Correlation and Prediction of Moisture-Mediated Dissolution Stability for Benazepril Hydrochloride Tablets

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Purpose. This report investigated dissolution stability of benazepril hydrochloride tablets.
Methods. Reduction in dissolution rate was observed for benazepril hydrochloride tablets when they were subjected to stressed storage condition (40°C/75% RH) for prolonged periods of time (1–3 months). Moisture contents of initial and stressed tablets were measured by Karl Fischer method. Comparative thermal and physical characterizations of initial and stressed tablets were also performed. A mathematical model that was used to predict possible reduction in dissolution rate was proposed and validated using experimental data.
Results. It was found that there was a direct correlation between moisture content of benazepril hydrochloride tablets and their percentage of dissolution at 10 min. At moisture content below 3.5%, there were no significant changes in dissolution values. Beyond that point, however, a close to linear decrease in dissolution was observed as a function of increase in moisture content. Results from thermal and X-ray analysis have ruled out possible changes in drug substance. Other physical characterization, such as scanning electron microscope and mercury porosimetry measurements, revealed changes in core structure of stressed tablets vs. initial tablets. Based on results from these measurements, "preactivation" of disintegrant was identified as the mechanism for reduction in dissolution rate above critical moisture content. A simple physical model for moisture uptake of benazepril hydrochloride tablets was also proposed for predicting when, based on water vapor transmission and critical moisture content, dissolution rate will decline.
Conclusions. Physical changes of tablets mediated by moisture were the main cause for reduction in dissolution. Inclusion of desiccant, although beneficial, cannot prevent reduction in dissolution completely. The simple physical model proposed in this report was found to be useful in predicting the dissolution stability of the dosage form.

KEY WORDS: dissolution stability; moisture; moisture–dissolution correlation; superdisintegrant.

INTRODUCTION

Reductions in dissolution rate of pharmaceutical solid dosage forms stored at stressed conditions have been studied and reviewed by a number of authors (1–4) for nalidixic acid (2), hydrochlorothiazide (1), and delavirdine mesylate tablets (4). Aging was frequently identified as one of the factors associated with reduction in dissolution rate; however, it was not clear what exactly occurred during aging. Changes in active drug substance, such as salt form, hydration state (4), or polymorph (5) can cause reduction in dissolution rate of the dosage form. Additionally, changes associated with excipients such as disintegrant and coating material may also affect dissolution stability (3). In one report, poor dissolution stability of hydrochlorothiazide capsule formulation was attributed to formation of trace amount of formaldehyde (1). Furthermore, reduction in dissolution rates has also been associated with disintegrant. When modified carboxymethylcellulose sodium (Nymcel) was used in nalidixic acid tablets, dissolution stability improved significantly (2). Adding both glycine and citric acid into triamterene/hydrochlorothiazide capsules successfully prevented cross-linking of the gelatin; as a result, dissolution profiles remained the same throughout 12-week accelerated stability studies, with marginal drop in dissolution values (6). In addition, reductions in dissolution rates do not necessarily correspond to decreases in *in vivo* absorption (7). It is essential, however, from the perspective of product quality, to maintain dissolution stability of the dosage form.

The objective of the current study is to investigate the cause for decline in dissolution rate of benazepril hydrochloride tablets upon storage at stressed conditions (40°C/75% RH). Reductions in dissolution rates are attributed to moisture uptake in the tablets and "preactivation" of the superdisintegrant. "Preactivation" can be defined as hydration and swelling of superdisintegrant in tablet due to moisture uptake prior to contact with aqueous testing media. The preactivation of the superdisintegrant results in changes in the pore structure of the tablets that hamper rapid disintegration of the tablets, which is followed by reduction in dissolution rate. By taking into consideration water-vapor transmission and critical moisture content, a simple model for predicting the kinetics of decrease in dissolution rate can be established.

MATERIALS AND METHODS

Materials

Benazepril hydrochloride bulk drug substance was manufactured by Novartis Pharmaceuticals Corporation (East Hanover, NJ, USA) and obtained from a standard production lot. Benazepril hydrochloride tablets were prepared by wet granulation with unit strength of 40 mg as the salt form. The tablet formulation also contained the superdisintegrant crospovidone, lactose monohydrate, microcrystalline cellulose as filler, pregelatinized starch as binder, silicone dioxide (Cab-O-Sil) as glidant, and magnesium stearate as lubricant.

METHODS

Stressed Stability Conditions

Tablets were stored in open or closed high-density polyethylene (HDPE) bottles without desiccant at 40°C, 50°C, 40°C/75% RH, and 30°C/60% RH for 1, 2, and 3 months. Relative humidity for samples stored at 40 ° and 50°C under normal pressure was 25% and 13%, respectively. Tablets were also stored in HDPE bottles with induction seals containing 1 g of Sorb-it desiccant.

Dissolution Tests

Dissolution tests of benazepril hydrochloride tablets were performed using USP apparatus I (basket apparatus) at

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100 rpm. The dissolution medium was 900 ml of 0.01 N HCl maintained at 37°C. Samples were withdrawn manually at 10, 20, 30, and 60 min, filtered, and then analyzed by High Pressure Liquid Chromatogram (HPLC) equipped with UV detector at 240 nm. All dissolution tests were done with six test units.

