
Methods. Amorphous QHCl samples were prepared by lyophilization from aqueous solutions. Solid-state characteristics were evaluated by DSC, PXRD, and optical microscopy. Chemical degradation was monitored by an HPLC assay.
Results. Amorphous QHCl samples obtained from lyophilization exhibited variable glass transition temperatures, depending on the pH and/or concentration of the starting aqueous solutions. Neutralized quinapril (Q) in the amorphous form, which has a T_g of 51°C, lower than that of its HCl salt (91°C), was significantly more reactive than QHCl at the same temperature. The T_g of lyophilized samples prepared at various initial pH values correlated well with values predicted for mixtures of QHCl and Q. Their different reaction rates were related to their glass transition temperature, consistent with the results from earlier studies obtained with amorphous samples made by precipitation from an organic solution and grinding of the crystal solvate.
Conclusions. Lyophilization of different QHCl solutions produces mixtures of amorphous QHCl and its neutralized form Q, with T_g values intermediate to the values of QHCl and Q. As the fraction of Q increases the overall rate of chemical degradation increases relative to QHCl alone, primarily due to the increase in molecular mobility induced by the plasticizing effects of Q.

KEY WORDS: amorphous; quinapril hydrochloride; lyophilization; chemical degradation; glass transition temperature; ACE inhibitor.

INTRODUCTION

A previous study from this laboratory reported on possible relationships between the physical characteristics of an ACE inhibitor, quinapril hydrochloride (QHCl), in the amorphous state and its chemical instability(1). In that study, amorphous QHCl samples made by grinding and heating of a crystalline solvate form and by rapid precipitation from a dichloromethane solution had essentially the same glass transition temperature, 91°C. They also underwent a thermal cyclization reaction to form the diketopiperizine product, DKP, (Scheme 1) with the same degradation rate under the same conditions. Preliminary experiments revealed that lyophilization of a QHCl solution produced an amorphous state with a T_g that was consistently a few degrees lower than 91°C, with a correspondingly greater rate of degradation. This study was designed to understand the underlying basis for such differences through a more systematic examination of possible factors that might affect the solid-state characteristics and chemical reactivity because of lyophilization. In particular, consideration was given to the acid-base equilibria associated with the initial aqueous solution, as reflected by both concentration and pH.

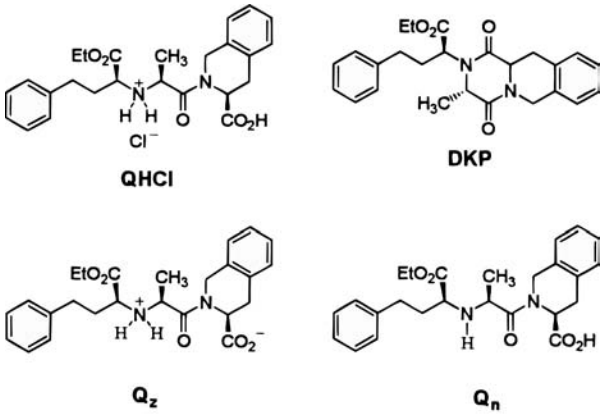
MATERIALS AND METHODS

Materials

Quinapril hydrochloride (QHCl) was a gift from the Chemical Processing Division of the Warner-Lambert Co. (Holland, MI). The major degradation product, quinapril diketopiperazine (DKP) was prepared according to methods reported in the literature. (2). Trifluoroacetic acid (99+%, spectrophotometric grade) and dichloromethane (99.8% anhydrous) were purchased from Aldrich Chemical Co, Inc. (Milwaukee, WI). Water was purified by a SYBRON Barnstead pressure cartridge system (PCS) (Boston, MA). HPLC grade acetonitrile and methanol were purchased from EM Scientific (Gibbstown, NJ). All chemicals were used without further purification, unless otherwise specified.

