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THE EFFECT OF LOW- AND HIGH-HUMIDITY AGING ON THE HARDNESS, DISINTEGRATION TIME AND DISSOLUTION RATE OF TRIBASIC CALCIUM PHOSPHATE-BASED TABLETS

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ABSTRACT

The effect of low- and high-humidity aging on hardness, disintegration time and dissolution rate of tribasic calcium phosphate-based tablets prepared at different initial moisture levels was studied. The tablet hardness, disintegration time and dissolution rate of the drug changed only slightly on aging under low humidity when the moisture contents at the time of compression were low. At higher initial moisture levels, the tablet disintegration time decreased and the dissolution rate increased, although no change in tablet hardness occurred on aging under low humidity. The tablets containing lower initial moisture decreased in hardness, increased in disintegration

time and decreased in dissolution rate on aging under high humidity. A small or variable change in hardness, a large increase in the disintegration time and a large decrease in the dissolution rate was seen in tablets containing higher initial moisture contents on aging under high humidity. The results indicate that the moisture content of the tablet granulation at the time of compression and moisture gained during aging plays a significantly important role on hardness, disintegration time and dissolution rate of tribasic calcium phosphate-based tablets.

INTRODUCTION

Recent studies (1-4) in our laboratories have demonstrated the importance of the initial tablet moisture and moisture gained during aging with regard to some of the important tablet parameters such as hardness, disintegration time and dissolution rate. A water soluble excipient, lactose, and a sparingly water soluble excipient, dibasic calcium phosphate dihydrate, were used in these studies.

The previous study (4) using dibasic calcium phosphate dihydrate-based tablets containing different initial moisture

contents indicated that on aging under low relative humidity the hardness increased while disintegration time and dissolution rates decreased. On aging under high relative humidity, hardness, disintegration and dissolution rates decreased at all initial moistures.

Tribasic calcium phosphate is used as a diluent or filler in tablet formulations (5) and has very low water solubility. The purpose of this investigation was to study the effect of aging tribasic calcium phosphate-based tablets under low- and high-humidity conditions on hardness, disintegration time and dissolution rate. It was hoped that a broader understanding of the effect of moisture on important tablet parameters would be valuable in the proper choice of excipients in developing tablet formulations.

MATERIALS

The following materials were used as received from the suppliers: tribasic calcium phosphate (J. T. Baker Chemical Company, Phillipsburg, NJ), corn starch (Staley Manufacturing Co., Decatur, IL), magnesium stearate (Mallinckrodt Chemical Works, St. Louis, MO) and naproxen (Syntex Research, Palo Alto, CA). All other chemicals were analytical reagent grade.

METHODS

Preparation of Granules

The formula contained 84% tribasic calcium phosphate, 10% starch, 5% naproxen and 1% magnesium stearate. The calcium phosphate and naproxen were mixed by geometric dilutions and then blended in a planetary mixer (Kitchen Aid Model K5-A, The Hobart Manufacturing Co., Troy, OH) for five minutes. The powder mix was granulated with water and the wet granulation was passed through a #12 mesh screen. The drying was carried out in open trays in a forced air oven at 55-60°C until the desired moisture level was reached. The dry granulation was screened through a #16 mesh screen and stored in tightly closed jars.

To obtain different levels of moisture, the granules were divided into several parts. Each part of the granulation was sieved through a #20 mesh screen and a calculated amount of water was mixed with the fines. The fine granules were screened through a #16 mesh screen and mixed thoroughly with the rest of the granules and the starch. The granules were allowed to equilibrate for 24 hours in tightly closed jars and mixed with magnesium stearate before compression.

Compression

Tablets were compressed by means of a single punch machine (Stokes Model F4) to a targeted hardness of 7-8 Strong-Cobb units using 0.95 cm flat-faced punches and die. The targeted tablet weight was 380 mg.

Moisture Determination

The granulation moisture was determined with a Cenco Moisture Balance by exposure to a 125-W IR lamp at a setting of 90-V until a constant weight was achieved. The weight loss on drying, in percent, was read directly from this instrument. The tablets were ground with a mortar and pestle, and the same procedure for the moisture determination was followed.

Storage Conditions

Tablets were stored under constant relative humidity (44% and 93%) and constant temperature (23°C) conditions in desiccators containing salt solutions. The tablets were sampled periodically for hardness, moisture content, disintegration and dissolution over a period of 17 weeks. For each sampling point at 93% relative humidity, some tablets were transferred to 44% relative humidity for one day and the same tests repeated on these tablets.

