J. Pharm. Pharmacol. 1980, 32: 10–14 Received April 24, 1979

The effect of low- and high-humidity ageing on the hardness, disintegration time and dissolution rate of dibasic calcium phosphate-based tablets

Z. T. CHOWHAN

Syntex Research Division of Syntex (U.S.A.) Inc., 3401 Hillview Avenue, Palo Alto, California 94307 U.S.A.

The effect of low- and high-humidity ageing on hardness, disintegration time and dissolution rate of dibasic calcium phosphate dihydrate-based tablets prepared at different initial moisture concentrations was studied. Hardness increased while disintegration and dissolution rate decreased on ageing in low humidity. The dissolution rate of tablets containing higher initial moisture was slower than the tablets containing lower initial moisture. On ageing in high humidity, hardness, disintegration and dissolution rates decreased at all initial moistures. The results suggest that the effects of moisture and humidity should be thoroughly investigated for dibasic calcium phosphate dihydrate-based tablets in order to ensure stability and bioavailability of the drug.

Dibasic calcium phosphate dihydrate is one of the commonly used excipients in the formulation of direct compression tablets. In a full factorial design experiment involving eight excipients, three disintegrants and common binders, the best direct compression formulation was dibasic calcium phosphate dihydrate-starch U.S.P. (Sangekar et al 1972). The relative ranking was based on maximum hardness, minimum change in disintegration time, minimum moisture uptake and minimum change in volume.

A decrease in dissolution efficiency without any changes in hardness or tablet size on ageing at different temperatures and humidities from dibasic calcium phosphate dihydrate tablets containing sodium starch glycolate, an alginate derivative, or povidone as a disintegrant was reported (Horhota et al 1976). This unpredictable decrease in dissolution efficiency was due to the loss of water of hydration during storage at high temperature and high humidity (Lausier et al 1977). At 25°C and 50% relative humidity, other factors such as case hardening were thought to play a major role in the decrease in disintegration and dissolution rates without notable changes in weight and hardness.

The physical effects of moisture in the tablet manufacturing process such as mixing, granulation, drying, flow into the die, compression and ejection from the die have been reported (Shotton & Rees 1966; Armstrong & Griffiths 1970; Esezobo & Pilpel 1976). The role of moisture in initial disintegration and dissolution (Pilpel et al 1978) of chloroquine phosphate/starch tablets indicated that the disintegration and dissolution rates of these tablets increased with increase in moisture content of the granules and attained maxima at about 4–5% w/w moisture. Recent studies in our laboratories (Chowhan & Palagyi 1978; Chowhan 1979) have indicated that the moisture content of the granulation at the time of compression plays an important role in the hardness increase of the resultant tablets on storage. Tablets prepared from lactose, a water-soluble excipient and naproxen, a water-insoluble drug, increased in hardness due to partial moisture loss on storage. This hardness increase did not affect the dissolution of the drug.

Since dibasic calcium phosphate dihydrate is almost insoluble in water, tablets made from this excipient and water-insoluble drug would not be expected to show large increases in hardness due to the moisture induced effect. The purpose of this report was to study the effect of ageing of dibasic calcium phosphate-based tablets under low and high humidities, each at a different initial moisture content on hardness, disintegration and dissolution. A broader understanding of the effects of moisture on hardness, disintegration and dissolution would be valuable in the development of tablet formulations which do not interfere with the bioavailability and stability of the drug.

MATERIALS AND METHODS

Materials

Dibasic calcium phosphate dihydrate and magnesium stearate from Mallinckrodt Inc., corn starch from Staley Manufacturing Co. and naproxen (>99%

pure) from Syntex Research were used. All other chemicals were analytical reagent grade.

Preparation of granules

The formula contained 84% dibasic calcium phosphate dihydrate, 10% starch, 5% naproxen and 1% magnesium stearate. The calcium phosphate dihydrate and naproxen were mixed by geometric dilutions and then in a planetary mixer for 5 min. The powder mix was granulated with water and passed through a screen having a 1·3 mm aperture. The drying was carried out in open trays in a forced air oven at 55–60 °C to a moisture content of 0·5%. The dried granules were passed through a screen having a 1·3 mm aperture and stored in tightly closed glass jars.

To obtain different concentrations of moisture, the granules were divided into several parts. Each part of the granulation was sieved through a screen having a 0·85 mm aperture and a calculated amount of water was mixed with the fines. The fine granules were screened through a screen having a 1·3 mm aperture and mixed thoroughly with the rest of the granules. The granules were allowed to equilibrate for 24 h in tightly closed glass jars and mixed with starch and magnesium stearate.

