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Comparative Aging Studies of Tablets Made with Diabasic Calcium Phosphate Dihydrate and Spray Dried Lactose

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Abstract

There are relatively few published reports on the aging of tablets (1-4) and thus, as an extension of previously published work, the aging of compressed tablets (prepared using either dibasic calcium phosphate dihydrate or spray[A] dried lactose as matrix) has been investigated over a sixty-five day period. All tablets contained 6% amaranth as a dye tracer, 0.5% magnesium stearate as lubricant and 2.5% sodium alginate as disintegrant. Tablets were prepared by direct compression on a single punch press and stored under three sets of stress conditions: (a) 25°C, 45% relative humidity (RH); (b) 35°C, 60% RH; (c) 45°C, 75% RH.

Tablets were evaluated by appearance (visual and photography); weigh; size; hardness (Erweka); disintegration time (U.S.P.); and dissolution (U.S.P.). A transient mottling phenomenon was evident in both systems under accelerated conditions. Significant weight variations were observed at all temperatures for the dibasic calcium phosphate dihydrate system, while lactose tablets showed only slight changes in weight. Under accelerated storage conditions, hardness appears to be related to disintegration times and dissolution rates with either system. However, it is not a reliable tool

[A]EMCOMPRESS

at room temperature. In addition, results at accelerated conditions do not appear to be directly related to those obtained at room temperature.

TABLE I - CALCIUM PHOSPHATE, 25°/45% R.H.

	Time 0	Day 7	Day 16	Day 65
Weight (mg)	200.9	201.1	201.0	201.2
std. dev.	0.0316	0.4	0.8	0.5
Diameter (mm)	6.8507	6.8624	6.8610	6.9095
std. dev.	0.00164	0.003	0.0047	0.003
Width (mm)	3.9716	3.9807	3.983	4.0290
std. dev.	0.00165	0.007	0.008	0.008
Hardness (Kg)	5.83	5.60	5.06	2.57
std. dev.	0.316	0.49	0.581	0.28

TABLE II - CALCIUM PHOSPHATE, 35°/60% R.H.

	Time 0	Day 7	Day 16	Day 65
Weight (mg)	200.9	202.1	201.5	185.7
std. dev.	0.0316	1.1	0.9	0.9
Diameter	6.8507	6.9291	6.936	6.9283
std. dev.	0.00164	0.005	0.081	0.0130
Width (mm)	3.9716	4.0219	4.028	4.0335
std. dev.	0.00165	0.0020	0.003	0.020
Hardness (Kg)	5.83	1.895	1.845	0.89
std. dev.	0.316	0.154	0.248	0.15

TABLE III - CALCIUM PHOSPHATE, 45°/75% R.H.

	Time 0	Day 7	Day 16	Day 65
Weight(mg)	200.9	194.2	189.5	178.4
std. dev.	0.0316	1.9	3.2	0.996
Diameter(mm)	6.8507	6.9166	6.922	6.9167
std. dev.	0.00164	0.010	0.0137	0.0198
Width(mm)	3.9716	4.010	4.012	4.0379
std. dev.	0.00165	0.010	0.012	0.024
Hardness(Kg)	5.83	1.24	1.155	0.62
std. dev.	0.316	0.160	0.249	0.235

TABLE IV - LACTOSE, 25°/45% R.H.

	Time 0	Day 7	Day 16	Day 65
Weight(mg)	196.5	197.0	197.4	197.9
std. dev.	0.85	2.5	1.4	1.524
Diameter(mm)	6.8514	6.8688	6.873	6.9128
std. dev.	0.00143	0.003	0.0028	0.0044
Width(mm)	5.1068	5.1282	5.128	5.1965
std. dev.	0.0107	0.0196	0.02	0.0019
Hardness(Kg)	4.33	5.55	5.54	2.78
std. dev.	0.54	0.50	0.8	0.72

TABLE V - LACTOSE 35°/60% R.H.

	Time 0	Day 7	Day 16	Day 65
Weight(mg)	196.5	198.2	198.0	199.1
std. dev.	0.85	0.90	3.0	0.7
Diameter(mm)	6.8514	6.9533	6.963	6.9645
std. dev.	0.00143	0.006	0.00611	0.0068
Width(mm)	5.1068	5.2147	5.208	5.30
std. dev.	0.0107	0.019	0.036	0.0188
Hardness(Kg)	4.33	1.93	1.595	1.8
std. dev.	0.54	0.2	0.265	0.258

TABLE VI - LACTOSE, 45°/75% R.H.