Preparation of Amorphous QHCl

Aqueous solutions of QHCl, for which the pH had been measured, were lyophilized using a commercial Dura-Stop tray dryer in combination with a Dura-Dry-MP condenser module from FTS Systems (Stone Ridge, NY). The vials were liquid scintillation vials from Research Products International Corp. (Mount Prospect, IL) with a volume of about 25 ml (diameter 27–28 mm and height 57.5 ± 1mm). Each vial contained 8 ml of solution which was frozen to −40°C and kept at this temperature for 10 hours before starting to apply the vacuum. After 24 hours, the temperature was raised to −30°C, −20°C, −10°C, and 0°C every subsequent 12 hours, and the secondary drying was performed at 25°C for 24 hours. The pH of selected reconstituted solutions was checked at this stage. Freeze-dried



Scheme 1

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samples were ground for 10 seconds using a Wig-L-Bug electron motor mini-grinder (Spectra-Tech Inc., Stamford, CT) and further dried at 45°C in a vacuum oven for 24 hours. Samples prepared by lyophilization were determined to be completely amorphous using a Scintag PadV x-ray powder diffractometer (Scintag Inc., Santa Clara, CA) and by the absence of birefringence under polarized light using an Olympus BH-2 optical microscope (Olympus Optical Co., LTD, Tokyo, Japan) (1). The water contents of the various samples were determined, using the Karl Fischer method (Aquastar C200, EM Science, Cherry Hill, NJ), and found to be less than 0.1% (w/w) in all cases using a minimum of three individual samples.

Preparation of Neutralized Quinapril (Q)

The neutralized form of quinapril (Q_z or Q_n, Scheme 1) was prepared by slowly adding a stoichiometric amount of sodium bicarbonate solution to an aqueous solution of QHCl in an ice bath. The precipitate was filtered and washed 2–3 times with ice water and then dried and stored in a desiccator containing P_2O_5 under vacuum. There was no Cl^- present in the product when checked with silver nitrate solution. The HPLC assay (1) showed only one peak with a retention time identical to that of quinapril HCl, and no degradation products were detected. The sample prepared by this method determined to be completely amorphous using both x-ray powder diffractometry and polarizing microscopy has a glass transition temperature of 51°C, as measured by DSC at a scanning rate of 20 K/min.

Differential Scanning Calorimetry (DSC)

The DSC thermograms and the glass transition temperatures of amorphous samples were determined using a Seiko I SSC/5200 differential scanning calorimeter (Seiko Instruments, Horsham, PA) equipped with a Hewlett Packard Model 712/60 data station. Dry nitrogen was used as the purge gas and liquid nitrogen as the coolant. High purity indium, gallium, and biphenyl were used for temperature and enthalpy calibration. Samples (5–10 mg) in nonhermetically crimped aluminum pans with a pin hole in the lid were measured under a nitrogen gas purge at 85 ml/min. Unless otherwise noted, heating and cooling rates of 20°C/min were used.

pH Measurement

A Model 701A/digital ionalyzer from Orion Research Incorporated (Cambridge, Mass.) equipped with a Corning semi-micro combination electrode (Cat. No. 476541) was used to measure the pH of various solutions. The pH meter was calibrated using standard buffer solutions of pH = 1.00 ± 0.01, 4.00 ± 0.01, and 7.00 ± 0.01 obtained from Fisher Scientific (Fair Lawn, NJ). Reported pH values are the average of two samples and at least three repetitions for each sample. The standard deviation for pH is 0.02.

Density Determination Using Helium Pycnometry

The densities of powdered amorphous QHCl and Q were determined at ambient temperature using a Quantachrome Multipycnometer (Syosset, NY). The sample cell volume was calibrated using standard steel balls and verified using crystalline sucrose which has a density of 1.587 g/cm^3. The densities of amorphous QHCl and Q were determined as 1.18 and 1.21 g/cm^3, respectively. Reported densities are an average of at least two independent samples and at least eight repetitions for each sample. The standard deviation for the densities is 0.01 g/cm^3.

Solid-State Stability

The solid-state thermal degradation of QHCl and Q was studied by placing samples of known weight (0.5–15 mg) into open 2 ml glass vials which were then placed into a desiccator containing P_2O_5 to maintain dryness. A Fisher Scientific Isotemp® Preminum Oven (Model 750G) was used to maintain constant temperature. The sample temperature was monitored using an Omega microprocessor thermometer (Model HH23) with a type-K thermocouple directly contacted with the solid sample. Samples were selected at different time intervals and dissolved in methanol immediately before the HPLC assay (1). All data analysis and curve fitting were carried out using Microcal Origin™ Version 4.1 from Microcal Software Inc.(Northampton, MA).