Compression

Tablets were compressed by means of a single punch machine (Stokes Model F4) to a hardness of 8 Strong-Cobb units using 0·95 cm flat-faced punches and die. The desired 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. Tablets were sampled periodically for hardness, moisture content, disintegration and dissolution over 14 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 (Heberlein Hardness Tester) immediately after compression. The hardnesses 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 U.S.P. method for uncoated tablets was used. The disintegration medium was 850 ml water maintained at 37 °C. Discs were not used in the test. The mean and standard error were calculated from the results for six tablets.

Dissolution

The dissolution apparatus consisted of a 1 litre beaker and a U.S.P. paddle, driven by a synchronous motor at 120 rev min^{-1}. The dissolution medium was 600 ml of 0·1 M 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 samples was determined spectrophotometrically at 332 nm.

RESULTS

The results for the effect of ageing under low relative humidity (44% and 23 °C) on the hardness of dibasic calcium phosphate dihydrate-based tablets, each at a different initial moisture content, are given in Fig. 1. The main increase in hardness occurred within one day after compression, after which there was no change. At lower initial moisture content (1·9%) there was essentially no change in the moisture content of the tablets on storage (Table 1). However, when the initial moisture concentrations were 2·5, 2·8, and 3·1%, some moisture was lost on ageing under low humidity.

The changes in hardness and moisture content of the dibasic calcium phosphate dihydrate-based tablets on ageing suggest that there is no relationship between moisture loss and hardness increase. This result is not unexpected in view of the water insolubility of the formulation. The increase in tablet hardness appears to be due to the general hardening through the bulk of the tablet.

Fig. 2 gives the results of the effect of ageing under low relative humidity on disintegration time of

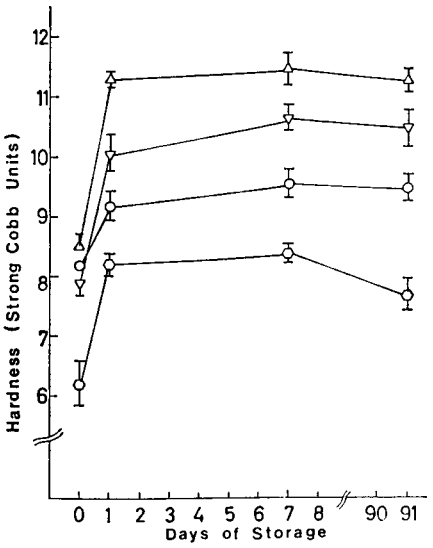

FIG. 1. Effect of ageing at 44% relative humidity, 23 °C, on hardness of dibasic calcium phosphate dihydrate-based compressed tablets. The granulation moisture content at the time of compression was :○, 1·9% ▽, 2·5%. △, 2·8%; ○, 3·1%. Vertical lines indicate standard error. The absence of vertical bars indicate that the standard error was too small to be shown.

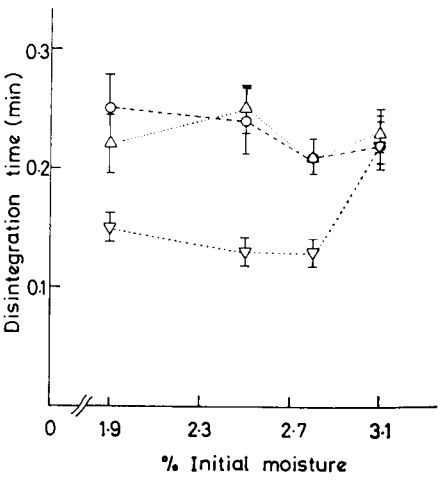

FIG. 2. Effect of ageing at 44% relative humidity, 23 °C, on disintegration time of dibasic calcium phosphate dihydrate-based compressed tablets containing different moisture concentrations at the time of compression. ○, inital; △, one day; ▽, 14 weeks. Vertical lines indicate standard errors.

dibasic calcium phosphate dihydrate-based tablets, each at a different initial moisture content. At all initial moisture concentrations, with the exception of 3·1%, the disintegration time decreased on ageing under low humidity for 14 weeks.

The 50% dissolution time (T50%) increased with increase in initial moisture content above the 2% level (Fig. 3). On ageing under low relative humidity, T50% also increased at all initial moisture concentrations. These results suggest no definite relationship between hardness increase and dissolution rate decrease on ageing under low humidity.

Fig. 4 gives the results of the effect of ageing under high relative humidity (93%, 23 °C). The hardness of the tablets decreased on ageing under high humidity and the rate and magnitude of the decrease was related to the initial moisture contents of the tablets.

Table 1. Initial moisture contents and moisture contents after ageing under 44% relative humidity and 23 °C.

