fective bactericidal agents against various bacteria.

2. The rate at which chlorine is transferred from an *N*-chloro compound to a nitrogen-containing receptor should be considered along with the chlorine potential of the molecules in estimating the likely bactericidal activity of the compound in solutions containing proteins and other organic material.

3. *N*-Chloro compounds that do not contain hydrogen atoms adjacent to the nitrogen–chlorine bond are likely to be more stable than those that do with respect to loss of bactericidal activity in aqueous solution.

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# Effect of Storage at Specified Temperature and Humidity on Properties of Three Directly Compressible Tablet Formulations


**S. T. HORHOTA *, J. BURGIO *, L. LONSKI *, and C. T. RHODES ˣ**



**Abstract** □ Direct compression tablets containing sodium starch glycolate, an alginate derivative, or povidone as a disintegrant, magnesium stearate as a lubricant, amaranth as a tracer, and dibasic calcium phosphate dihydrate as the matrix were stored for 30 days at 23° and 75% relative humidity (R.H.), 45° and 75% R.H., and 65° and 40% R.H. Samples were evaluated after 0, 10, 20, and 30 days for size, hardness, and dissolution characteristics. Although no significant changes in the dimensions or hardness of the three tablet formulations, prepared at three different compaction pressures, were observed, the dissolution efficiency of the systems showed significant changes, some systems dissolving more rapidly and some more slowly after storage. In some cases, the changes were so substantial as to indicate the possibility of significant changes of the bioavailability of drugs formulated in such systems. The relevance of this work to the problem of evaluating aging effects on the physical properties of tablets is discussed.



**Keyphrases** □ Tablets, direct compression—size, hardness, and dissolution, effect of storage at various temperatures and humidity □ Size, tablet—effect of storage at various temperatures and humidity □ Hardness, tablet—effect of storage at various temperatures and humidity □ Dissolution, tablet—effect of storage at various temperatures and humidity □ Dosage forms—direct compression tablets, size, hardness, and dissolution, effect of storage at various temperatures and humidity


Methods for evaluating the chemical stability of drug substances and pharmaceutical products are well established, and the industry now makes considerable use of storage under temperature stress conditions to predict chemical shelflife. Recently, the problem of biological availability has received considerable attention, both scientific and political, and there is particular concern about factors that may modify the dissolution of drugs from compressed tablets (1, 2).

The problem of tablet aging with accompanying changes in dissolution time has received little attention, although it has been the cause of some recalls, and there now is increasing concern within the industry regarding this problem. Some formulators are using accelerated storage samples to screen for possible aging effects. Furthermore, some workers are placing considerable reliance on tablet hardness as a general indicator of tablet aging, the implicit assumption being that invariance in hardness contraindicates changes in dissolution. Unlike simple chemical decomposition, no well-established theory relates the effects of storage under stress conditions to shelflife.

The present paper reports a study of the effect of storage of compressed tablets, under three sets of stress conditions, on tablet hardness, size, and dissolution properties. The purpose of this investigation was to determine if any simple relationship exists between changes in dissolution properties and storage under