Moisture Content Determination

Water contents of the tablets were measured by a volumetric Karl Fischer method using single solution Karl Fischer Reagent (Fisher Scientific SK3, Fair Lawn, NJ). Tablets were pulverized into powder using a mortar and pestle, and a weighed portion was then rapidly introduced into a titration chamber. Water content was reported as percentage by weight normalized by sample size.

Powder X-Ray Diffraction

Powder X-ray diffraction (PXRD) patterns of benazepril hydrochloride drug substance and formulations were obtained using PXRD (Rigaku RINT 2200, equipped with a Cu target X-ray tube, 40 kV, 40 mA, and scanned from 2° to 40° at 2° stepwise, Prairieville, LA). PXRD has extensively been used to monitor solid-state changes of the drug substance, such as salt form and hydration state. Due to the high drug loading of the current formulation (>50%), any significant change in the physical state of the drug substance should have been detected by PXRD.

Thermal Analysis

Differential scanning calorimetry (DSC) and thermogravimetric analysis (TGA) measurements of benazepril hydrochloride drug substance and formulations were obtained using TA Instruments Model 2920 differential scanning calorimeter and TA Instruments Model 2950 thermogravimetric analyzer (New Castle, DE), respectively. Samples (~5 mg) were placed in flat crimped aluminum pans and were heated at a rate of 10°C/min under N_2 purge (50 ml/min). Potential changes in drug substance, such as salt forms, hydration state, or polymorphs were monitored using results from DSC and TGA.

Moisture Absorption Isotherms

Moisture absorption isotherms of benazepril hydrochloride tablets were measured at 40°C using an automated vapor absorption system (symmetric vapor sorption analyzer, SGA-100, VTI Corporation, Hialeah, FL). The unit is equipped with a microbalance for mass determination and a hygrometer for relative humidity (RH) measurement. The procedure involved RH scans in steps of 5 or 10% and simultaneous determination of weight change of the sample. Equilibrium was assumed to be established when the weight change was less than 0.001% within 3 h. Theoretical difference in equilibrium moisture of tablets stored under 40°C vs. 40°C/75% RH could be obtained from the moisture absorption curve based on a relative humidity of 25% for samples stored under 40°C.

Scanning Electron Microscope

Scanning electron microscopy (SEM; JEOL 6301FXV, JEOL USA, Inc., Peabody, MA) at 3.0 kV with different magnifications was used to monitor the surface and cross-sectional morphology of the tablets. SEM of both initial and stressed tablets were captured and compared, and any physical or morphological changes between samples were noted.

RESULTS AND DISCUSSION

Benazepril hydrochloride is an angiotensin-converting enzyme (ACE) inhibitor developed for the treatment of hypertension. Benazepril hydrochloride is freely soluble in water (solubility = 78 mg/ml), therefore, it is expected that the dosage form would have rapid dissolution independent of testing conditions. A new dose, 40 mg, was developed to meet clinical needs for higher dosage strength. During development, it was observed that storage under stressed condition (40°C, 75% RH) had a negative effect on tablet dissolution. Tablets stored at stressed conditions for 3 months fail dissolution specification (Fig. 1). A literature survey demonstrates that reduction in dissolution may be caused by a number of factors, including chemical degradation, salt form conversion, initial moisture content, porosity of tablets, and swelling capacity of disintegrants (8,9). Chemical degradation of the drug substance was ruled out because no degradation products appeared in the stability-indicating HPLC assay when stressed tablets were tested. Possible salt to free base conversion was monitored by X-ray diffraction and DSC.

Powder X-Ray Diffraction

Powder X-ray diffraction patterns of drug substance and tablets were examined using the method described earlier. As illustrated in Figs. 2c and 2d, the PXRD pattern for stressed tablets (40°C, 75% RH for 3 months) was the same compared to that for initial tablets, indicating no physical change of drug substance had occurred during storage. Given the extent of the reduction in dissolution (Fig. 1, dissolution at 30 min reduces from 96.36% to 39.10%), formation of the free base, or change in hydration state, if any, would have been apparent by PXRD and thermal analysis. The overlapping of the PXRD pattern for initial and stressed tablets with characteristic peaks from benazepril hydrochloride indicated that drug substance remained unchanged.

Physical Properties of the Initial and Stressed Benazepril Hydrochloride Tablets

Physical properties of initial and stressed tablets (3 months at 40°C/75% RH) of benazepril hydrochloride were

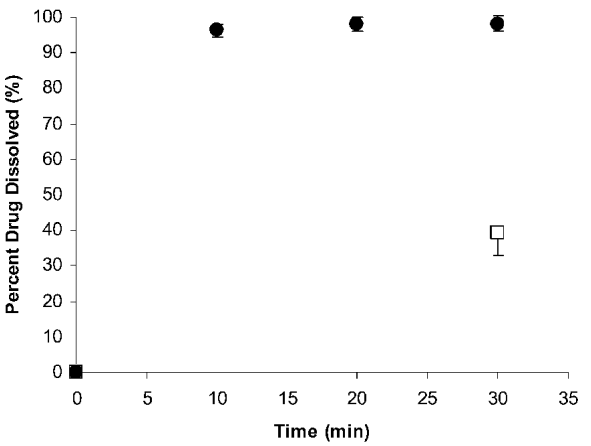

Fig. 1. Comparison of dissolution profiles of formulation stored under 40°C/75% RH in HDPE bottle without desiccant pack: ● initial; □ 40°C/75% RH, 3 months (n = 6).

