DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(10), 1375-1387 (1988)

STUDIES ON A DIBASIC CALCIUM PHOSPHATE - MANNITOL MATRIX TABLET FORMULATION - A COMPLEMENTARY COMBINATION

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ABSTRACT

A tablet formulation made up principally of a dibasic calcium phosphate-mannitol matrix showed small but noticeable decreases in tablet breaking strength (hardness) on temperature and humidity aging. An investigation directed toward pinpointing the causative agent(s) was initiated wherein various formulations were stressed at elevated temperature and humidity conditions in open petri dishes.

Calcium phosphate dihydrate was found mainly responsible for the adverse effects induced by the storage conditions. By coupling it with a hydrophilic material like mannitol, however, physical stability is improved. Thus, the physical stability induced by mannitol is complemented by the ease of processability conferred by calcium phosphate.

INTRODUCTION

Dibasic calcium phosphate dihydrate is a common excipient in tablet formulations, though decidedly less popular when compared to either lactose or microcrystalline cellulose. This may be due to its marked hydrophobicity, leading to formulations exhibiting poor bio-absorption[1,2] and/or a tendency to induce intense densification during wet granulation[3]. In dosage form development where a chemical incompatibility between, for example, an amine drug and aldehydic lactose or microcrystalline cellulose is possible it frequently becomes an excipient of choice and/or necessity.

Changes in the physical stability of tablets with calcium phosphate matrices are not infrequent and this observation has received considerable attention[4-7]. Rhodes et al[4] noting that tablets containing dibasic calcium phosphate when stored at 45°C, 75% relative humidity (RH) lost weight explained that this was due to the loss of water of hydration from the excipient. Tablet hardness was found to decrease linearly and a reasonable correlation between hardness and disintegration time at accelerated conditions was noted. Since, however, room temperature dissolution results differed significantly from elevated temperature/humidity data, the authors concluded that the usefulness of such studies in predicting the physical shelf life of tablets could be equivocal. The effect of humidity on the physical stability of dibasic calcium phosphate-based tablets was

also reported by Chowhan[5]. In these studies, tablets at high humidity decreased in hardness and in their disintegration and dissolution rates.

In these laboratories, tablets of a poorly water soluble drug formulated with a 3:1 dibasic calcium phosphate dihydrate-mannitol matrix, were observed to decrease moderately in hardness when stored in glass and plastic bottles closed with metal caps as well as in polyvinylchloride blisters at exaggerated conditions. Given the history and background information on formulations containing dibasic calcium phosphate these changes were not surprising. Nevertheless, they provided the impetus for the effort described herein. Principally the objective was to determine precisely the material or materials responsible for the observed changes. An uncomplicated experimental design defining stepwise elimination of materials one at a time was employed. Tablets were aged as described below.

EXPERIMENTAL

The principal formulation (A), included: drug, (9% w/w), mannitol (18%), calcium phosphate dihydrate (56%), intra-granular starch (9%), pre-gelatinized starch (1.8%), extra-granular starch (5%), and magnesium stearate (0.77%). Other formulations eliminated one ingredient at a time viz; (P)-no drug, thus mannitol at 21% and calcium phosphate at 62%; (B)-no mannitol hencecalcium phosphate at 74%; and (C)-no calcium phosphate thus

mannitol at 75%. An additional formulation -(D) was also studied where two water insoluble drugs were combined in the matrix in a 1.6:1 ratio.

Wet granulations were made in a high intensity mixer. Compressed tablets were stored in open petri dishes at 40°C, 60°C and 80°C, and at 23°C/75%RH; 30°C/75%RH; and 40°C/75% RH. Tablet hardness (kp) was measured on a Schleuniger Tester (Schleuniger Model 2E-106, Solothurn, Switzerland). Tablet weight and thickness were also determined.