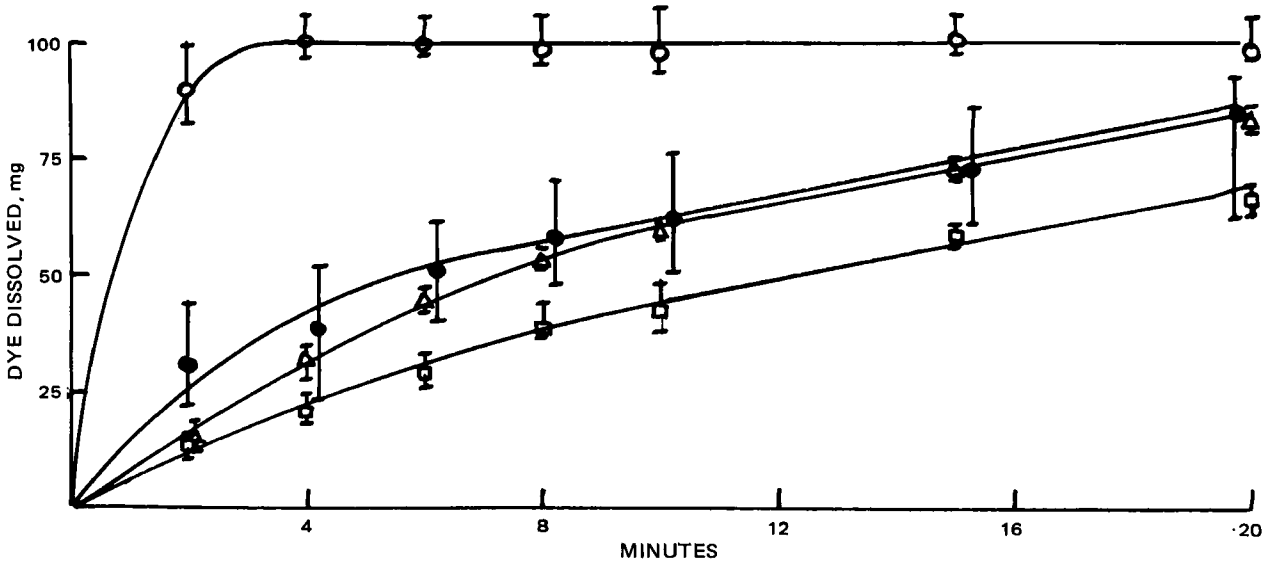


**Figure 1**—*Typical dissolution profile (III-C, 23°, and 75% R.H.). Key: ○, zero time; □, 10 days; △, 20 days; and ●, 30 days.*

conditions of varying stress. It also seemed useful to check whether changes in dissolution properties of tablets were reflected by changes in hardness.

## EXPERIMENTAL

**Materials**—Dibasic calcium phosphate dihydrate[1], sodium starch glycolate[2], an alginate derivative[3], povidone[4], amaranth[5], and magnesium stearate[6] were used as received.

Three formulations (I, II, and III) were each prepared at three compaction pressures: A (low), B (medium), and C (high). All formulations contained 0.5% magnesium stearate, 2.5% disintegrant (sodium starch glycolate in I, alginate in II, and povidone in III), 7.5% amaranth, and dibasic calcium phosphate dihydrate to 100%; the theoretical tablet weight was 200 mg.

**Methods**—Amaranth was blended with an equal weight of dibasic calcium phosphate dihydrate, and the mixture was passed twice through a 100-mesh screen. The disintegrant and the remaining dibasic calcium phosphate dihydrate were blended with the color mixture, and the product was passed once through a 60-mesh screen. Magnesium stearate was added, and the product was bag blended for 5 min. Compression was effected using a single-punch tablet[7] press with 8-mm dies and flat punches.

Hardness values, five replicate readings for each sample, were determined using an electric tablet hardness tester[8].

Thickness and diameter values, 10 tablets for each sample, were evaluated in millimeters by use of a micrometer screw gauge.

Dissolution properties of the tablets, three tablets for each sample, were determined using a USP dissolution apparatus. Samples were withdrawn (appropriate volumes of solvent being added to compensate for those removed) at 0, 2, 4, 6, 8, 10, 15, and 20 min and passed through a paper filter[9]. Samples were assayed, without dilution, on a single-beam spectrophotometer[10] at 525 nm.

The Beer–Lambert law was obeyed over the concentration range used in this work. Dissolution efficiency values at 20 min were calculated as described by Khan and Rhodes (3), using the trapezoidal rule to integrate areas under the dissolution curves.

Tablets were stored on petri dishes in ovens at 23 ± 2, 45 ± 2, or 65 ± 2°. Humidity control was effected by storing large beakers containing saturated sodium chloride solution in the ovens. If care was taken to minimize opening of the oven doors, the humidity remained quite constant. Checks, conducted during storage, indicated that the relative humidity (R.H.) values were 75 ± 3% at both 23 and 45° and 40 ± 4% at 65°.