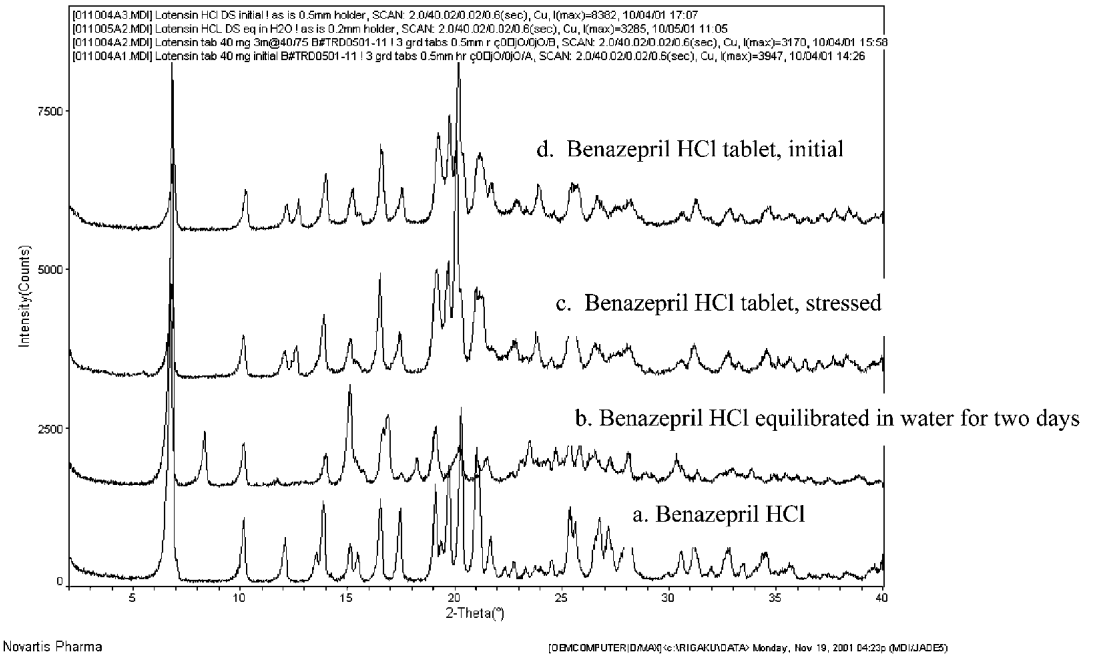

Fig. 2. Powder X-ray diffraction pattern of benazepril hydrochloride tablets: (a) benazepril HCl drug substance (b) benazepril HCl drug substance equilibrated in water for 2 days, (c) benazepril HCl tablet, stressed sample (40°C/75% RH, 3 months), and (d) benazepril HCl tablet, initial sample.

measured and tabulated in Table I. As demonstrated in Table I, an increase in tablet hardness from 5.0 to 6.8 kp for stressed tablets was observed; this, however, was accompanied by significant increase in disintegration time. In addition, a decrease in dissolution at 30 min from 96.36% to 39.10% was observed (Fig. 1). Changes in hardness and dissolution have been reported to correlate with absolute moisture content (10) of the tablets in the literature, yet, this type of physical change was often hard to isolate due to the complex and heterogeneous nature of the dosage form.

The observed phenomenon may have been the result of preactivation of the disintegrant. To test this hypothesis, stressed tablets (stored under 40°C/75% RH for 3 months) were pulverized and divided into two portions. They were then compressed into 75-mg tablets with target hardness of 4 and 7 kp. The first half was compressed "as is," whereas the second half was compressed with "freshly added" 2 mg of crospovidone in each tablet. Experiments showed that recompressed "as is" tablets have a significantly longer disintegration time compared with the "fresh added" tablets. At 4 kp, the "fresh added" tablets take 1 min to disintegrate compared with >10 min for "as is" tablets, whereas the values for 7-kp tablets are 21 min and >25 min, respectively. On the other hand, when similar experiments were carried out for unstressed tablets, only a minimal difference in disintegration time was noted between "as is" and "fresh added" tablets. Combined with data from PXRD, these results suggested that reduction in dissolution for stressed tablets was most likely due to physical (i.e., loss of disintegrant efficiency) instead of chemical changes. Later efforts were therefore focused on possible physical changes of the tablets.

Table I. Physical Properties of Benazepril Hydrochloride Initial and Stressed Samples

Physical properties	Initial (t = 0) (n = 6)	Stressed (40°C/75% RH, 3 month)* (n = 6)
Thickness (mm)	2.92 (±0.01)	2.96 (±0.02)
Diameter (mm)	6.01 (±0)	6.02 (±0)
Hardness (kp)	4.98 (±0.57)	6.83 (±0.06)
Disintegration time (min)	2–3	>10

* Closed bottle, induction sealed, no desiccant.