Hardness Determination

Initial hardnesses were determined (Schleuniger Hardness Tester Model 2E) immediately after compression. The hardness of the stored tablets were determined immediately after removal from the desiccators. Ten tablets were used in each determination and the mean and the standard error were calculated.

Disintegration

The USP method for uncoated tablets was used. The disintegration medium was 850 ml water maintained at 37°C. Discs were used in the test. The mean and the standard error were calculated from the results for six tablets.

Dissolution

The dissolution apparatus consisted of a one-liter beaker and a USP Paddle driven by a six-spindle drive with a variable speed control (Model 72R, Hanson Research Corporation, Northridge, CA) and a water bath. The speed of the stirrers was set at 120 rpm. The dissolution medium was 600 ml of 0.1M pH 7.4 phosphate buffer maintained at 37°C in a constant temperature water bath. The distance between the bottom of the beaker and the bottom of the paddle was kept constant at 1.8 cm. Samples were filtered using polypropylene filter holders

with 0.8 μm pore diameter filters. The dissolution medium volume was kept constant with fresh phosphate buffer. At least three tablets were used for each determination. The absorbance of the sample was determined at 332 nm using a Unicam SP 1800 Spectrophotometer.

RESULTS AND DISCUSSION

The results of the effect of aging under low relative humidity (44% and 23°C) on hardness of tribasic calcium phosphate-based tablets, each at a different initial moisture content, are given in Figure 1. Table I gives the initial moisture contents and the moisture contents after aging under low relative humidity. When the initial moisture content of the tablets was 1.5%, tablets gained moisture on aging under low humidity, which is reflected in the tablet hardness decrease. At higher initial moisture contents, the tablets lost moisture on aging under low humidity until an equilibrium value was reached. This moisture loss affected the tablet hardness only slightly with the possible exception of 2.5% initial moisture, where the tablets increased in hardness on aging.

Figure 1 also gives the results of the effect of aging under low relative humidity on the disintegration time of

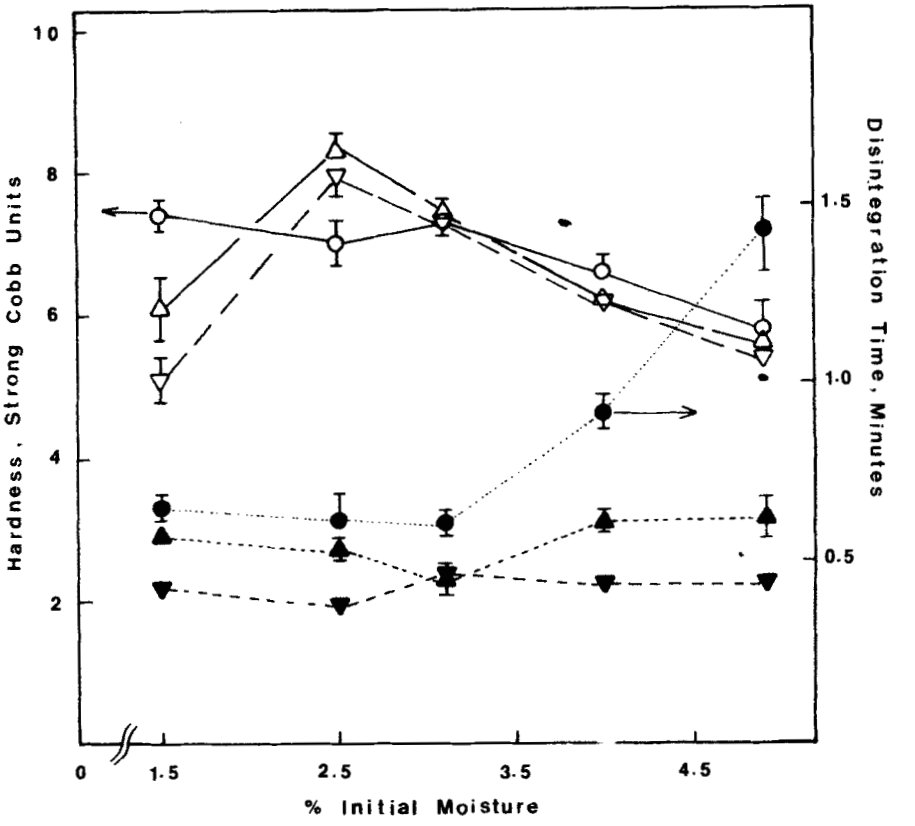

FIGURE 1:

Effect of aging uder 44% relative humidity and 23° C on hardness and disintegration time of tribasic calcium phosphate-based tablets containing different moisture levels at the time of compression.

