methylaniline is relatively nonpolar because of the alkyl shielding and need not be derivatized to show good chromatographic properties except during separation from other intractable anilines (7). The standard is prepared as an aqueous solution to minimize evaporation of the solvent and solute as well as to simulate actual conditions.

Linearity of response was tested by injecting standard solutions of varying concentrations of dimethylaniline containing a fixed amount of the internal standard. A linear regression analysis of seven points in the concentration range of 3–200 ppm yielded a statistically significant squared multiple correlation coefficient of 0.9998 ($p > 0.01$). To improve the precision and reliability of electronic integration, the use of a standard approximating the concentration of the analyte in the unknown while maintaining identical instrument parameters is recommended. Method reliability was verified by spiking samples of ostensibly dimethylaniline-free ampicillin with different amounts of standards. Recoveries in excess of 99% were obtained, although residual dimethylaniline was occasionally detected at low concentrations (*e.g.*, <25 ppm).

Chromatography was performed at a low temperature, which is capable of detecting but is limited to relatively nonpolar substances of low molecular weights. Confirmation of identity by the relative retention times of the peaks attributed to dimethylaniline and naphthalene was obtained by combination GLC and electron-impact mass spectrometry applied to several bulk materials. However, conditions were inadequate to characterize the occasional foreign peaks.

Several samples were extracted directly with cyclohexane but did not manifest the presence of dimethylaniline until alkali was added. The logical presumption is that dimethylaniline was bound as a hydrochloride salt. Thus, a measure of total chlorine might correlate with the dimethylaniline content and with other quantitative tests as well. However, the results listed in Table II clearly show that the total chloride content obtained by neutron activation analysis (8), which ranges up to 7.3 mg/g, is far greater than the equivalent amount of dimethylaniline, indicating that other contaminants are present. In this context, the amount of dimethylaniline found in ampicillin has not demonstrated any correlation with the potency or concordance results obtained as prescribed in the regulations (9).

REFERENCES

(1) "Code of Federal Regulations," Title 21, part 211 (1975).

(2) "Analytical Profiles of Drug Substances," vol. 2, K. Florey, Ed., Academic, New York, N.Y., 1973.

(3) M. Margosis and K. Tsuji, *J. Pharm. Sci.*, **62**, 1836 (1973).

(4) M. Margosis, *ibid.*, **63**, 435 (1974).

(5) M. Margosis, *J. Chromatogr.*, **70**, 73 (1972).

(6) M. Margosis, *J. Pharm. Sci.*, **64**, 1020 (1975).

(7) R. A. Dove, *Anal. Chem.*, **39**, 1188 (1967).

(8) M. Margosis, J. T. Tanner, and J. P. F. Lambert, *J. Pharm. Sci.*, **60**, 1550 (1971).

(9) "Code of Federal Regulations," Title 21, part 440.5 (1975).

ACKNOWLEDGMENTS AND ADDRESSES

Received August 4, 1976, from the *National Center for Antibiotic Analysis, Food and Drug Administration, U.S. Department of Health, Education, and Welfare, Washington, DC 20204.*

Accepted for publication January 21, 1977.

Presented at the American Chemical Society, San Francisco, Calif., August 1976.

The author thanks Robert P. Barron, Division of Drug Chemistry, Food and Drug Administration, for mass spectral analyses.

Aging of Tablets Made with Dibasic Calcium Phosphate Dihydrate as Matrix

J. M. LAUSIER, CHIA-WHEI CHIANG, H. A. ZOMPA, and C. T. RHODES ˣ

Abstract □ The aging of direct compression tablets made using dibasic calcium phosphate dihydrate as the tablet matrix was investigated over 16 weeks. The formula included 6% amaranth as a dye tracer. Two sets of stress storage conditions were used: 25° and 50% relative humidity and 45° and 75% relative humidity. Tablets were evaluated periodically by visual inspection; determination of the weight of 10 separate tablets, the size of 10 tablets measured by a micrometer screw gauge, and the hardness of 10 tablets as indicated by a Strong–Cobb hardness tester; the USP disintegration time test; and the USP dissolution test. Tablets stored at 25° and 50% relative humidity showed an approximately linear increase in disintegration and dissolution time over 16 weeks with no other significant changes. Storage at 45° and 75% relative humidity resulted in significant changes in most measured parameters; tablets showed blotching, substantial weight loss, and complex changes in disintegration and dissolution. The changes at elevated temperatures are related to loss of water of hydration; changes at 25° must be due to other causes.