RESULTS AND DISCUSSION

Structured, long-term, stability studies on the single and multi-drug formulations showed that some small, but noticeable, decrease in tablet hardness occurred after 1 year at 30°C when the tablets were stored in glass and plastic bottles as well as in polyvinylchloride blisters. A decrease in tablet hardness of greater magnitude was noted at 40°C and 40°C/75% RH. Coincidently, a small decrease in tablet moisture, measured quantitatively, was noted at 40°C; the significance of which is discussed below. Disintegration and dissolution rates, however, remained unchanged with the tablets remaining robust as reflected by their low friability.

Effect of Temperature: The change in hardness at 50°C as a percent of its initial value is shown in Figure 1. Formulation (B), that showing the greatest change, contained drug and

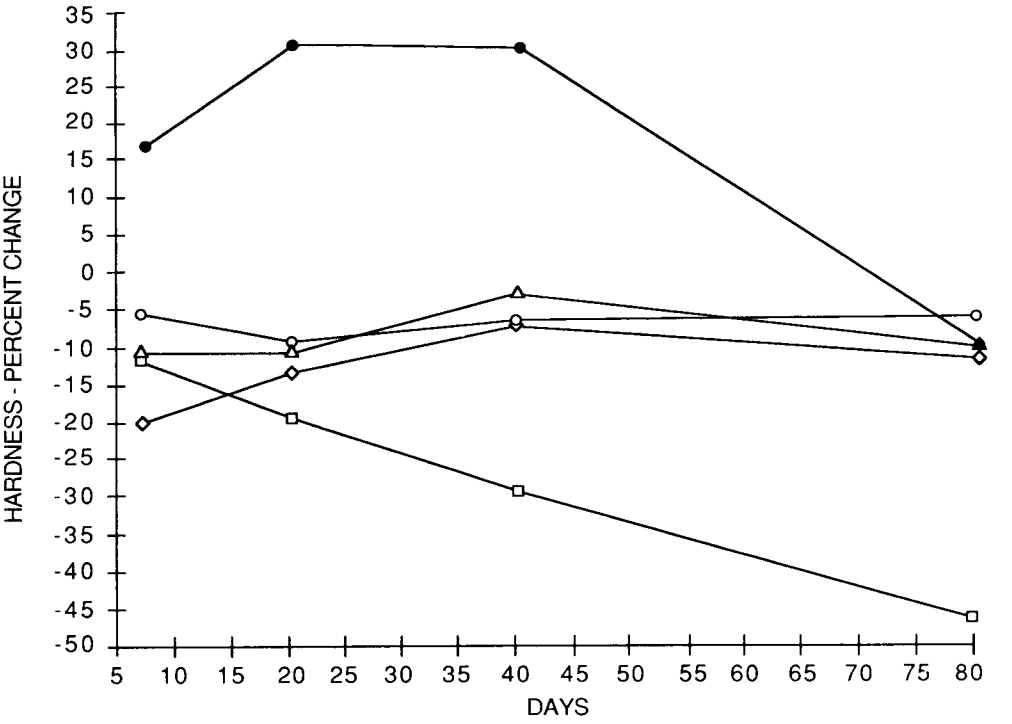

FIGURE 1

Hardness (percent Change) Versus Time at 50°C

Key: △ - Formulation A

□ - Formulation B

○ - Formulation C

◇ - Formulation D

● - Formulation P

calcium phosphate dihydrate but no mannitol. The decrease noted was essentially linear and produced a relationship between hardness - kg (y) and time - days (x) of:

$$y = 13.60 - 0.077x$$

correlation coefficient -0.979.

Most other formulations showed some initial hardness decrease followed by an equilibration about one kp lower than the initial value observed. Formulation (P) was somewhat different in that there was an initial increase followed by an eventual unit decrease. This initial increase may be attributed to the additional mannitol substituting for the drug which prevents matrix disruption, as discussed below.