[1] Encompress Special, Edward Mendell Co., Carmel, N.Y.
[2] Primogel, Edward Mendell Co., Carmel, N.Y.
[3] Langoline, Edward Mendell Co., Carmel, N.Y.
[4] Plasdone XL, GAF Corp.
[5] Amend Drug and Chemical Co., New York, N.Y.
[6] Ruger, New Brunswick, N.J.
[7] Erweka.
[8] Strong-Cobb.
[9] Whatman No. 40.
[10] Hitatchi model 139.

## RESULTS AND DISCUSSION

Figure 1 exemplifies the type of dissolution profile determined in this study. In all cases, the general form of the curve was the same; lag times (as are often seen in capsule dissolution) were never observed. Therefore, measurement of dissolution efficiency provides a convenient and precise way of characterizing *in vitro* dissolution.

Tables I–III list the hardness values, and Table IV and Fig. 2 show the dissolution efficiency data. The thickness and diameter measurements showed no significant change in any system and are not

**Table I—Strong-Cobb Hardness (±*SD*) of Tablets Stored at 23° and 75% R.H.**

| | Days of Storage | | | |
|---|---|---|---|---|
| Batch | 0 | 10 | 20 | 30 |
| I-A | 5.98 (1.24) | 2.84 (0.50) | 3.54 (0.40) | 2.88 (0.62) |
| I-B | 5.82 (1.47) | 2.74 (0.73) | 2.72 (0.50) | 2.26 (0.85) |
| I-C | 9.06 (2.07) | 4.70 (0.73) | 4.22 (0.94) | 4.22 (0.98) |
| II-A | 5.84 (1.03) | 2.94 (0.21) | 2.88 (0.39) | 2.50 (0.71) |
| II-B | 5.26 (1.03) | 2.70 (0.26) | 2.84 (0.52) | 1.82 (0.49) |
| II-C | 5.74 (0.06) | 3.30 (0.56) | 3.14 (0.15) | 2.30 (0.97) |
| III-A | 4.02 (1.00) | 1.32 (0.28) | 1.48 (0.23) | 1.30 (0.14) |
| III-B | 4.70 (0.92) | 1.52 (0.11) | 1.84 (0.64) | 1.34 (0.22) |
| III-C | 6.92 (1.98) | 2.52 (0.28) | 2.40 (0.40) | 2.60 (0.29) |

**Table II—Strong-Cobb Hardness (±*SD*) of Tablets Stored at 45° and 75% R.H.**

| | Days of Storage | | | |
|---|---|---|---|---|
| Batch | 0 | 10 | 20 | 30 |
| I-A | 5.98 (1.24) | 2.50 (0.60) | 4.04 (1.03) | 3.92 (1.00) |
| I-B | 5.82 (1.47) | 3.10 (0.27) | 3.02 (0.52) | 3.61 (0.97) |
| I-C | 9.06 (2.07) | 4.80 (0.82) | 4.82 (1.13) | 5.00 (0.73) |
| II-A | 5.84 (1.03) | 6.24 (2.35) | 5.16 (1.56) | 5.76 (0.95) |
| II-B | 5.26 (1.03) | 3.96 (0.88) | 4.04 (0.53) | 4.32 (0.80) |
| II-C | 5.74 (0.06) | 5.38 (0.22) | 5.66 (1.62) | 5.18 (0.84) |
| III-A | 4.02 (1.00) | 2.04 (0.67) | 1.70 (0.20) | —[a] |
| III-B | 4.70 (0.92) | 3.22 (1.14) | 2.64 (0.78) | 3.06 (0.42) |
| III-C | 6.92 (1.98) | 4.76 (0.46) | 4.42 (1.03) | 4.34 (0.87) |

[a] Hardness too low to measure.