	Time 0	Day 7	Day 16	Day 65
Weight (mg)	196.5	198.2	197.0	194.6
std. dev.	0.85	1.2	3.1	5.6
Diameter (mm)	6.8514	6.9791	6.972	6.976
std. ev.	0.00143	0.007	0.0093	0.007
Width (mm)	5.1068	5.2624	5.236	5.238
std. dev.	0.0107	0.020	0.0409	0.050
Hardness (Kg)	4.33	1.67	1.87	1.68
std. dev.	0.54	0.20	0.235	0.579

Experimental

Tablets were prepared by direct compression on a single punch press[1] using either dibasic calcium phosphate dihydrate or spray

[1] Stokes Model F, Warminster, PA

dried lactose as tablet matrix. The following formulation was used: 6% amaranth as a dye tracer, 0.5% magnesium stearate as lubricant, 2.5% sodium alginate as disintegrant, and 91% tablet matrix. All tablets were obtained from a single batch with a given formulation and had an average tablet weight of 200 mg. After manufacture, the tablets were stored under conditions: (a) 25°C 45% relative humidity (RH); (b) 35°C, 60% RH; and (c) 45°C, 75% RH. Temperature was controlled ± 2°C and relative humidity ± 3%.

Representative tablets were removed and evaluated over a 65 day period by the following parameters: (a) appearance by visual inspection and photography; (b) size (using micrometer screw gauge); (c) weight; (d) hardness (Erweka); (e) disintegration time (U.S.P.); and (f) dissolution time (U.S.P.).

Results and Discussion

Tablets stored at 35°C, 60% RH and 45°C, 75% RH showed, in varying degrees, a deterioration in appearance. During the first two weeks of the study, both storage conditions produced a mottling on the tablet surface, indicating the presence of moisture. This effect was transient, disappearing within four weeks and accompanied by a loss of luster on the tablet surface. Photography was a very useful tool during this phase of the evaluation and allowed detailed study of the tablet surface. In particular, the lactose matrix produced a very drab tablet associated with changes in color at the surface. Tablets stored at 25°C, 45% RH did not show this effect. An evaluation of weight data over the course of the study shows complex changes. Tablets made with dibasic calcium phosphate dihydrate showed considerable changes in weight at elevated temperatures (Fig. 1). At 45°C, 75% RH, the weight loss was similar to that observed in a previous study (2), suggesting a loss of water of hydration from the tablet matrix. The tablets stored at 35° C, 60% RH showed a similar decrease in weight, but to a lesser degree. Although the lactose tablets showed a small degree of mottling,

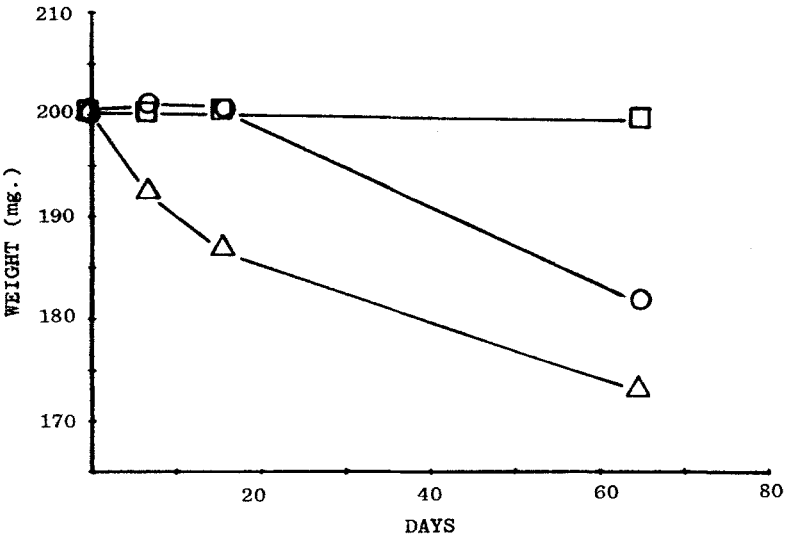

Figure 1

CHANGE IN WEIGHT, Dibasic Calcium Phosphate Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

they did not undergo significant weight changes (Fig. 2). These results would suggest that the mottling is due to moisture present in the formulation at the time of manufacture which then migrates to the surface of the tablet. As expected, tablets stored at 25°C, 45% RH showed very little changes in weight with either matrix.