Figure 2 shows that hardness decreases to be directly correlated with a time-dependent decrease in tablet density; tablet density being calculated by dividing tablet weight by its thickness. Keeping a constant punch shape and size eliminated the need for an 'area' term in the denominator. Paralleling the data on hardness is an essentially linear decrease in tablet density shown by formulation (B). Hardness on this formulation at the different storage conditions is shown in Figure 3. Initially, decreases appear dependent on the intensity of temperature, however, at 80°C and at approximately 20 days, the hardness increases and then levels off though it continues to decrease linearly at lower temperatures.

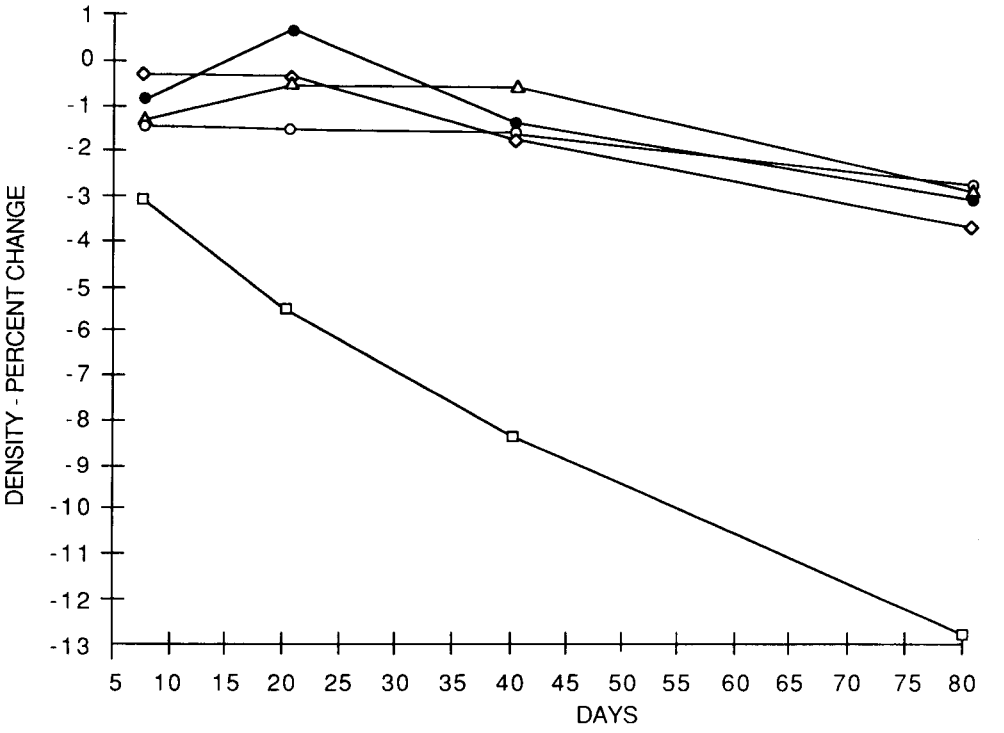

FIGURE 2

Density (percent Change) Versus Time at 50°C

Key:
△ - Formulation A
□ - Formulation B
○ - Formulation C
◇ - Formulation D
● - Formulation P