KEY: ○, initial; △, 1 day; ▽, 17 weeks. Open symbols represent hardness and closed symbols represent disintegration time. Vertical bars indicate standard error; the absence of vertical bars indicates that the standard error was too small to be shown.

TABLE I

INITIAL MOISTURE CONTENTS AND MOISTURE CONTENTS AFTER AGING UNDER 44% RELATIVE HUMIDITY AND 23° C.

Days of Storage	% Moisture				
Initial	1.5	2.5	3.1	4.0	4.9
1 Day	1.7	2.0	2.1	2.0	2.2
7 Days	1.9	1.9	1.8	2.0	1.9
119 Days	1.9	2.0	2.0	2.1	2.1

tribasic calcium phosphate-based tablets containing different moisture contents at the time of compression. The disintegration time of all tablets decreased on aging under low humidity, although a larger decrease in the disintegration time occured in tablets containing higher moisture contents at the time of compression.

The results of the effect of aging under low relative humidity on drug dissolution from tribasic calcium phosphate-based tablets containing different initial moisture contents are given in Figure 2. The higher the initial moisture of the tablets, the lower the initial dissolution rate. On aging under low humidity, the dissolution rate of the

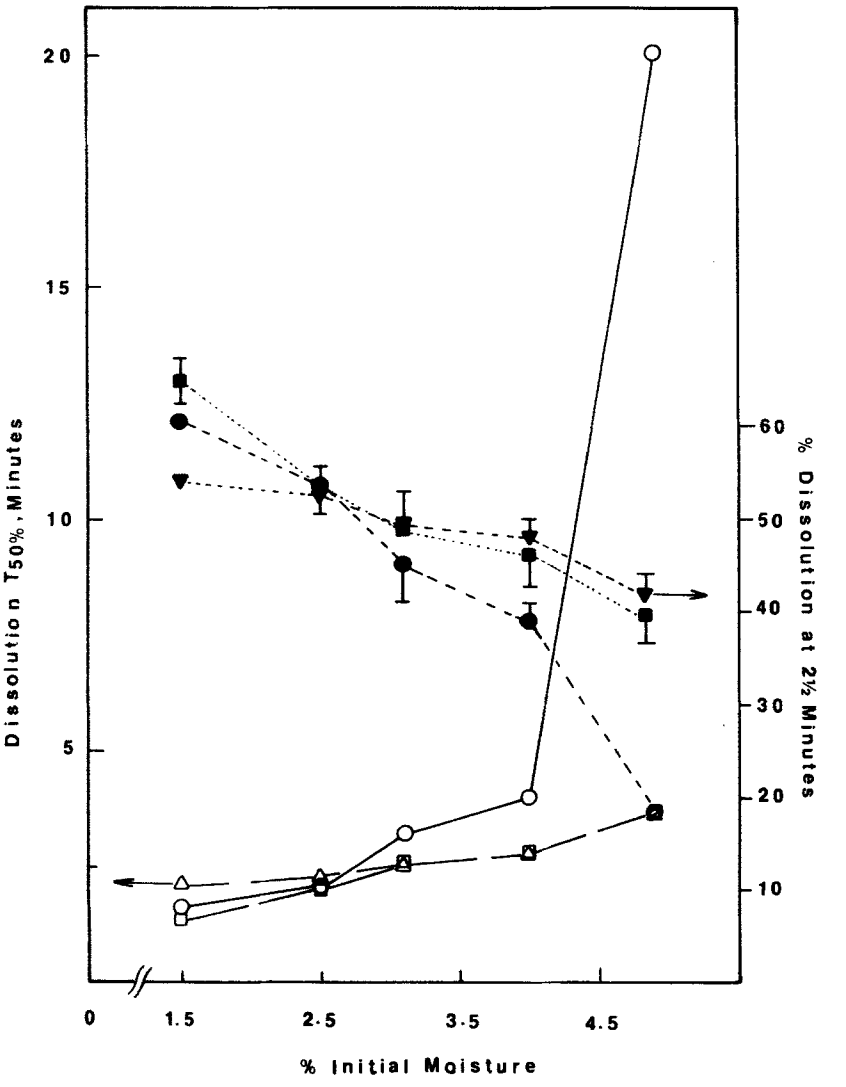

FIGURE 2:

Effect of aging under 44% relative humidity and 23° C on *in vitro* dissolution of tribasic calcium phosphate-based tablets containing different moisture levels at the time of compression.