Changes in size as seen in Figs. 3, 4, 5, and 6 show slight increases in diameter and width. Relaxation phenomena, coupled with increased humidity conditions would probably account for these results since tablets stored at higher humidities showed larger increases in size. Tablets made with lactose showed a higher degree of expansion than those made with dibasic calcium phosphate dihydrate. The density of the matrix and its chemical characteristics probably account for this result.

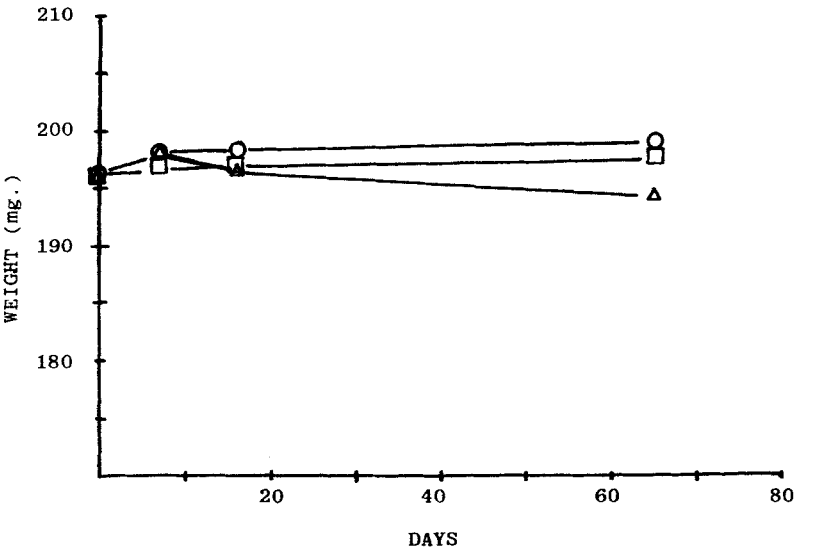

Figure 2-CHANGE IN WEIGHT, Lactose Formulation
Key: □, 25°C/45% R.H.; ○ 35°C/60% R.H.; △, 45°C/75% R.H.

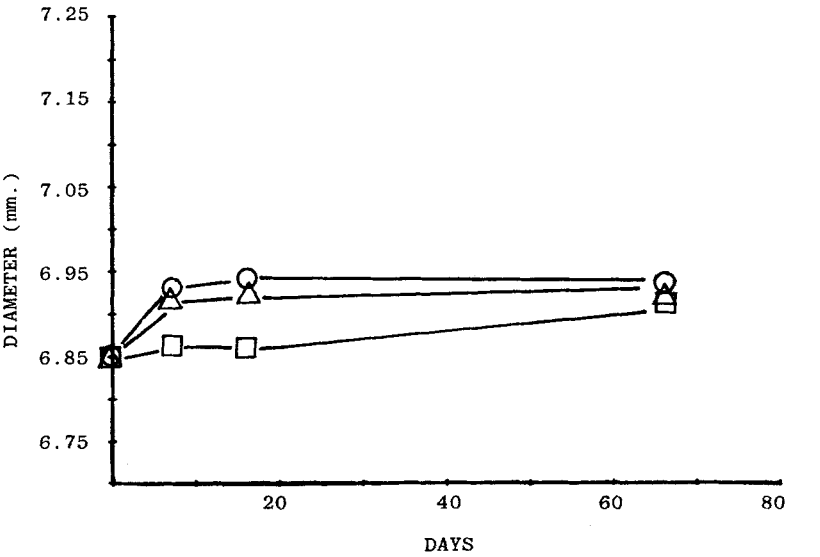

Figure 3
CHANGE IN DIAMETER, Dibasic Calcium Phosphate Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