Thermal Analysis and Moisture Sorption Isotherm

Differences in the thermal behaviors of initial and stressed tablets were monitored by DSC (Fig. 3) and TGA (Fig. 4). Lactose monohydrate (Fig. 3a) dehydration endotherm commenced at 97°C, peaked at 144°C, and returned to baseline at 167°C. A melting endotherm commenced at 202°C, peaked at 223°C, and returned to baseline at 227°C. Peak broadening and shifting of the lactose monohydrate dehydration peak was observed (Figs. 3c and 3d). This was also reported by Vromans et al.(11), which could be attributed to changes in the state of bound water and increase in particle sizes due to the wet granulation process. It has been reported by Vromans *et al.* that lactose with larger particle size would result in a shift of dehydration to higher temperature. Current experimental results seem to confirm such a conclusion.

The melting benazepril drug substance (Fig. 3b, 180°C) and lactose anhydrate (Fig. 3a, 223°C) were shifted to lower temperature in both initial and stressed tablets due to existence of other excipients. The extra endothermic peak appearing at 200°C for the initial tablets was probably due to the decomposition of lactose (Fig. 3a). The experiments were carried out in duplicate using the same procedure. It was noted that samples were charred after the experiments, indicating possible decomposition of the sample. In addition, this par-

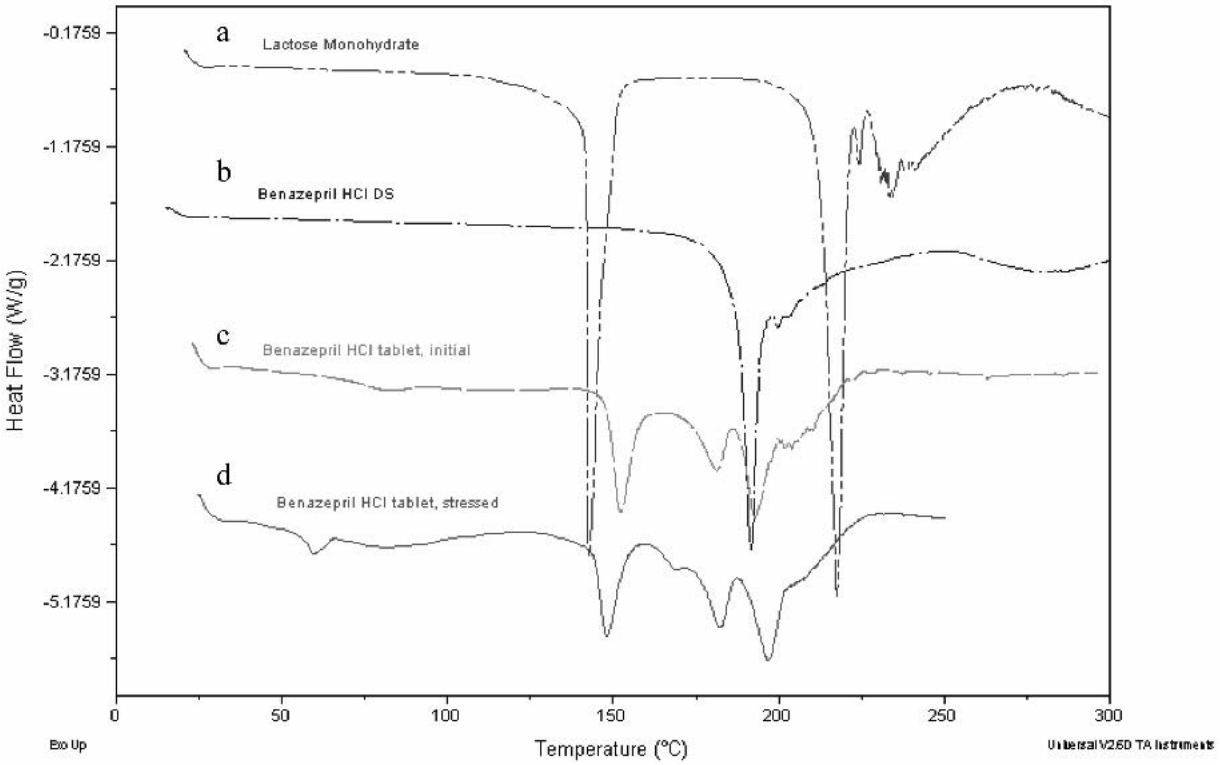

Fig. 3. Comparative DSC curves of benazepril hydrochloride tablets: (a) lactose monohydrate, (b) benazepril HCl drug substance, (c) benazepril HCl, initial sample, and (d) benazepril HCl, stressed sample.