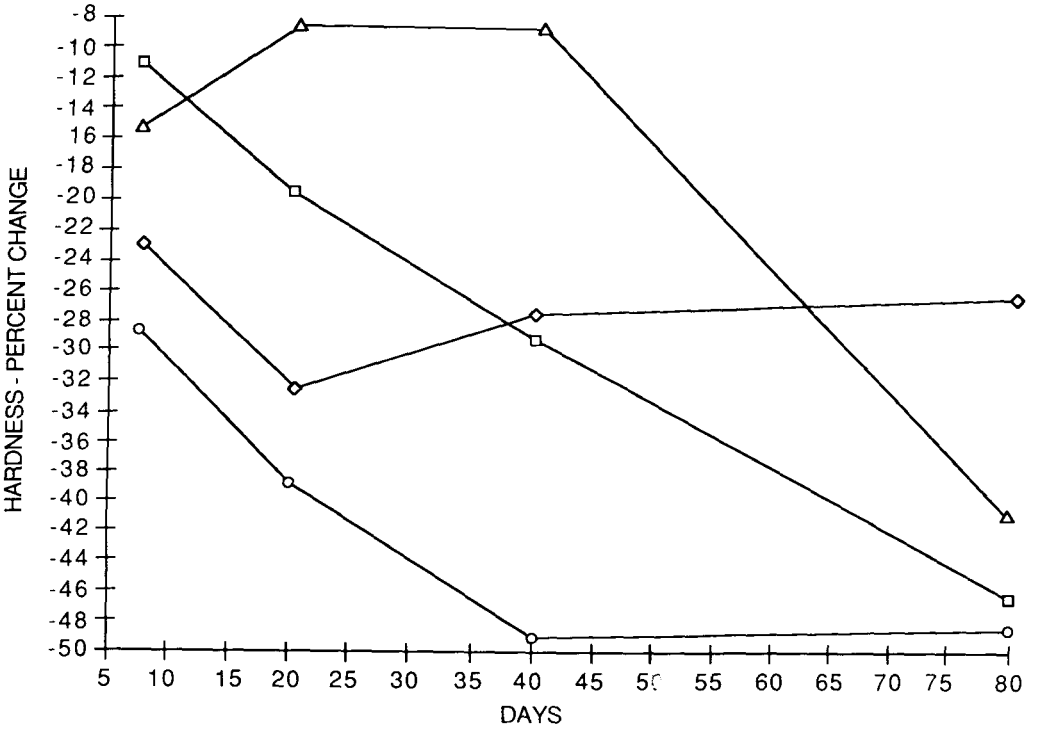

FIGURE 3

Hardness (percent Change) Versus Time for Formulation B

Key: △ - 40°C

□ - 50°C

◇ - 80°C

○ - 40°C,75%RH

These observations suggest that dehydration and a subsequent disruption of the tablet matrix is taking place thus leading to a decrease in tablet density and hence tablet strength. At a lower temperature, (40°C), a lag time precedes this phenomenon. It is suggested that the equilibrium observed at 80°C is due to the complete expulsion of the hydrate moisture then the formation of solid bridges due to a crystallization of soluble components in the spaces left by the expelled moisture. At this point, the 10% tablet weight loss noted mathematically approaches the matrix dihydrate concentration. It should be noted that where high humidity conditions are present an equilibration in hardness also occurs. A further elaboration on this point can be found in discussions below.

While the drug is also a dihydrate it is not believed to be reponsible for any of the observed changes since no physical changes in it were noted by infrared and the x-ray diffraction techniques after it had been exposed to high temperatures.

In the other formulations containing dibasic calcium phosphate temperature induced adverse effects are less obvious. This, it is suggested, is due to the presence of mannitol which because of its hydrophilicity, retains the mobile water.

Effect of Humidity: Data on changes in hardness at 40°C, 75%RH are presented in Figure 4. All formulations containing drug show decreases in hardness of approximately 50%. Lesser decreases are noted in the placebo. It has been shown[8] that free