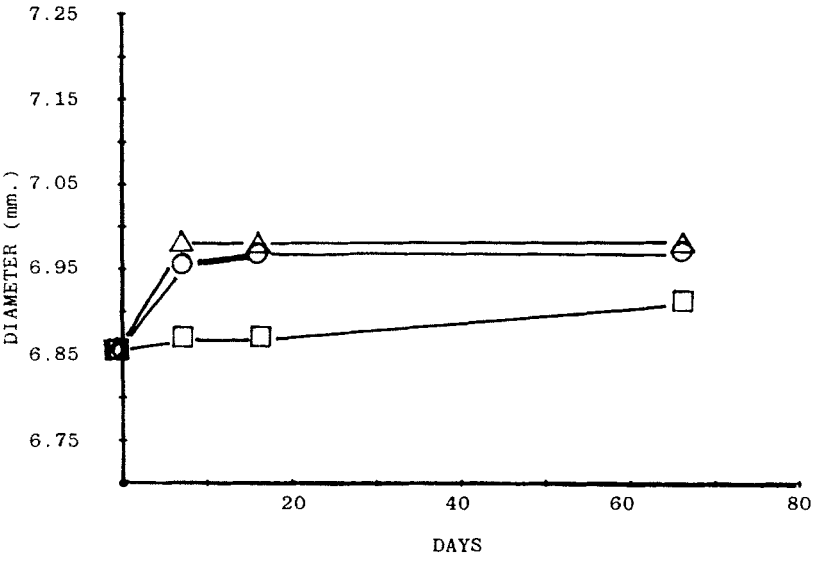

Figure 4-CHANGE IN DIAMETER, Lactose Formulation
Key: □ , 25°/45% R.H.; ○ , 35°/60% R.H.;
△ , 45°/75% R.H.

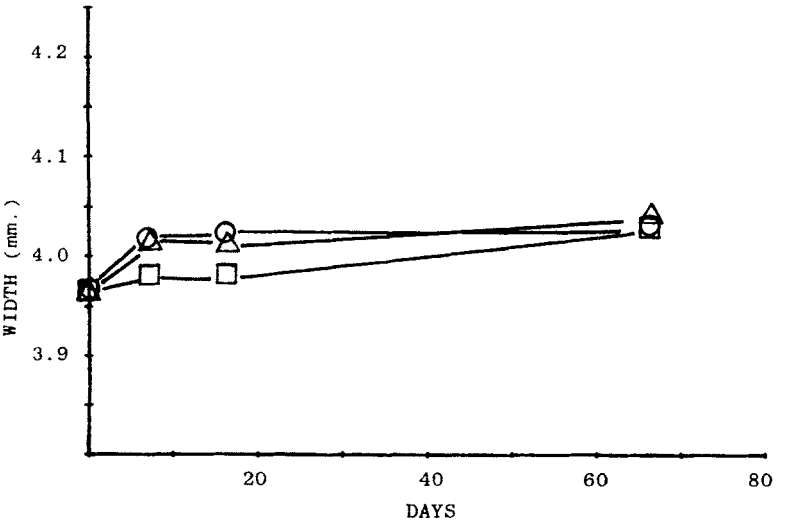

Figure 5
CHANGE IN WIDTH, Dibasic Calcium Phosphate Formulation
Key: □ ,25°C/45% R.H.; ○ , 35°C/60% R.H.;△ , 45°C/75% R.H.

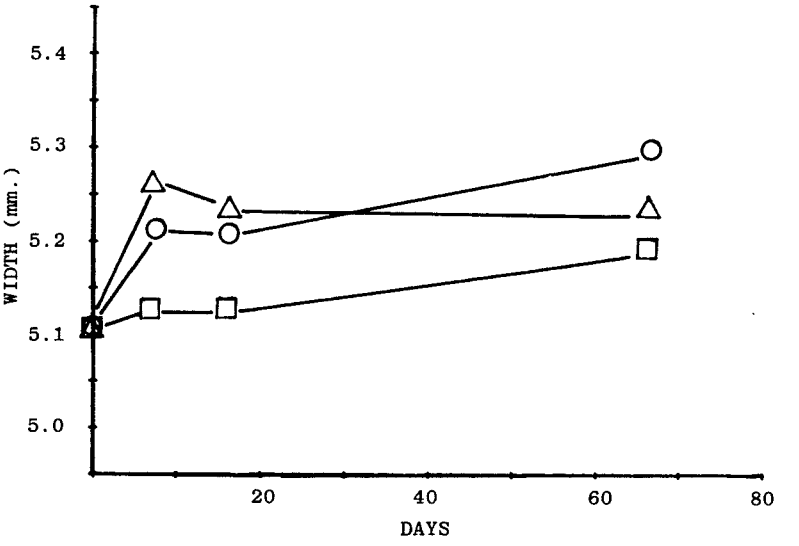

Figure 6-CHANGE IN WIDTH, Lactose Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.
△, 45°C/75% R.H.