KEY: ○, initial; □, 1 day; ▽, 17 weeks. Open symbols represent dissolution $T_{50\%}$ and solid symbols represent % dissolution at 2.5 minutes. Vertical bars indicate standard errors.

drug from the tablets containing higher initial moistures increased, and the magnitude of this increase was related to the initial moisture contents of the tablets.

These results clearly indicate that minimal changes in hardness, disintegraton time and dissolution rate would occur if the moisture content of the tablets at the time of compression is carefully controlled and the tablets are stored uner low relative humidity conditions.

Figure 3 gives the results of the effect of aging under high relative humidity (93% and 23°C) on hardness of tribasic calcium phosphate-based tablets, each at different initial moisture contents. The tablets after high humidity exposure were allowed to equilibrate at 44% relative humidity for one day. The hardness data of these tablets is also given in Fig. 3. The moisture contents of these tablets are given in Table II. A large decrease in tablet hardness occured at low initial moisture contents of the tablets, and the hardness increased only slightly after one day storage at 44% relative humidity. When the moisture content of the tablets at the time of compresson was 4.9%, no significant change in hardness occured. However, after one day exposure to 44% relative

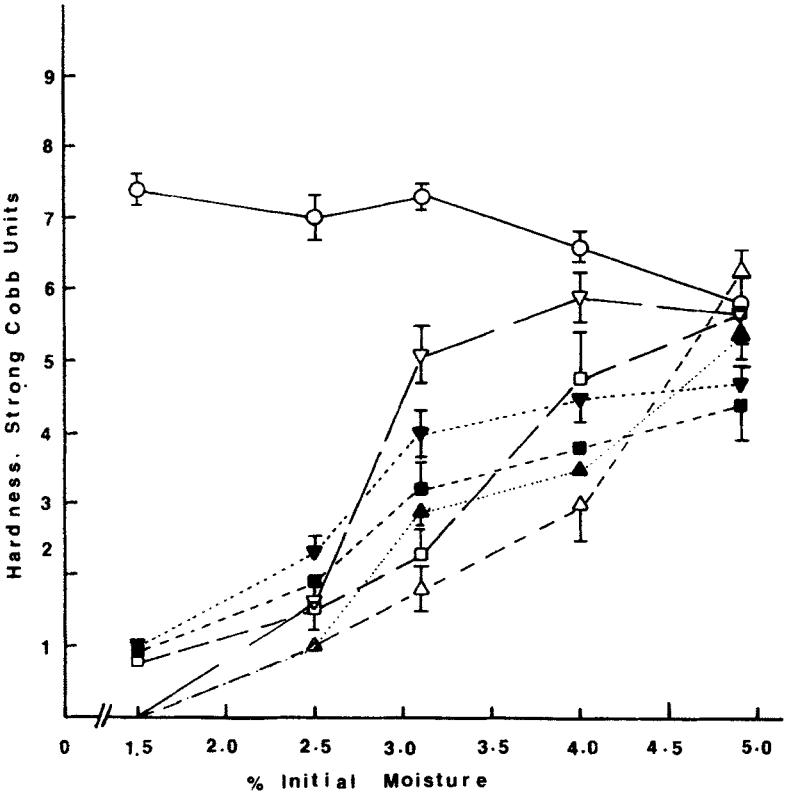

FIGURE 3:

Effect of aging under 93% relative humidity and 23° C on hardness of tribasic calcium phosphate-based tablets containing different moisture levels at the time of compression.

KEY: ○, initial; □, 1 week; △, 4 weeks; ▽, 17 weeks. Closed symbols represent one day storage at 44% relative humidity after high humidity aging. Vertical bars indicate standard error; the absence of vertical bars indicate that the standard error was too small to be shown.

TABLE II

INITIAL MOISTURE CONTENTS AND MOISTURE CONTENTS AFTER AGING UNDER 93% RELATIVE HUMIDITY AND 23°C. FOLLOWED BY ONE DAY EXPOSURE TO 44% RELATIVE HUMIDITY

Storage Time and Conditions	% Moisture				
a. Initial	1.5	2.5	3.1	4.0	4.9
b. 7 Days (93% RH)	3.6	4.0	3.7	4.1	4.3
1 Day (44% RH)	1.7	1.8	1.8	2.1	2.0
c. 28 Days (93% RH)	4.7	4.5	5.3	5.6	5.4
1 Day (44% RH)	2.1	1.8	2.2	2.4	2.2
d. 119 Days (93% RH)	6.2	6.3	6.3	6.4	6.3
1 Day (44% RH)	2.1	2.1	2.5	2.5	2.3

humidity, these tablets decreased in hardness resulting from moisture loss (Table II).