RESULTS

Comparison of Amorphous Forms of Quinapril HCl

In our previous study (1), it had been shown that amorphous QHCl can be prepared by either grinding a crystalline form or by solvent evaporation from an organic solution. The lyophilization process represents the change from a more disordered system (solution) to a less disordered system (solid), thus resembling the solvent evaporation method. Crystallographically, the amorphous samples prepared by all three methods are characterized by a PXRD amorphous halo pattern centered around 20° 2θ.

The preliminary study indicated that some characteristics, such as T_g, of the final amorphous QHCl samples prepared from lyophilization were slightly affected by the concentration of the initial aqueous solution, in that products from the higher concentration (i.e., 50 mg/ml) gave slightly higher T_g values than those from lower concentrations (i.e., 10 mg/ml), but still slightly lower than those of samples prepared by grinding of the crystal and by solvent evaporation (see Table 1 footnote). Also, the reconstituted solutions of these lyophilized samples consistently showed a slight increase in pH when compared to those of the initial solutions. To further investigate the possible effect of pH on the properties of the final amorphous product, we purposely adjusted the pH of the initial solutions using a small amount of acid or base before lyophilization. Table 1 shows a distinct effect of the initial pH on the T_g of the final amorphous products, in that a lower initial pH value correlates to a higher T_g, similar to the concentration effect discussed above. When the pH of a particular solution was adjusted below 2.39 by adding various amounts of hydrochloric acid, the loss of extra HCl during lyophilization was shown by the increase of pH values of the reconstituted solutions. The amorphous samples made by this procedure (lower pH) are very similar and most resemble the amorphous QHCl prepared from the other two methods. When the pH of the initial solution was

Table 1. Effect of Initial Concentration and pH on the T_g of Lyophilized QHCl

Conc. (mg/ml)	Initial pH[a]	Reconstituted pH[a,b]	T_g (°C)[a,d]
10	2.83	2.70[c]	77.0
10	2.61	2.57[c]	86.7
10	2.39	2.49	88.9
25	2.17	2.26	89.8
50	2.08	2.22	90.3
10	1.97	2.42	91.3
10	1.84	2.44	91.4
10	1.39	2.44	91.1

[a] See experimental section.
[b] Reconstituted to initial concentration.
[c] Partially soluble.
[d] Scanning rate 20K/min, the T_g of amorphous QHCl samples prepared from grinding of the crystal and solvent evaporation are 91.3°C and 91.7 °C, respectively.

adjusted above 2.39, T_g of the lyophilized product was lower and, in some cases, an insoluble precipitate appeared when reconstituted with water. Since no chemical degradation was observed from HPLC analysis, the observation can be attributed to a composition change, i.e., the existence of some zwitterionic or neutral form of quinapril (Q_z or Q_n, Scheme 1). Since the T_g of Q is 51°C, it appears that the presence of some Q in the lyophilized products may be responsible for their lower T_g.

Chemical Degradation of Amorphous Q and QHCl

Figure 1a shows the degradation of amorphous QHCl prepared from the lyophilization of a 10 mg/ml aqueous solution without pH adjustment ($T_g \sim 89$°C), compared with amorphous samples made from solvent evaporation and grinding of the crystal ($T_g \sim 91$°C). It can be seen that the amorphous sample, obtained by lyophilization, exhibited a slightly higher degradation rate (~15%) than the amorphous samples prepared from the previous reported methods (1). Since the physical characteristics, such as T_g, of the amorphous QHCl samples prepared by lyophilization are affected by the pH of the initial aqueous solution, and this change is probably associated with the composition change of the two species of significantly different chemical reactivity (QHCl and Q), we studied the chemical degradation of the amorphous samples prepared from lyophilization of aqueous solutions with different pH (Fig. 1b). Notice the slower degradation rates for samples of lower initial lyophilization pH (corresponding to a higher T_g, Table 1). When the initial lyophilization pH value is below 2.08, the degradation rate reaches a minimum, with values essentially the same as those of amorphous QHCl samples made by other two methods. This observation is attributed to the presence of various amounts of neutralized quinapril form (Q) in these lyophilized samples.