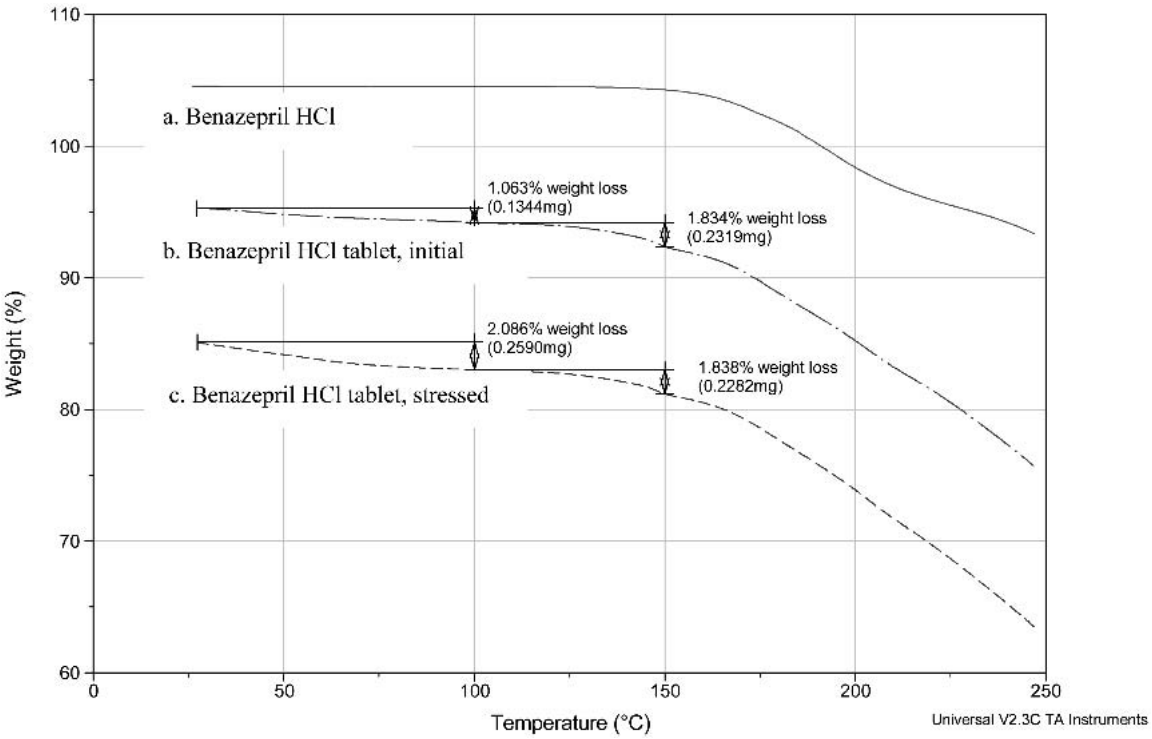

Fig. 4. Comparative TGA curve of benazepril hydrochloride tablets: (a) benazepril HCl drug substance, (b) benazepril HCl tablet, initial sample, and (c) benazepril HCl tablet, stressed sample.

ticular endotherm does not appear to be reproducible, which might be related to sample packing.

In addition to the broad endothermic peak (50–100°C) for initial tablets, a sharp endothermic peak (~60°C) was also evident for stressed tablets. The additional endothermic peak corresponded to a difference in weight loss of 2.1% (stressed tablets, Fig. 4c) compared with 1.1% (initial tablets, Fig. 4b) from TGA measurements. Lactose monohydrate dehydration occurred at temperatures around 144°C (Fig. 3), corresponding to a second phase weight loss of around 1.8% for both initial and stressed tablets (Fig. 4). The difference in the state of water (i.e., unbound free water vs. bound hydrate water) was evident from the change in stepwise weight loss from TGA curves.

Based on these results, it appeared that difference in moisture (~1%) between initial and stressed tablets might be the cause for reduction in dissolution rate. To test this hypothesis, moisture absorption isotherm of tablets at 40°C was measured. As can be seen from Fig. 5, moisture uptake for tablets increased rapidly at RH above 60%. Difference in equilibrium moisture between 45% RH (initial) and 75% RH (stressed) approximated 0.9%, which agreed with the TGA measurement. Thiber *et al.* reported the hydration–dehydration behavior of superdisintegrants (12), where the superdisintegrant powders expanded upon exposure to high humidity (80% RH), but did not regain their original shape even after drying (40% RH). It was most likely that similar superdisintegrant "preactivation" had taken place in the current formulation.

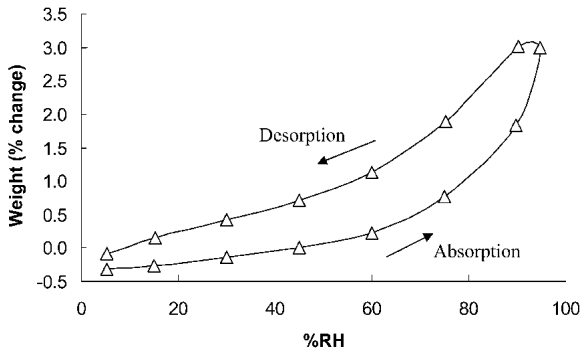

Fig. 5. Moisture absorption isotherm (40°C) for benazepril hydrochloride tablets, initial pulverized sample.