An evaluation of hardness showed very complex and somewhat unexpected changes over the study period (Fig. 7-8). Significant changes in hardness occurred in both formulations and under all storage conditions. Tablets stored under accelerated conditions produced great decreases in hardness (6 to 1.5) within on week. This effect was seen in a previous study of dibasic calcium phosphate dihydrate tablets (2), and became essentially invarient after the first two weeks. Hardness changes at 25°, 45% RH were not expected. Dibasic calcium phosphate dihydrate tablets decreased in hardness in a linear fashion (6 to 2.5) over the course of the study. A previous study (2) did not show this result. Lactose tablets showed a complex change in hardness. There was an initial increase in hardness at this storage temperature during the first week, followed by a week in which no change was observed, and a significant decrease (4.5 to 3.0)

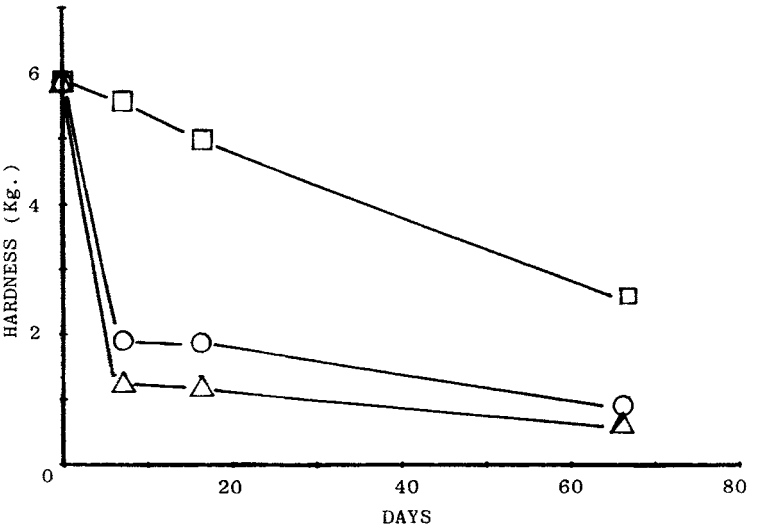

Figure 7

CHANGE IN HARDNESS, Dibasic Calcium Phosphate Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

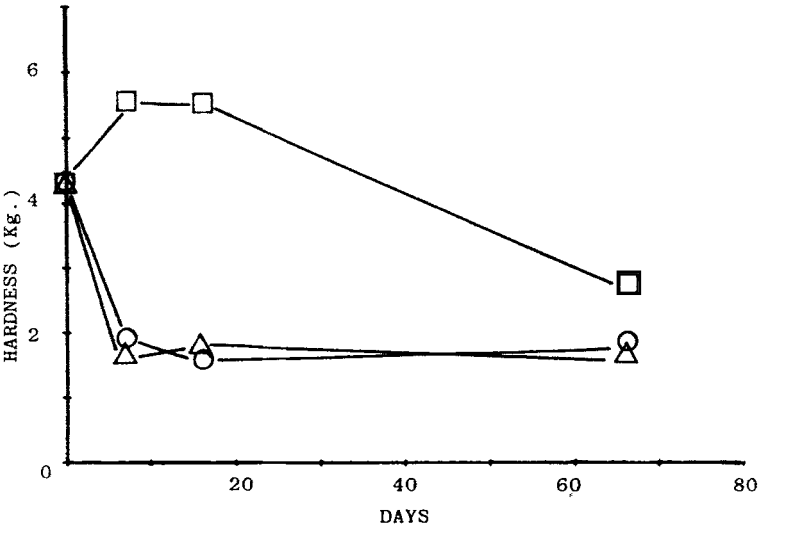

Figure 8-CHANGE IN HARDNESS, Lactose Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.
△, 45°C/75% R.H.

by the end of the study. The initial increase with this formulation may be attributed to case hardening, but it is difficult to identify the cause)s) for the decreases which occurred with both systems, although one can correlate most of the changes in hardness to the expansion of the tablet matrices mentioned above.

When disintegration data, (Figs. 9-10), are compared to hardness data, results at accelerated conditions show a reasonable correlation between hardness and disintegration time with both systems. The sharp decrease in hardness which occurred under accelerated conditions produced sharp decreases in disintegration times.