Table III—Strong-Cobb Hardness (±*SD*) of Tablets Stored at 65° and 40% R.H.

| Batch | Days of Storage 0 | 10 | 20 | 30 |
|---|---|---|---|---|
| I-A | 5.98 (1.24) | 3.86 (1.05) | 3.94 (0.77) | 2.92 (0.58) |
| I-B | 5.82 (1.47) | 2.72 (0.80) | 2.48 (0.56) | 2.86 (0.74) |
| I-C | 9.06 (2.07) | 5.06 (1.35) | 4.40 (0.98) | 4.56 (0.79) |
| II-A | 5.84 (1.03) | 1.62 (0.16) | 2.50 (0.54) | 2.60 (0.52) |
| II-B | 5.26 (1.03) | 1.90 (0.52) | 1.96 (0.33) | 1.85 ($n = 2$) |
| II-C | 5.74 (0.06) | 2.54 (0.13) | 2.08 (0.40) | 2.05 ($n = 2$) |
| III-A | 4.02 (1.00) | 1.32 (0.27) | 1.38 (0.25) | —[a] |
| III-B | 4.70 (0.92) | 1.48 (0.13) | 1.26 (0.22) | 1.53 ($n = 2$) |
| III-C | 6.92 (1.98) | 1.86 (0.50) | 1.80 (0.41) | 2.02 (0.65) |

[a] Hardness too low to measure.

reported in detail; a representative set of data, given in Table V, exemplifies the general findings.

Tables I–III show that, with few exceptions, the same general pattern emerged. Storage at all three stress conditions caused a substantial reduction in hardness in the first 10 days, after which there was little change. Moreover, hardness values did not have a direct relationship with changes in dissolution. The reduction in hardness after 30 days was, somewhat surprisingly, greatest in the systems stored at 23° and least in those stored at 45°.

For the sodium starch glycolate at time zero, the best dissolution efficiency was obtained at the higher compression values (B and C). On storage, the systems prepared at all three compaction pressures showed a similar pattern. The systems stored at 23 and 45° showed no significant change in dissolution efficiency over the storage period. Those stored at 65° showed little change in the first 10 days (the period when hardness values changed most significantly) but then showed a substantial decrease, with a possible leveling out or increase in the last 10 days.

Table V—Change in Thickness and Diameter (±*SD*) of Tablet Batch I-A Stored at 45° and 75% R.H.

| | Days of Storage 0 | 10 | 20 | 30 |
|---|---|---|---|---|
| Thickness, mm | 2.346 (0.30) | 2.32 (0.08) | 2.227 (0.10) | 2.278 (0.13) |
| Diameter, mm | — | 8.119 (0.16) | 7.972 (0.05) | 7.986 (0.04) |

Type II systems (alginate) had more complex dissolution efficiency changes. The initial dissolution efficiency, which showed little evidence of dependence on compaction pressure, was significantly lower than for the sodium starch glycolate formulations. For the system prepared at all three compaction pressures and stored at 23°, the dissolution efficiency decreased to less than 30% of the original value after 10 days and then returned to approximately the original value. The systems stored at 63° showed an initial increase after 10 days and little change thereafter. Systems stored at 45° showed a slight increase in dissolution efficiency after 10 days and then little further change.

The systems containing povidone as a disintegrant showed an initial high dissolution efficiency. On storage at 65°, little change occurred. However, after 10 days of storage at 23°, dissolution efficiency in III-A and III-B dropped to less than 30% of the initial value; the decrease in III-C was somewhat less. After 10 days of storage, all systems stored at 23° showed no further decrease in dissolution efficiency. Systems stored at 45° showed a decrease and then an increase.

Consideration *in toto* of the reported results leads to several general conclusions for the systems studied. First, neither hardness nor measurement of thickness and diameter bears any relationship to changes in dissolution efficiency. Indeed, substantial changes in dissolution efficiency occur without any changes in either hardness or tablet size. The appearance of the tablets at the start in no way