To better understand the possible effect of Q on T_g and the degradation rate, we prepared amorphous Q and studied its physical and chemical properties. The degradation reaction rate of Q was found to be much faster than that of amorphous QHCl under the same conditions, which seems to agree with the solid-state behavior of another ACE inhibitor of similar structure (3). Degradation of Q produces DKP as the only product and the data can be described by first order kinetics. In our previous study on the degradation kinetics of amorphous QHCl (1), we observed different reaction rates with changing sample weight. This was attributed to a morphology change (agglomeration and sintering) of drug particles, which affected the first step of the cyclization reaction by impeding the loss of gaseous HCl. It was of interest, therefore, to investigate the possible absence of a sample weight effect with Q, since the removal of HCl is not involved with this system. The first-order degradation rate constants of Q were plotted as a function of sample weight (Fig. 2). Here, it can be noted that there is a negligible sample weight effect, except for a small trend of slightly increasing reaction rate constants with larger weight samples at 60°C. The possible reasons for this observation will be discussed in more detail later.

The temperature dependence of degradation rate constants for both Q and QHCl in the amorphous state using 10 mg samples, is compared in Fig. 3 in the forms of regular Arrhenius plots and those normalized to the T_g of Q and QHCl, to take into account possible temperature-dependency of molecular mobility effects on chemical degradation (to be discussed).

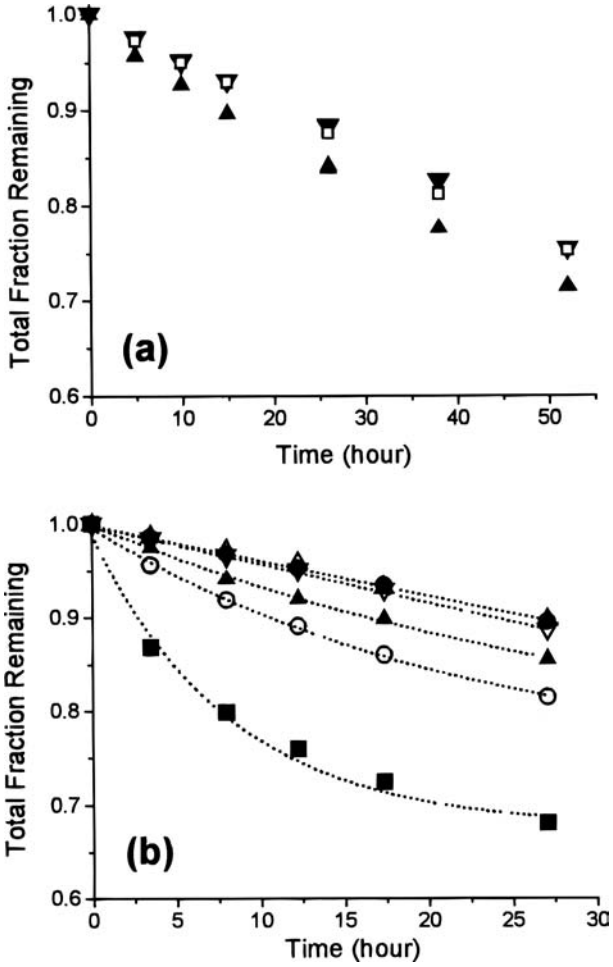

Fig. 1. Degradation of amorphous QHCl samples prepared from solvent evaporation (▼), grinding of crystal (□), and lyophilization (▲) (a), and amorphous samples from lyophilization of a 10 mg/ml solution with initial pH at 2.83 (■), 2.61 (○), 2.39 (▲), 1.97 (▽), 1.84 (△), and 1.39 (●) (b) at 80 °C.