Hardness of tablets stored at 25°C, 45% RH could not be used as an indicator of disintegration time with either formulation. In the case of dibasic calcium phosphate dihydrate tablets, disintegration times increase dramatically during the first two weeks of the study and then remained invariant. This effect is

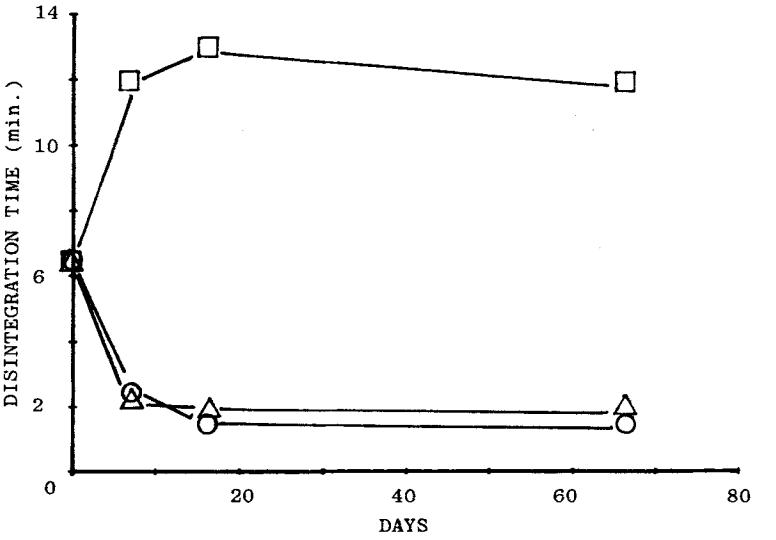

Figure 9
CHANGE IN DISINTEGRATION TIME, Dibasic Calcium Phosphate Formulation. Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

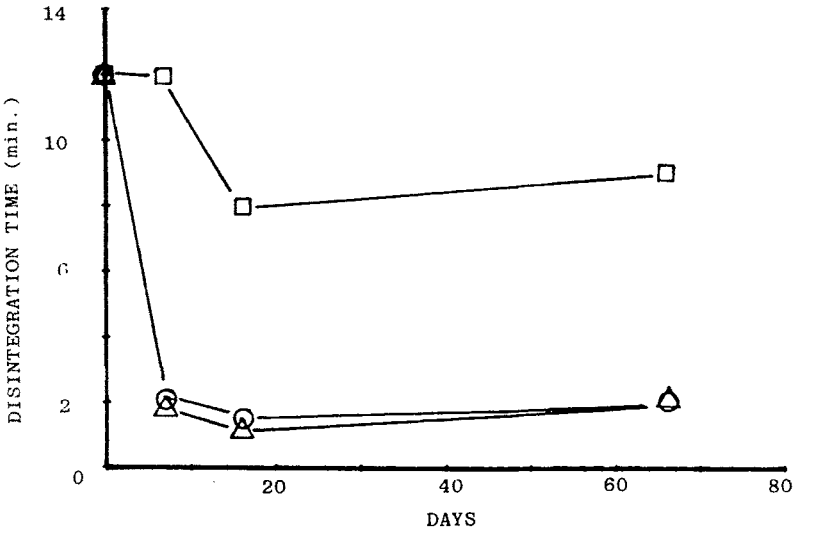

Figure 10-CHANGE IN DISINTEGRATION TIME, Lactose Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.;
△, 45°C/75% R.H.

in contrast to the linear decrease in hardness which was observed at this storage condition. A previous study of this matrix showed a linear increase in disintegration time with no significant changes in hardness. Similarly the lactose formulation showed very complex changes in disintegration time under this storage condition. During the first week of study, no change in disintegration was observed. However, during the second week, the time decreased significantly (12 min. to 8 min.). This was followed by an increase in disintegration time to approximately nine minutes at 65 days. These results emphasize the unreliability of hardness as a predictor of disintegration time at room temperature. In addition, they also demonstrate the limitation of hardness and disintegration data obtained under accelerated conditions in predicting shelf-life of tablets stored at room temperature. It is evident from this study that another para-

meter should be used to evaluate stability if accelerated aging is to be a useful tool in predicting shelf-life.

An evaluation of dissolution data shows interesting changes within a given system at various temperatures, and between the two systems as a function of time. Typical dissolution curves, (Figs. 11 & 12) during the test period show a significant difference in dissolution rate between tablets stored at room temperature and tablets stored under accelerated conditions. In both systems, the tablets at room temperature showed slower rates of dissolution, with dibasic calcium phosphate dihydrate tablets showing consistently greater deviations. A comparison of dissolution rates (as expressed by percent drug in solution after four minutes) during the test period illustrates the variation observed with room temperature conditions (Figs. 13 & 14). In both systems the room temperature conditions showed a significant difference in dissolution rate from tablets stored under accelera-