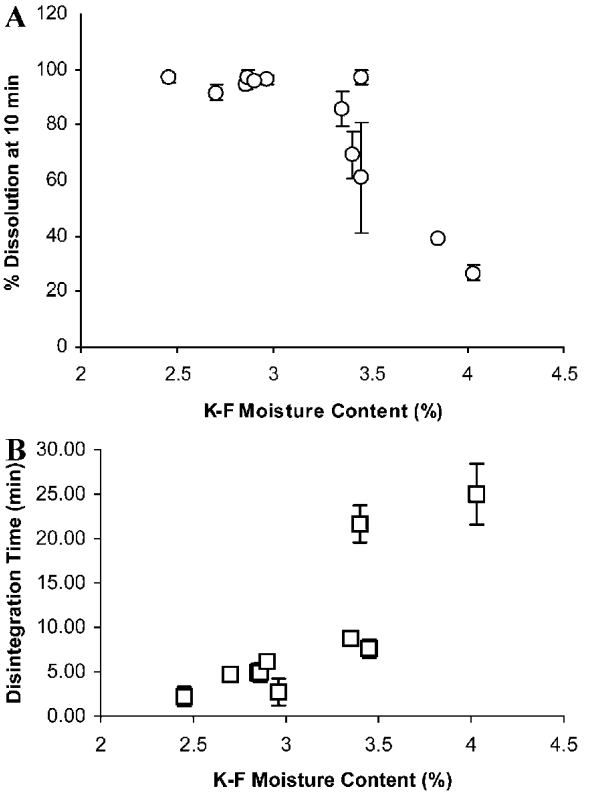

Fig. 6. (A) Dissolution–moisture content correlation; (B) disintegration time–moisture content correlation (n = 6).

Moisture–Dissolution Correlation

Water content measured by the Karl Fischer method was found to correlate well with dissolution of the tablets at 10 min. At moisture content below 3.5%, there was no significant reduction in dissolution for tablets. However, a linear decline in dissolution was observed at moisture content above the critical value (Fig. 6A). Similar trend was noted between moisture content and disintegration time (Fig. 6B), where disintegration time increased linearly with moisture content above a critical value of 3.5%. The scatter in Fig. 6B was likely because of the accuracy of the measurement in disintegration time.

The reduction in dissolution rate was not only a function of the moisture content in the stressed tablets, but also a function of time. Reduction in dissolution rate was more evident when tablets were stored at a stressed condition for a longer period of time. Tablets with the most significant dissolution reduction were those that were stored at 40°C/75% RH for 3 months, whereas those with less dissolution rate reduction were samples stored at milder conditions.

Porosity of benazepril hydrochloride tablets was found to approximate 29.5% from mercury pycnometer measurements. When the cumulative pore volume distribution and the pore size distribution function (13) were considered (Fig. 7), there appeared to be more pores between the size of 0.01–1 μm for the stressed tablets (circle) compared to that from the initial tablets (square). When the distribution of the pore size D(r) was plotted, a shift in pore size distribution toward larger values was evident for stressed tablets.

These observations were further confirmed by results from SEM measurements (Fig. 8). Comparison of both surface (Fig. 8B) and cross-sectional (Fig. 8C) SEM photos of initial and stressed tablets demonstrated a more relaxed pore structure for stressed tablets. As demonstrated in Fig. 8, signs of "tablet stress" were evident from fractures that appeared on the surface of stressed tablets (Fig. 8B). Under higher magnification (×2000), many porous structures were apparent for stressed tablets (Fig. 8C). Direct view of the tablets also revealed rougher surface characteristics for stressed tablets (Fig. 8A). A correlation between porosity and dissolution rate constant was established by Cruaud *et al.* (14) and Graaff *et al.* (15), where it was reported that larger pore size was usually favorable for rapid dissolution, whereas other reports had shown that dissolution was independent of porosity (16) of the tablets. Under such a scenario, efficiency of the disintegrant would be of more importance. These reports focus on different aspects of rate-limiting step for tablet dissolution.

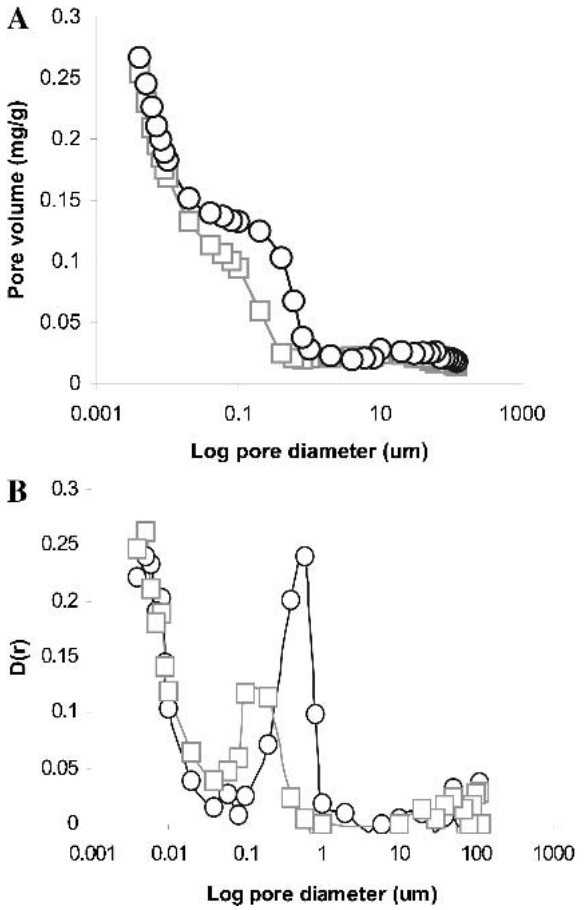

Fig. 7. The effect of stressed storage condition on the cumulative pore size distribution (upper plot) and pore size distribution function (lower plot) of benazepril hydrochloride tablets: (A) pore volume, ml/g; (B) distribution function, $D(r) = dV/d(\log D)$. $D(r)$ is the derivative of cumulative pore volume vs. log pore diameter plot (○ stressed tablets; □ initial tablets).