The results of the effect of aging under high relative humidity on disintegration time of tribasic calcium

phosphate-based tablets containing different moisture contents at the time of compression are given in Fig. 4. The disintegration time of all tablets increased on aging under high humidity. One day storage at 44% relative humidity after high humidity aging improved the disintegration time in most cases.

The initial dissolution rate at high (4.9%) initial moisture content was considerably lower compared to the tablets with low initial moisture contents. A large decrease in the dissolution rate of the drug occured when tribasic calcium phosphate tablets were aged under high relative humidity. These results are shown in Fig. 5 which gives the dissolution T_{50}% vs initial tablet moisture plots. The results of the drug dissolution from tablets stored at 44% relative humidity after high humidity aging are also given in Fig. 5. Under these storage conditions, the dissolution rate increased in most cases, so that the large decrease in the dissolution rate on aging under high humidity was minimized.

It is interesting to note that at low (1.5%) and high (4.9%) initial moisture contents, the dissolution rate after aging under high humidity followed by one day exposure to low humidity became similar to the initial dissolution rate.

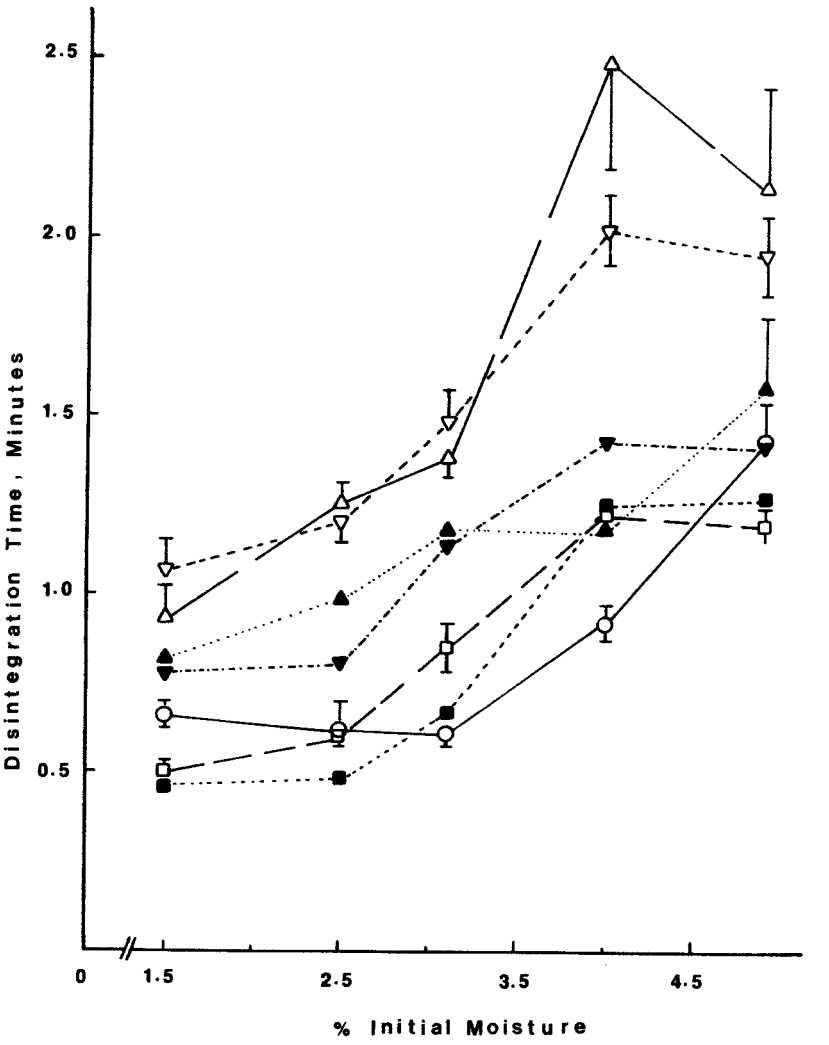

FIGURE 4:

Effect of aging under 93% relative humidity and 23°C on disintegraton time of tribasic calcium phosphate-based tablets containing different moisture levels at the time of compression.