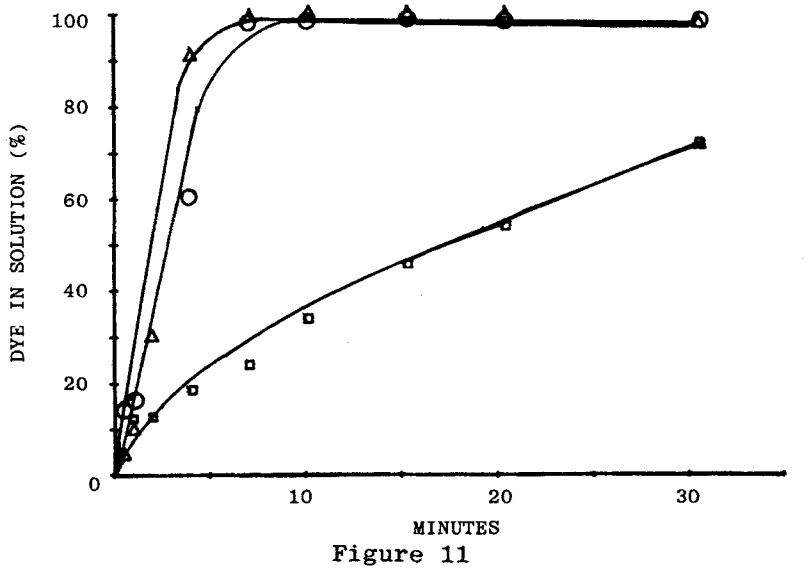

Figure 11

DISSOLUTION CURVES; DAY 7, Dibasic Calcium Phosphate Formulation. Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

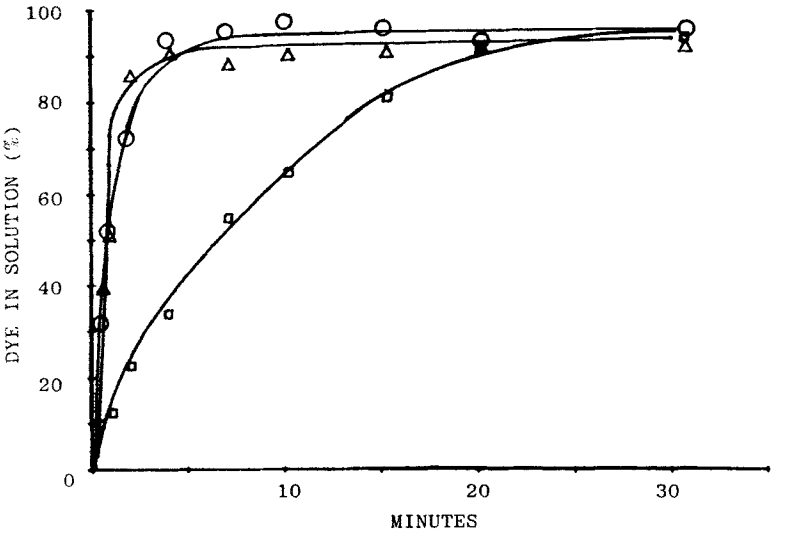

Figure 12-DISSOLUTION CURVES; DAY 7, Lactose Formulation Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

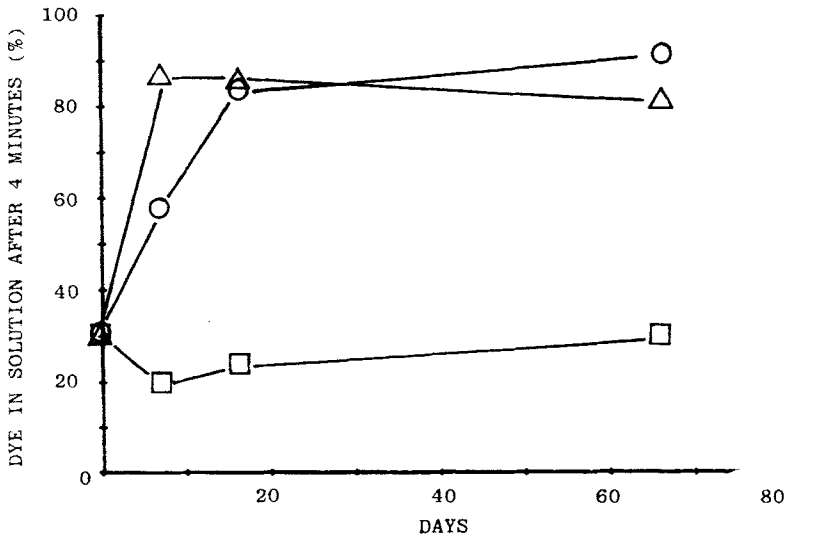

Figure 13

CHANGE IN DISSOLUTION TIME, Dibasic Calcium Phosphate Formulation Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.; △, 45°C/75% R.H.