Keyphrases □ Calcium phosphate, dibasic—direct compression tablets, aging, effect of temperature and humidity □ Tablets, direct compression—dibasic calcium phosphate, aging, effect of temperature and humidity □ Aging—direct compression dibasic calcium phosphate tablets, effect of temperature and humidity □ Dosage forms—direct compression tablets, dibasic calcium phosphate, aging, effect of temperature and humidity

Recently, the physical aging of compressed tablets was studied, and it was found that complex changes of hardness and dissolution may occur over a relatively short period (1). However, because of the limited preliminary nature of that study, no hypothesis was proposed to rationalize these changes. The present report concerns a more detailed investigation of the aging of a directly compressed tablet formulation. In addition to dissolution and hardness measurements, diameter, thickness, disintegration, and tablet weight were evaluated over 16 weeks.

EXPERIMENTAL

The tablets were prepared by direct compression on a single-punch press[1] as described previously (1). The following formulation was used:

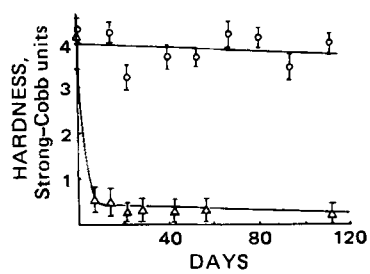

Figure 1—*Plot of hardness data over 16 weeks for dibasic calcium phosphate dihydrate tablets at 25° and 50% relative humidity (○) and at 45° and 75% relative humidity (△).*

[1] Stokes model F, Warminster, Pa.

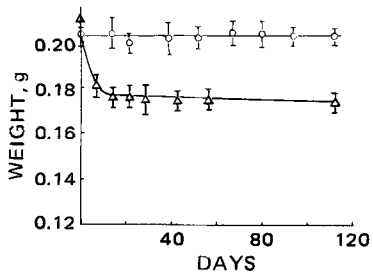

Figure 2—*Plot of weight variation over 16 weeks for dibasic calcium phosphate dihydrate tablets at 25° and 50% relative humidity (○) and at 45° and 75% relative humidity (△).*

6.0% (w/w) amaranth as the dye tracer, 0.5% (w/w) magnesium stearate as the lubricant, 2.5% (w/w) sodium alginate as the disintegrant, and 91.0% (w/w) dibasic calcium phosphate dihydrate as the matrix.

All tablet samples were obtained from a single batch of the formulation and had an average weight of 200 mg. Tablets were placed under two sets of stress storage conditions: 25° and 50% relative humidity and 45° and 75% relative humidity. Temperature was controlled ±3°, and relative humidity remained ±5%. Techniques for temperature and humidity control were as previously described (1).

Representative samples were removed and evaluated over 16 weeks by the following parameters: visual inspection, size measurements using micrometer screw gauge, individual weights of 10 tablets, hardness of 10 tablets made with pneumatic Strong-Cobb hardness tester, USP disintegration time of six tablets, and USP dissolution test. Dissolution tests were performed as previously described (1).

RESULTS AND DISCUSSION

Storage conditions of 45° and 75% relative humidity produced significant changes in most measured parameters. During the first 6 weeks, the tablets were blotchy, indicating that appreciable moisture was collecting on the tablet surface. This phenomenon disappeared by the 8th week.

While tablet size did not change appreciably under this storage condition, tablet hardness decreased dramatically during the 1st week (from 4.0 to 0.5). The hardness then became invariant (Fig. 1). Although hardness did not change during the later part of the study, both disintegration and dissolution continued to change. This result supports the previous finding that hardness and disintegration changes are not always related.