KEY: ○, initial; □, 1 week; △, 4 weeks; ▽, 17 weeks. Solid symbols indicate the effect of one day storage at 44% relative humidity after high humidity aging. Vertical bars indicate standard errors; absence of vertical bars indicate that the standard error was too small to be shown.

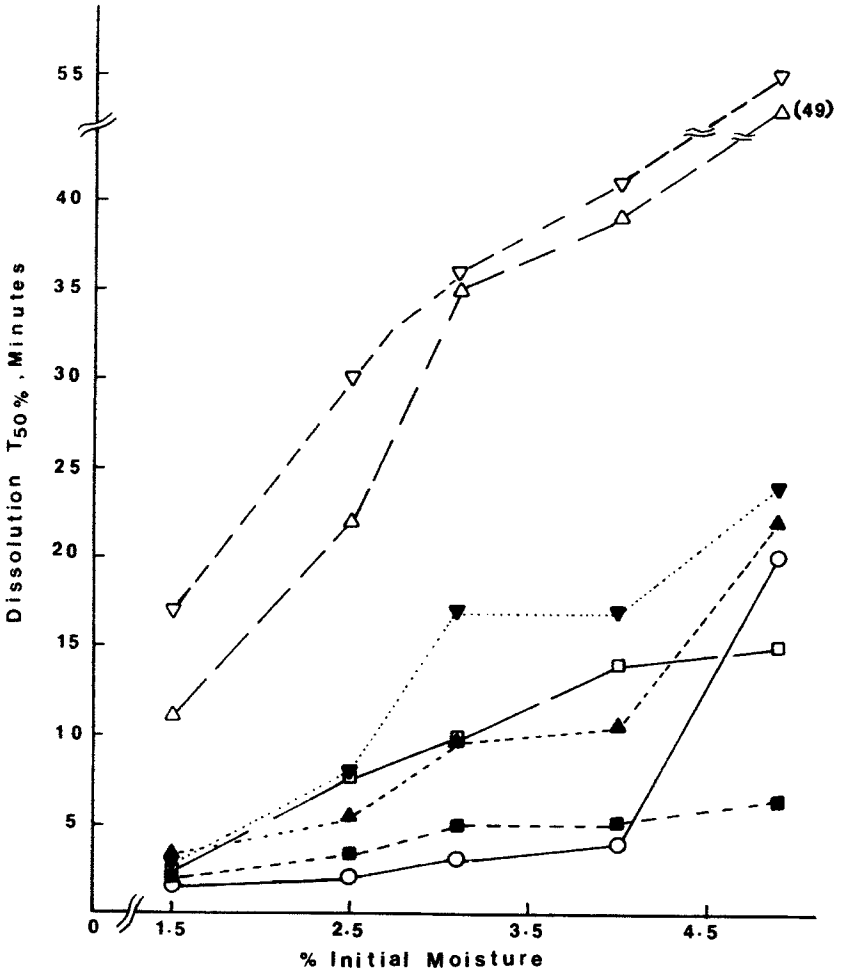

FIGURE 5:

Effect of aging under 93% relative humidity and 23° C on *in vitro* dissolution of the drug from tribasic calcium phosphate-based tablets containing different moisture levels at the time of compression.

KEY: ○, initial; □, 1 week; △, 4 weeks; ▽, 17 weeks. Closed symbols indicate the effect of one day storage at 44% relative humidity after high humidity aging.

However, only at the high initial moisture content was the resulting change in hardness minimal.

CONCLUSION

The moisture contents of tribasic calcium phosphate-based tablets at the time of compression and the moisture gained or lost during aging plays a significant role on important tablet parameters such as hardness, disintegration time and dissolution rate. On aging under low relative humidity, only small changes in hardness were seen at all initial moisture contents. The initial dissolution rate for tablets containing higher initial mositure contents was slow compared to the tablets containing lower initial moisture contents. On aging under low relative humidity, the dissolution rate of tablets containing higher initial moisture contents increased, thus narrowing the dissolution rate differences between different initial moisture contents.

On aging under high relative humidity, the dissolution rate of all tablets decreased. The hardness also decreased and the decrease was large at low initial moistures. There was a large increase in the dissolution rate of high relative

humidity aged tablets after these tablets were exposed to low relative humidity for one day.

Although the changes in hardness, disintegration time and dissolution rate of tribasic calcium phosphate-based tablets on aging are less significant compared to the dibasic calcium phosphate dihydrate-based tablets (4), it is important to note that the effect of moisture on important tablet parameters should be thoroughly investigated before selecting these excipients for formulating compressed tablets.

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