Days of storage	% Moisture			
Initial	1·9	2·5	2·8	3·1
1 Day	2·1	2·3	2·3	2·3
7 Days	2·0	2·3	2·4	2·5
91 Days	2·0	2·4	2·3	2·5

The softened tablets had picked up moisture on storage under high humidity (Table 2). The effect of one-day exposure to low relative humidity after high humidity ageing was some increase in hardness (Fig. 4) and loss of some of the gained moisture.

At all initial moisture contents, the dibasic calcium phosphate-based tablets disintegrated rapidly after compression (Fig. 5). However, on ageing for 14 weeks under high humidity, the disintegration time

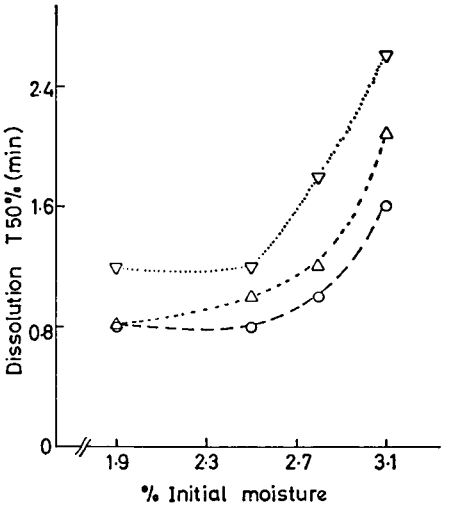

FIG. 3. Effect of ageing at 44% relative humidity, 23 °C, on in vitro drug dissolution of dibasic calcium phosphate dihydrate-based compressed tablets containing different moisture concentrations at the time of compression. ○, initial; △, one day; ▽, 14 weeks.

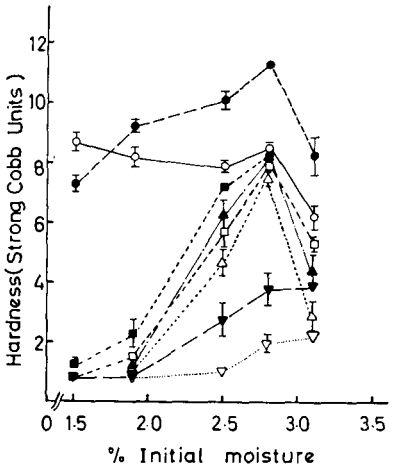

FIG. 4. Effect of ageing at 93% relative humidity, 23 °C, on hardness of dibasic calcium phosphate dihydrate-based tablets containing different moisture concentrations at the time of compression. ○, initial; □, one week; △, three weeks; ▽, 14 weeks. Closed symbols represent one day storage at 44% relative humidity after high humidity ageing. Vertical lines indicate standard error; the absence of vertical lines indicate that the standard error was too small to be shown.

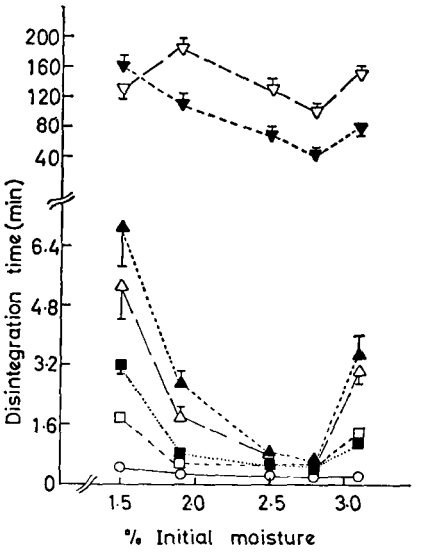

FIG. 5. Effect of ageing at 93% relative humidity, 23 °C, on disintegration time of dibasic calcium phosphate dihydrate-based compressed tablets containing different moisture concentrations at the time of compression. ○, initial; □, one week; △, 3 weeks; ▽, 14 weeks. Closed symbols represent one day storage at 44% relative humidity after high humidity ageing. Vertical lines indicate standard error. The absence of vertical lines indicate that the standard error was too small to be shown.

increased several hundred fold. At 2·8% initial moisture the effect of ageing on increasing disintegration time was less compared with other initial moistures. One day exposure to low relative humidity after ageing under high relative humidity resulted in some decrease in the disintegration time.

The effect of ageing under high relative humidity on drug dissolution is given in Fig. 6. T50% increased on ageing under this condition. The initial moisure contents of the tablets did not affect the drug dissolution on ageing, and the effect of one-day exposure to low humidity after ageing under high humidity was only a slight increase in the dissolution rate.

DISCUSSION

Because of the insolubility of the drug-excipient combination in small amounts of moisture in the

Table 2. Initial moisture content and moisture contents after ageing under 93% relative humidity.