Similar effects were observed in tablet weight evaluations. An initial weight of 200 mg decreased to an average value of 174 mg after the 2nd week (Fig. 2). Calculations of formula weight of the tablet matrix suggest that the loss in weight was approximately equivalent to the water of hydration in the matrix, thus indicating a release of this substance from the matrix material. This fact would explain the blotching observed on the tablet surface in the first few weeks.

The similarity of results in hardness and weight evaluations at this storage condition indicates that the loss of water of hydration from the tablet matrix affected the integrity of the dosage form in direct relation

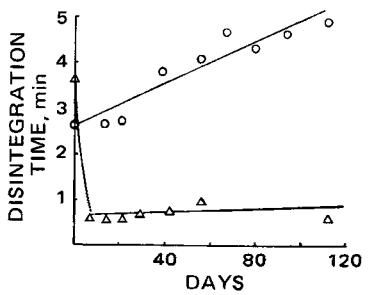

Figure 3—*Plot of disintegration times over 16 weeks for dibasic calcium phosphate dihydrate tablets at 25° and 50% relative humidity (○) and at 45° and 75% (△).*

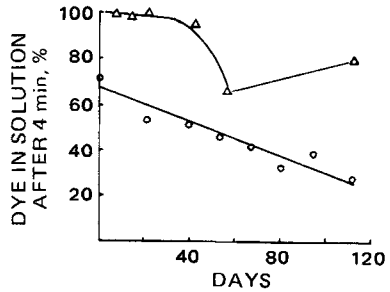

Figure 4—*Plot of release rate of dye over 16 weeks from dibasic calcium phosphate dihydrate tablets at 25° and 50% relative humidity (○) and at 45° and 75% relative humidity.*

to the amount of water lost. An initial sharp decrease in both weight and hardness suggests that most of the water loss occurred during the first 2 weeks of stress.

Figure 3 shows the effect of increased storage temperature and relative humidity on disintegration time. At 45° and 75% relative humidity, the disintegration time decreased substantially after 1 week (from 3.5 to 0.5 min) and remained constant thereafter. Since the hardness evaluation showed parallel decreases, this result was not unexpected.

Dissolution data (expressed as percentage of dye in solution after 4 min) showed a complex change over the test period (Fig. 4). There was no substantial change in the rate until the 8th week, at which time the amount of dye in solution decreased significantly (from 98 to 65%), and then the rate increased to 80% by the end of the study. These results suggest that loss of water of hydration from the matrix alters the dissolution characteristics of the tablet in a presently unpredictable manner. However, other aging factors are probably occurring simultaneously, making the evaluation process complex.

Tablets stored at 25° and 50% relative humidity were sampled at appropriate intervals over 16 weeks. There were no significant changes in size or physical appearance. Hardness and weight data, as represented by Figs. 1 and 2, respectively, indicate that loss of water of hydration did not occur under these storage conditions and would not be a factor in the interpretation of disintegration and dissolution data.

Disintegration time under these storage conditions increased in an approximately linear fashion (Fig. 3) from an initial value of 2.5 to 5.0 min at 16 weeks. The release rate of dye (Fig. 4) showed a corresponding linear decrease (from 75 to 25%) over the same period, which would be expected in light of the disintegration data.

A comparison of test results shows that a multifaceted evaluation must be performed in aging studies. At an elevated temperature of 45° and 75% relative humidity, the loss of water of hydration not only affected the disintegration and dissolution characteristics of the tablets but also significantly altered their weight and hardness. Since this phenomenon did not occur at 25° and 50% relative humidity, other factors, such as case hardening, must play an important role in the aging process.

Results of this study support the previous finding (1) that evaluation of tablet hardness is not a reliable measure of physical aging of tablets. In the present study, some significant changes occurred when hardness was not changing to any appreciable extent. Of course, this study and the previous report (1) dealt only with one type of tablet matrix. It will be useful to study other systems, but the results presented here indicate that tablet aging is a complex problem, the causes of which are not fully understood.

REFERENCE

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

ACKNOWLEDGMENTS AND ADDRESSES

Received July 21, 1976, from the *Department of Pharmacy, College of Pharmacy, University of Rhode Island, Kingston, RI 02881.*

Accepted for publication January 27, 1977.

Supported by Edward Mendell, Inc.

ˣ To whom inquiries should be directed.