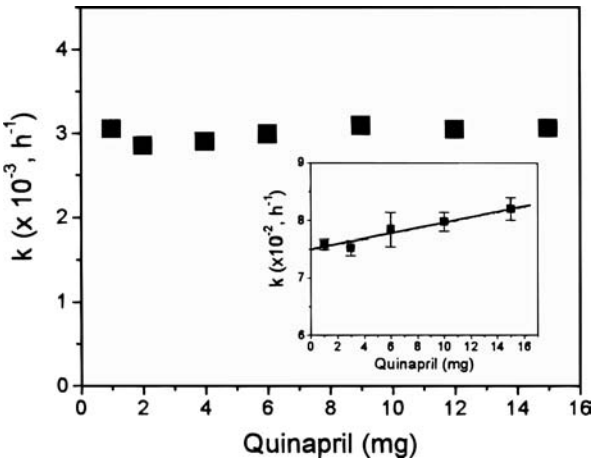

Fig. 2. Plots of first order degradation rate constants of amorphous Q as a function of sample weight at 50°C and 60°C (inset).

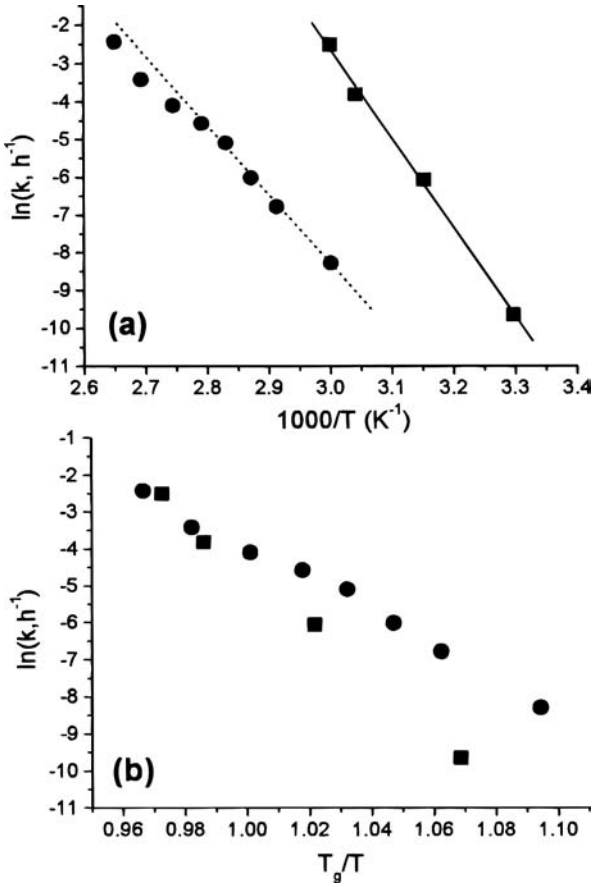

Fig. 3. Arrhenius plots (a) and ln(k) versus T_g/T plots (b) of amorphous QHCl samples prepared by lyophilization (●) and amorphous Q (■).

DISCUSSION

Effects of Lyophilization and the Formation of Neutralized Quinapril, Q

From the results of this study it can be seen that the glass transition temperature of amorphous QHCl prepared by lyophilization is affected by the pH of the initial solution. We hypothesize that this is caused by a shift of QHCl to its neutralized form. Thus, the original observation of a slightly lower T_g and a greater degradation rate for the sample lyophilized from the aqueous solution appears to be explained by the presence of a small amount of Q, which most likely is caused by a pH shift due to the loss of a small amount of HCl under lyophilization conditions. A slight pH increase of reconstituted solution was also reported in another study when acidic solutions with volatile acids (i.e., HCl, acetic acid) were lyophilized (3). On the other hand, the amorphous product assumed characteristics close to those of amorphous QHCl samples prepared by solvent evaporation and crystal grinding (1) when the pH of the initial lyophilization solution was kept below 2.08 (Table 1) and the amount of Q formed was negligible.

In aqueous solution, like most amino acids and peptides, neutralized quinapril probably exists as the zwitterionic form. In the solid state, however, both neutral (Q_n) and zwitterionic (Q_z) forms (see Scheme 1) are possible. Since quinapril (Q) molecules most likely are connected by H-bonds between the ammonium (or amine) and the carboxylate (or carboxylic acid) groups in the solid state, it may be difficult to distinguish these two forms in the solid state. The possibility of the formation of both neutral and zwitterionic forms of quinapril as an intermediate in the cyclization reaction of amorphous QHCl has been discussed previously (1).