Time of storage	% Moisture				
Initial	1·5	1·9	2·5	2·8	3·1
1 Week	3·0	2·9	3·0	3·3	3·5
3 Weeks	3·0	3·1	3·4	3·7	3·4
14 Weeks	3·6	4·0	3·9	3·6	3·7

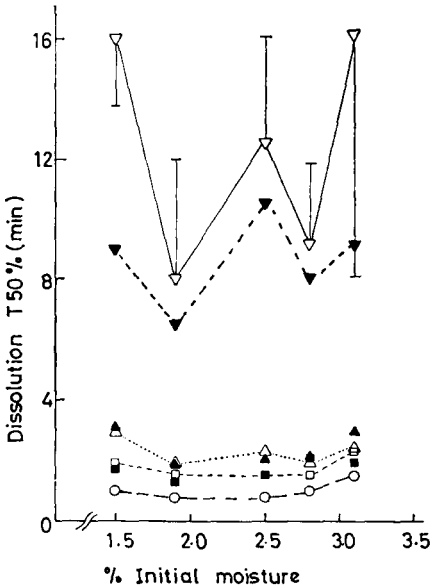

FIG. 6. Effect of ageing at 93% relative humidity, 23 °C, on in vitro dissolution of the drug from dibasic calcium phosphate dihydrate-based compressed tablets containing different moisture concentrations at the time of compression. ○, initial; □, one week; △, 3 weeks; ▽, 14 weeks. Closed symbols represent one day storage at 44% relative humidity after high humidity ageing.

tablets, hardness was not expected to increase on ageing under low humidity due to the partial moisture loss, as observed earlier with lactose-based tablets (Chowhan & Palagyi 1978; Chowhan 1979). The increase in hardness on one-day exposure under low humidity could be attributed to general hardening through the bulk of the tablet and limited dissolution and crystallization of the calcium phosphate in the available water in the tablet.

Dibasic calcium phosphate dihydrate-based tablets containing sodium alginate as a disintegrant decreased in disintegration and dissolution rates with no effect on hardness after ageing under 50% relative humidity at 25 °C (Lausier et al 1977). The differences in the effect of ageing on hardness, disintegration and dissolution between the work of Lausier et al and the present study could be due to the use of different disintegrants and the influence of initial moisture on these parameters.

On ageing under high humidity, dibasic calcium phosphate dihydrate-based tablets decreased in hardness and decreased in disintegration and dissolution rates. In a non-reactive disintegration medium (water), the tablets remained intact for a long time. These observations suggested that after ageing under high humidity, the disintegrant function of the starch was partially lost. In a reactive dissolution medium (pH 7·4 buffer), the drug dissolved by diffusion through the tablet matrix. The large variations observed in the dissolution rate after 14 weeks ageing under high humidity was due to the large variations in surface area resulting from poor disintegration of the tablets.

No physical change in the dibasic calcium phosphate dihydrate was obvious due to ageing under low and high humidities, as evidenced by the i.r. spectrum and the x-ray diffraction pattern. No noticeable loss in the water of hydration of dibasic calcium phosphate was observed after storage. The cause of a decrease in the drug dissolution rate on ageing under low humidity could be due to the limited dissolution and recrystallization of the cacium phosphate in the available water in the tablet. A large decrease in the dissolution rate on ageing under high humidity appears to be caused by the expansion/contraction and general opening of the structure of the starch grains and their bonding, via water molecules, to the calcium phosphate dihydrate. Whatever the actual mechanism of the decrease in the dissolution rate of the drug may be, the dibasic calcium phosphate dihydrate-based tablets on storage undergo change in hardness, increase in the disintegration time and a decrease in the dissolution rate.

Acknowledgement

The author thanks Mr A. A. Amaro for the technical help.

REFERENCES

Armstrong, N. A., Griffiths, R. V. (1970) Pharm. Acta Helv. 45: 583–588, 692–700

Chowhan, Z. T., Palagyi, L. (1978) J. Pharm. Sci. 67: 1385–1389

Chowhan, Z. T. (1979). Drug Development and Industrial Pharmacy 5: 41–62

Esezobo, S., Pilpel, N. (1976) J. Pharm. Pharmacol. 28: 8–16

Horhota, St., Burgio, J., Lonski, L., Rhodes, C. T. (1976) J. Pharm. Sci. 65: 1746–1749

Lausier, J. M., Chiang, C. W., Zoma, H. A., Rhodes, C. T. (1977) Ibid. 66: 1636, 1636–1637

Pilpel, N., Otuyemi, S. O., Kurup, R. R. (1978) J. Pharm. Pharmacol. 30: 214–219

Sangekar, S. A., Sarli, M., Sheth, P. R. (1972) J. Pharm. Sci. 61: 939–944

Shotton, E., Rees, J. E. (1966) J. Pharm. Pharmacol. 20: 323–324