When freshly prepared tablets were studied (14,15), it appeared that the correlation between pore structure and dissolution existed because the pore size was directly related to the wicking effect of the tablets, therefore, reflecting the efficiency of the disintegrant. However, when stressed tablets were studied (16), this was no longer true due to changes occurring to the disintegrant. In such cases, disintegration time is a better measurement of the efficiency of the disintegrant instead of pore size. As demonstrated in the current report, the observed physical changes for stressed tablets of benazepril hydrochloride and correlations between moisture contents and disintegration time clearly indicated that decline in dissolution, in the current formulation, was directly related to the disintegration time.

Moisture Equilibrium Model

Mathematical treatments of dissolution stability have been reported by a number of authors (17,18). Such attempts were made to estimate the dissolution shelf-life of a product and minimize experimentation. Often, a certain critical moisture level of the product was required for initiation of dissolution change (3). In this report, a simple moisture equilibrium model was proposed to estimate dissolution stability for benazepril tablets under stressed storage conditions and to predict the effect of desiccant on dissolution rate of benazepril tablets.

The following assumptions have to be made for such an estimation: (i) benazepril tablets are packaged in a 120-ml commercial HDPE bottle, 100 tablets/bottle; (ii) there is a constant rate of water-vapor transmission into the HDPE bottle from the 40°C/75% RH environment that is independent of the moisture level inside the package; (iii) moisture distribution among tablets and the desiccant can be determined proportionally by the equilibrium moisture difference between ambient (25%) and 75% RH, and the distribution is independent of moisture levels; and (iv) reduction in dissolution rate has a direct correlation with moisture content in the tablets.

Moisture content in the HDPE bottle, water vapor transmitted into the HDPE bottle over time, and the amount of moisture distributed to tablets can be calculated based on the following equations:

$$X_1 = V \times D \tag{1}$$

$$X_2 = P \times T \times V \tag{2}$$

$$X = X_1 + X_2 \tag{3}$$

$$X_T\% = \frac{N \times W_T \times M_T}{N \times W_T \times M_T + W_S \times M_S} \tag{4}$$

$$X_T = X \times X_T\% \tag{5}$$

where V is volume of the HDPE bottle (120 ml), D is density of moist air (1.1019 mg/ml), P is transmission rate of water vapor through the sealed HDPE bottle (1.5 $mg \cdot day^{-1} \cdot l^{-1}$), T is time (3 months), N is number of tablets in the HDPE bottle (100), W_T and W_S are weight of the tablet and Sorb-it desiccant (75 mg and 1 g, respectively), and M_T and M_S are difference of equilibrium moisture for benazepril hydrochloride tablets and Sorb-it desiccant between RH 45 and 75% (1.0% and 12% respectively).

X_1, X_2, and X_T are defined as amount of moisture in the HDPE bottle, water vapor transmitted over time, and amount of moisture that is available for the tablets, respectively.

Based on Eqs. (1)–(5), total amount of moisture and those available for tablets can be calculated. Once X_T is obtained, the distribution of moisture in individual tablets can be calculated. This value is calculated to be 0.76% based on the values provided in the aforementioned discussion. Therefore, assuming an initial moisture content of 2.8%, which is the average of several measurements of initial tablets, tablet moisture would be 3.56% if the tablets were stored for 3 months at 40°C/75% RH. From the dissolution–moisture correlation, the dissolution at 10 min for these tablets should be between 60 and 70% (Fig. 6).

Real-time tests were also carried out, and comparisons of the dissolution profiles for initial and stressed tablets are outlined in Fig. 9. These tablets were stored under 40°C/75% RH in a sealed HDPE bottle with 1 g of Sorb-it desiccant for 1, 2, and 3 months. It was obvious from the comparison that although there were no prominent changes in dissolution values at 30 min for these samples, some reduction in dissolution has occurred, as can be seen from dissolution at 10 min. Mean percent dissolved changed from 93.7% (initial) to 89.7% (2 month) and 61.1% (3 month). The implication from the physi-