Glass Transition Temperature for Mixtures of QHCl and Q

Since the neutralized quinapril (Q) in the amorphous form has a much lower glass transition temperature (51°C) than QHCl (91°C), a molecular dispersion of Q and QHCl would be expected to have a T_g intermediate to that of Q and QHCl depending on the composition. Based on the pK_a of QHCl (~ 3.0), we are able to estimate the ratio of excess Q and QHCl in the initial solution which could be carried over to the solid-state after the solution had being lyophilized. Such a calculation reveals, for example, that a pH change of the 10 mg/ml solution, from 2.4 to 2.8, increases the Q/QHCl ratio to nearly 50%.

To test the hypothesis that the observed changes in T_g for lyophilized systems at different initial pH are due to the presence of Q, we can use an equation that predicts the glass transition temperature of an ideally miscible binary system ($T_{g(mix)}$) knowing the individual weight fractions, w_Q and w_{QHCl}, and glass transition temperatures, $T_{g(Q)}$ and $T_{g(QHCl)}$. Here,

$$T_{g(mix)} = \frac{w_Q\, T_{g(Q)} + K w_{QHCl}\, T_{g(QHCl)}}{w_Q + K w_{QHCl}} \quad (1)$$

where K is a constant. Based on free volume theory, Eq. 1 is the Gordon-Taylor equation (4), and using the Simha-Boyer rule (5), it can be shown that

$$K \approx \frac{T_{g(Q)}\rho_Q}{T_{g(QHCl)}\rho_{QHCl}} \quad (2)$$

where ρ represents the density of each component.

Equation 1, based on the thermodynamic treatment of Couchman and Karasz (6), uses a constant K determined as

$$K = \frac{\Delta C_{p(QHCl)}}{\Delta C_{p(Q)}} \quad (3)$$

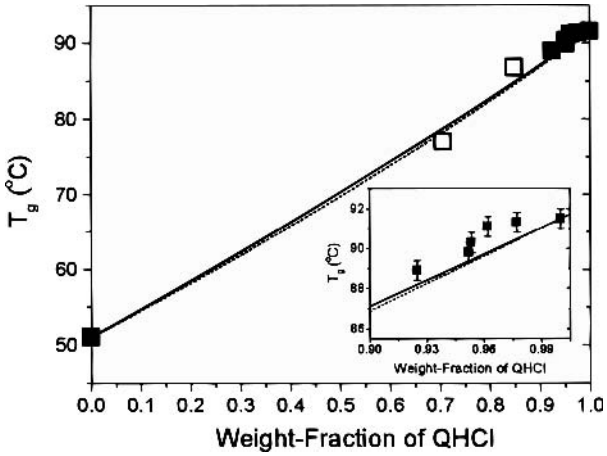

Fig. 4. T_g values of lyophilized QHCl as a function of composition. Symbols represent measured T_g values at compositions calculated from solution pH (■) or chloride analysis (□). Error bars are within the size of symbols depicting data points. The solid line represents the prediction of the Gordon–Taylor equation, and the dotted line represents the prediction of the Couchman–Karasz equation.

where ΔC_p is the change in heat capacity at the glass transition temperature of each form.

In Fig. 4, we present the theoretical plots of T_g vs the composition of Q and QHCl using Eqs. 1–3, and compare them with experimental results for amorphous samples made by lyophilization. Estimates of the ratio of Q to QHCl in those samples were made from pH measurements of the reconstituted solution and the pK_a of QHCl, except in the cases of amorphous samples obtained from the lyophilization of base-adjusted solutions, where chloride analysis was used since the amorphous product was not totally soluble in water. Within the limited number of compositions it is clear that the T_g observed for samples from different initial pH conditions does appear to be due to the formation of an amorphous solid dispersion of Q in QHCl.