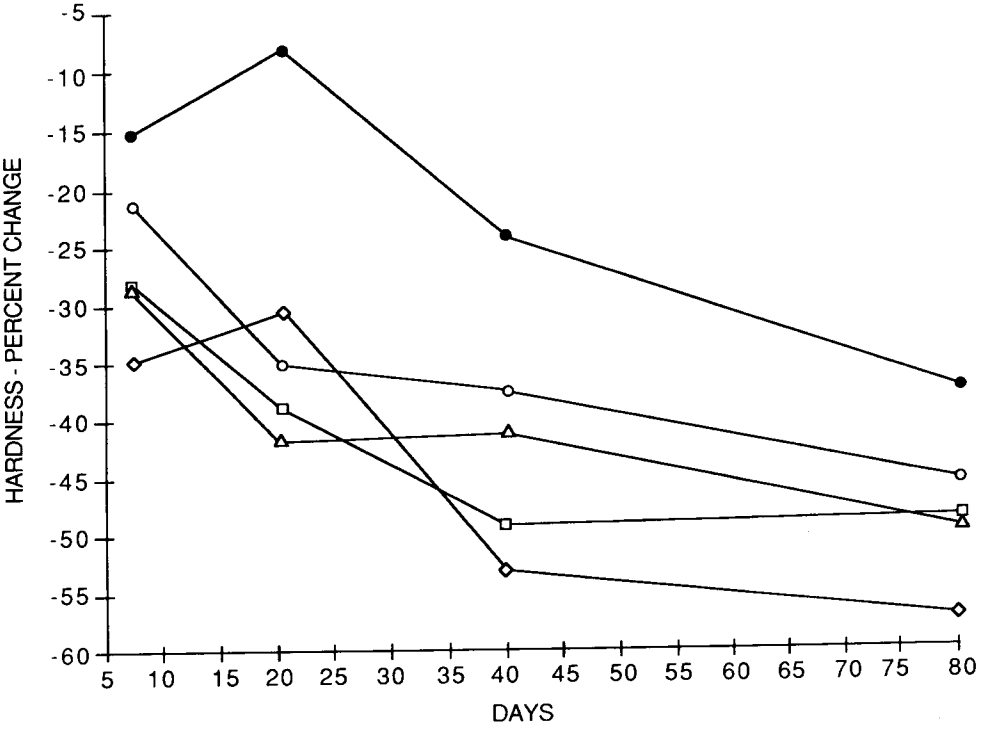

FIGURE 4

Hardness (percent Change) Versus Time at 40°C,75%RH

Key:
- △ - Formulation A
- □ - Formulation B
- ○ - Formulation C
- ◇ - Formulation D
- ● - Formulation P

moisture exists in solids in at least two states; a 'pendular' state where liquid bridges occur between individual particles and a 'capillary' state where all the pores of the solid are filled with liquid forming concave menisci at the pore ends. Accordingly, the decreases in hardness noted may due to the presence of 'capillary' water which removes interparticulate bonds by dissolution, separating the points of solid contact and minimizing the magnitude of the molecular forces of cohesion. This phenomenon becomes of added significance with calcium phosphate which is known to compact by brittle fracture and to generate numerous inter-particulate bonds within tablets.

Though the maximum hardness decrease was identical at all humidity conditions, viz. 23°C/75%RH, 30°C/75%RH and 40°C/75%RH, the rate of decrease was higher at the lower temperatures. At 40°C moisture uptake is opposed by moisture expulsion till the former predominates.

Disintegration Time and Dissolution Rate: The disintegration time and the dissolution rate of tablets from formulations A and D, remained unaffected by temperature and/or humidity. Chowhan[5] noted that tablets composed of dibasic calcium phosphate show an increase in the disintegration time and a decrease in the dissolution rate at low humidity because of the limited dissolution and recrystallization of calcium phosphate in the available water in the tablet. The adverse change in dissolution rate after aging under high humidity was explained as being

caused by the expansion/contraction and general opening of the structure of the starch grains and their bonding, via water molecules, to calcium phosphate. In the above examples, the absence of any adverse effect on these two parameters is attributed to the presence of mannitol: At high humidity calcium phosphate molecules preferentially bond to mannitol rather than to starch thus preserving the disintegrant efficiency of the latter; and at low humidity recrystallization of calcium phosphate is inhibited due to matrix water preservation.

CONCLUSIONS

Dibasic calcium phosphate dihydrate is sensitive to elevated temperatures. Under certain temperature stress molecular water can be expelled creating the potential for the disruption of the properties of any tablet matrix in which it is a component. Typically, reductions in tablet hardness with time are oberved. These studies again verified these effects. By coupling it with a hydrophilic material like mannitol, however, physical stability is improved. This excipent combination is complementary because formulations retain efficient and cost effective process characteristics typical of calcium phosphate matrices.

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