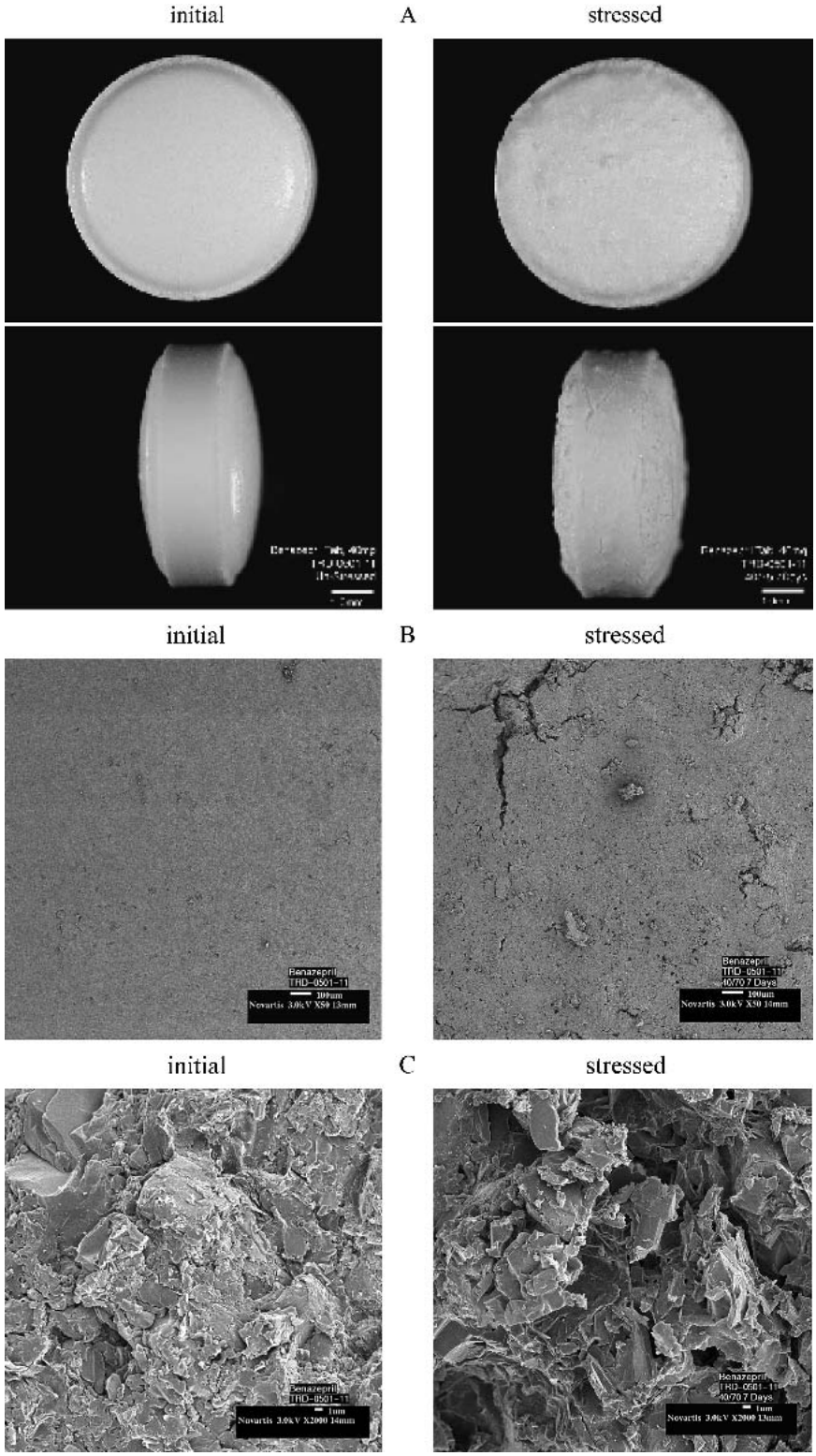

Fig. 8. SEM photo of benazepril hydrochloride tablets, initial (left panel) and stressed (right panel) samples (A). Direct view; (B). Surface of tablets, magnification x50; (C). Cross section of tablets, magnification ×2000.

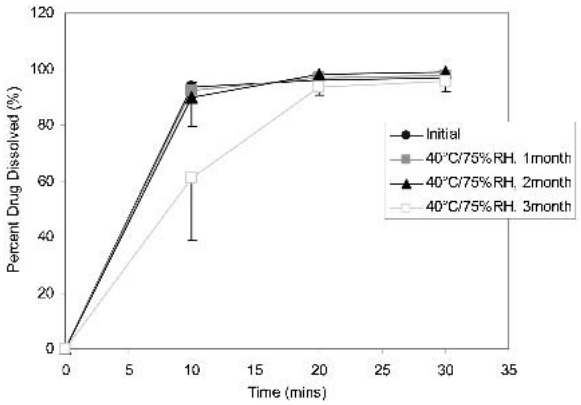

Fig. 9. Comparison of dissolution profiles of formulation stored under 40°C/75% RH in sealed HDPE bottle with desiccant pack: ● initial; ■ 40°C/75% RH, 1 month; ▲ 40°C/75% RH, 2 months; □ 40°C/75% RH, 3 months (n = 6).

cal model (60–70%) is roughly in agreement with the real-time measurement (61.1%).

It appeared that reduction in dissolution rate during stress storage conditions can be mitigated by inclusion of desiccant in the package; however, such phenomena cannot completely be prevented.

CONCLUSIONS

This report provided a thorough investigation on reduction in the dissolution rate for benazepril hydrochloride tablets when they were stored under stressed conditions (40°C/75% RH). Increase in moisture content was identified as the root cause for reduction in dissolution rates. Increase in moisture content induced "preactivation" of the disintegrant, which then resulted in structural change of the tablets. The structural change was further confirmed by data obtained from SEM and porosity measurements. Finally, a simple physical model for moisture equilibrium was proposed; when the worst-case scenario (40°C/75% RH, 3 months) was considered, the predicted value of dissolution at 10 min was found to be comparable to the real-time measurement.

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