Chemical Degradation

From the results of this study it appears that the increased degradation of quinapril for samples with higher initial solution pH values (Fig. 1b) is due to the presence of a certain proportion of the neutralized form (Q) relative to QHCl. From Fig. 3a we may note that, under the same experimental conditions, pure Q exhibits significantly greater rates of degradation than pure QHCl within the experimental temperature range. Hence it is not surprising that any initial pH change producing a sample with some Q in it would give greater degradation rates than for QHCl alone. That this enhanced degradation of Q relative to QHCl as a function of temperature is somehow related to the much lower T_g of Q, is seen very well in Fig. 3b, where the rate constants are compared after normalizing the temperature to the respective values of T_g. Thus now we see that, relative to their T_g values, degradation rates of Q and QHCl are closer, especially near and above T_g ($T_g/T \leq 1$). Below T_g, however, Q actually appears to be reacting more slowly. If the Arrhenius plots in Fig. 3b, normalized to T_g, had been identical for both QHCl and Q, we could conclude that the temperature dependencies for molecular mobility, reflected in relaxation times, were identical for both species relative to T_g and that differences in the temperature range where reactivity occurs is completely linked to molecular mobility differences. As shown previously for QHCl (1), it is not possible to directly obtain relaxation times at temperatures of interest in this study because of chemical degradation during the timescale of any experiments. As was shown earlier (7), however, it is possible to measure T_g as a function of DSC scanning rate, q, to obtain an approximate estimate of the temperature dependence of relaxation time in the vicinity of T_g and from this to estimate various measures of its fragility as defined by Bohmer *et al.* (8) Consequently, T_g for Q was measured at scanning rates of 5–40 K/min (data not shown) and the results were compared to those obtained for QHCl previously (1). From a plot of ln(q) vs. $1/T_g$ it was possible to estimate an activation energy for enthalpy relaxation of Q equal to about 50 kcal/mole, as compared to about 140 kcal/mole for QHCl, indicating that QHCl is significantly more fragile than Q, and that the change in relaxation times with temperature are not identical for the two species with that of Q being less than that of QHCl. Thus, we might tentatively conclude that the lower T_g of Q is indeed a major determinant of the temperature range over which degradation occurs. However, the steeper slope for Q (higher apparent activation energy) in Fig. 3b reveals that the lower reactivity for Q, particularly at higher values of T_g/T, is also reflecting a basic contribution to the overall activational energy for Q because of reaction mechanism differences that may be unrelated to molecular mobility.

Further insight into the differences noted for the degradation of Q and QHCl in the amorphous state may be obtained from an analysis of Fig. 2, which shows that the sample weight effects noted for QHCl (1), i.e., a decreased rate of degradation with increasing sample weight, do not occur with Q. Interestingly, at higher temperature (60 °C), it appears that there is a small increase in the rate of degradation of Q with increase in sample weight (Fig. 2 inset), as opposed to a decreased rate noted with QHCl. The lack of decrease in degradation with sample weight is consistent with the earlier hypothesis that with QHCl, the removal of HCl gas becomes rate-limiting with increased sample weight and agglomeration of drug particles (1). In the absence of HCl, as with pure Q, this cannot occur. However, agglomeration and sintering still occur at experimental temperatures; and perhaps water, produced during the formation of DKP, is retained more at higher sample weights and acts as a plasticizer to slightly speed up the reaction.

Further analysis of the Arrhenius plots of QHCl and Q, as shown in Fig. 3 and Table 2, provides some additional insights into the changes in degradation rate with lyophilization conditions. In Fig. 3, we see the Arrhenius plot for an amorphous

Table 2. Degradation Kinetic Parameters of Amorphous Q and QHCl Samples[a]

	lnA	E_a(kcal/mol)	ΔH‡(kcal/mol)	ΔS‡(cal/mol K)
Q	68.1 ± 2.8	46.9 ± 1.8	46.3 ± 1.8	58.5 ± 5.5
QHCl[b]	46.1 ± 1.7	36.3 ± 1.2	35.4 ± 1.2	14.6 ± 3.4

[a] Sample weight: 10 mg.
[b] Amorphous sample from freeze-drying without initial pH adjustment, least-squares linear fitting of data below T_g.