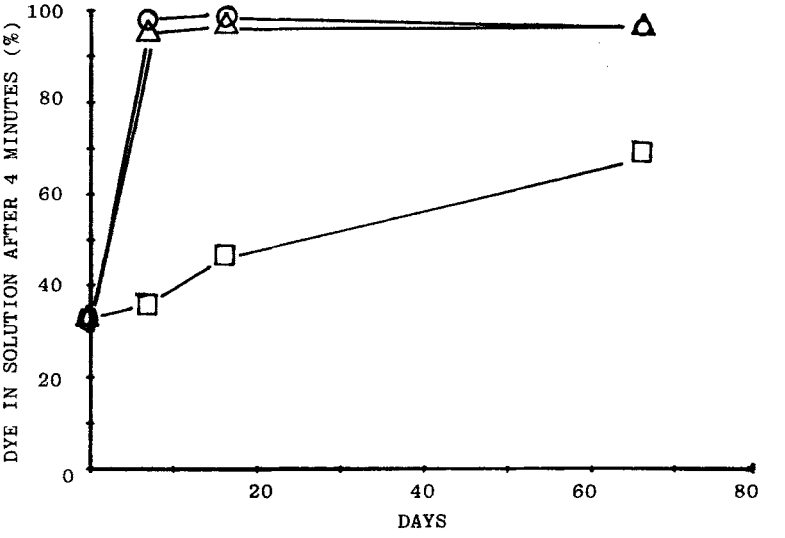

Figure 14-CHANGE IN DISSOLUTION TIME, Lactose Formulation
Key: □, 25°C/45% R.H.; ○, 35°C/60% R.H.;
△, 45°C/75% R.H.

ted conditions. In the case of dibasic calcium phosphate dihydrate tablets, an initial decrease in dissolution rate during the first week was followed by a relatively invariant level corresponding to time 0 results. This decrease and subsequent invariance correspond to the increase and invariance observed in disintegration times for these tablets (Fig. 9). Again the hardness data at this temperature does not predict changes which are occurring in the dissolution profiles.

Lactose data, (Fig. 14), show similar results. As with the dibasic calcium phosphate dihydrate tablets, accelerated dissolution rates are predictable from both hardness and disingration results. However, at room temperature, these correlations are not as evident. An increase in dissolution rates during the first three weeks of the study would correspond with decreases in disintegration times. The gradual decrease in dissolution rate

after this time period would be predicted from the disintegration graph. However, when hardness data (Fig. 8) are evaluated with dissolution data for lactose, it is clear that this parameter is not a good predictor of tablet dissolution. While dissolution rates at 25°C, 45% RH were increasing, hardness was also increaing, and when the dissolution rate stabilized, the hardness continued to decrease significantly.

It is apparent from this study that under accelerated aging conditions, hardness can be used as a predictor of disintegration rates and dissolution rates. However, this same correlation cannot be made under room temperature storage conditions. Under these conditions, other factors are apparently playing a significant role in the aging process. Hardness is an invalid tool for predicting shelf-life under these coditions. Under these conditions, other factors are apparently playing a significant role in the aging process. Hardness is an invalid tool for predicting shelf-life under these conditions. It would also appear that accelerated aging results are not directlyapplicable to tablets stored at room temperature. In both systems studied, there were significant parallel differences in hardness, disintegration times, dissolution rates, weight and size at the different temperatures as would be expected. However, room temperature results are not parallel to the accelerated temperature data in either system. The usefulness of accelerated studies for predicting shelf-life thus appears to be suspect, since results are unreliable for the studied systems.

1. S. T. Horhota, J. Burgio, L. Lonski, and C. T. Rhodes, J. Pharm. Sci. 65, 1746 (1976).

2. J. M. Lausier, Chei-Whei Chiang, H. A. Zompa, and C. T. Rhodes, J. Pharm. Sci. 66, 1636 (1977).

3. S. A. H. Khalil, L. M. M. Ali, and M. M. A. Khalek, Pharmazie, 29, 36 (1974).

4. Z. T. Chowdam, Drug Development and Industrial Pharmacy 5, 41 (1979).