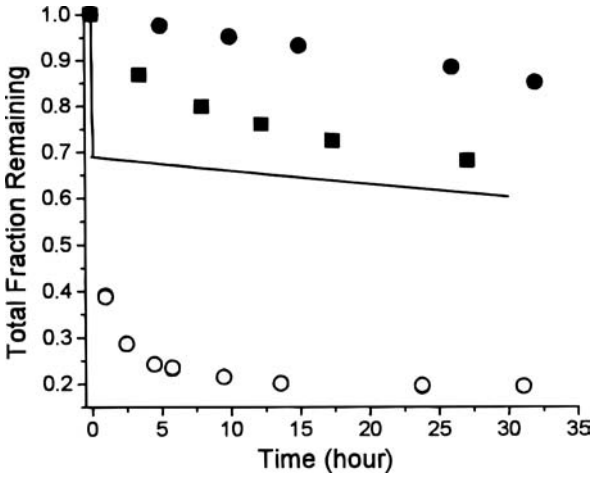

Fig. 5. Degradation profiles at 80 °C for lyophilized amorphous QHCl sample with known Q/QHCl ratio (31/69, mol/mol) (■), theoretical prediction for a physical mixture of the same composition (solid line), pure amorphous Q (○), and QHCl (●). Error bars are within the size of symbols depicting data points.

sample prepared from a 10 mg/ml solution of QHCl. Since the estimated amount of Q in this sample is quite small (~8%), the Arrhenius plot is very similar to those observed earlier for amorphous QHCl samples prepared by other methods (1), in that a deviation in linearity also occurs above T_g. This deviation was related to the significant agglomeration and sintering of the sample and a retardation of HCl gas release (1). The Arrhenius plot of Q in Fig. 3, on the other hand, shows no significant nonlinear deviation around the glass transition temperature, which agrees well with the absence of a sample weight effect related to HCl release. The degradation kinetic parameters obtained for both systems show that the activation energy for Q is significantly larger than QHCl (Table 3), and that the higher reaction rate of Q relative to QHCl in the amorphous state at the same temperature appears to be due to a larger entropy change between the transition state and the starting material. The higher activation energy and relatively lower reactivity at temperatures normalized to T_g (Fig. 3b) may suggest that the neutralized quinapril (Q) prepared in this study, to some extent, resembles more to the zwitterionic form, like an amino acid in the solid-state (9); while as an intermediate produced *in situ* from the degradation of amorphous QHCl, probably is in the neutral form, the more reactive form.

To further investigate the interactions between Q and QHCl in their mixtures, we carry out the following analysis. At 80 °C, Q has a reaction constant about 700 times higher than QHCl from the extrapolation of the Arrhenius plot. If we take a given molar ratio of Q to QHCl of 31:69, we can estimate the rate of reaction of a physical mixture of Q and QHCl from their individual rate constants in term of two independent parallel reactions. This is shown in Fig. 5 as the solid line. Also included in this plot is the actual degradation profiles for a lyophilized sample with a ratio of Q and QHCl equal to 31:69 based on elemental analysis. Clearly, from the experimental results, the degradation of the lyophilized sample is much slower and smoother than that predicted for the physical mixture. We believe that the lyophilized sample is a fairly ideally mixed molecular dispersion of Q and QHCl, and that the presence of QHCl with a higher T_g and more acidic environment probably reduces the reactivity of Q, i.e., stabilizes Q. From the practical standpoint, this "cushioning" effect can be assumed to be an advantage.

CONCLUSIONS

This study reveals that the lyophilization of an aqueous solution of quinapril HCl (QHCl) produced an amorphous sample that can contain a mixture of QHCl and its neutralized form (Q) depending on the initial pH condition. Since Q has a T_g that is about 40 °C lower than that of amorphous QHCl, its presence lowers the T_g of the lyophilized amorphous sample in proportion to the amount of Q present. Because of its lower T_g and hence greater molecular mobility, Q exhibits significant greater chemical degradation at the same temperature and, to some extent, contributes to the observed decrease of solid-state stability of any lyophilized sample in proportion to the initial pH of the solution used for lyophilization.

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