Table IV—Dissolution Efficiency (Percent) of Various Tablet Batches Stored under Different Stress Conditions[a]

| Batch | Storage Time, days | 23° and 75% R.H. | 45° and 75% R.H. | 65° and 40% R.H. |
|---|---|---|---|---|
| I-A | 0 | 83.3 (82.6–84.1) | — | — |
| | 10 | 86.3 (84.5–88.6) | 85.0 (80.7–91.5) | 78.8 (67.0–85.2) |
| | 20 | 84.4 (79.1–88.5) | 85.5 (83.3–89.7) | 28.4 (25.8–30.5) |
| | 30 | 88.4 (86.4–90.0) | 79.6 (77.0–82.1) | 30.4 (28.7–33.2) |
| I-B | 0 | 75.7 (75.2–76.2) | — | — |
| | 10 | 83.9 (81.9–86.4) | 83.8 (82.1–85.9) | 82.2 (81.3–83.7) |
| | 20 | 75.7 (75.3–75.9) | 74.7 (74.4–75.3) | 49.9 (43.8–53.4) |
| | 30 | 82.4 (81.3–83.7) | 79.8 (77.6–80.9) | 31.8 (26.9–35.0) |
| I-C | 0 | 79.8 (74.3–83.2) | — | — |
| | 10 | 87.3 (86.1–88.9) | 86.2 (84.5–88.2) | 86.3 (83.7–89.9) |
| | 20 | 77.5 (69.1–84.1) | 78.6 (71.7–83.4) | 28.9 (26.9–30.7) |
| | 30 | 84.6 (84.1–85.5) | 73.9 (71.2–77.2) | 32.2 (28.1–39.2) |
| II-A | 0 | 67.2 (62.0–75.0) | — | — |
| | 10 | 26.7 (20.9–36.5) | 81.8 (72.9–94.3) | 110.2 (102.2–124.5) |
| | 20 | 36.4 (27.6–50.0) | 81.1 (78.5–84.7) | 91.6 (80.4–101.1) |
| | 30 | 75.4 (73.7–78.3) | 78.1 (75.9–81.3) | 97.3 (95.2–100.5) |
| II-B | 0 | 63.0 (61.9–64.1) | — | — |
| | 10 | 32.7 (31.4–33.4) | 52.9 (50.0–62.1) | 94.4 (90.8–101.1) |
| | 20 | 44.8 (41.3–48.1) | 88.1 (81.4–92.3) | 95.9 (93.1–98.9) |
| | 30 | 66.7[b] | 70.1 (67.2–71.8) | 93.9[b] |
| II-C | 0 | 69.8 (63.6–77.9) | — | — |
| | 10 | 28.2 (26.8–29.1) | 52.0 (50.9–52.9) | 96.1 (95.2–97.6) |
| | 20 | 33.5 (17.0–53.2) | 91.6 (88.4–93.9) | 97.0 (94.1–98.9) |
| | 30 | 47.6[b] | 75.2 (74.0–77.6) | 89.9[b] |
| III-A | 0 | 94.8 (86.6–102.8) | — | — |
| | 10 | 25.3 (23.2–27.4) | 31.8 (28.6–36.5) | 92.5 (90.6–95.3) |
| | 20 | 31.9 (30.7–32.8) | 39.2 (36.5–42.1) | 94.9 (93.6–96.4) |
| | 30 | 29.8[b] | 68.9 (67.7–70.1) | — |
| III-B | 0 | 92.9 (92.5–93.4) | — | — |
| | 10 | 27.9 (23.3–36.3) | 87.9 (79.5–94.2) | 91.9 (87.5–96.2) |
| | 20 | 32.4 (22.1–38.6) | 60.6 (38.3–75.1) | 89.4 (74.0–74.9) |
| | 30 | 35.2 (34.1–36.2) | 97.2 (96.7–97.8) | 95.4 (94.7–96.1) |
| III-C | 0 | 96.9 (94.2–101.0) | — | — |
| | 10 | 42.0 (40.9–42.9) | 57.1 (55.5–59.9) | 96.4 (94.2–98.9) |
| | 20 | 55.4 (54.9–55.6) | 67.5 (64.4–69.6) | 95.6 (95.0–96.5) |
| | 30 | 58.7 (39.1–71.0) | 97.7 (96.1–99.4) | 97.0 (94.0–99.5) |

[a] Values are the means (range) for three trials unless otherwise noted. [b] Single determination.

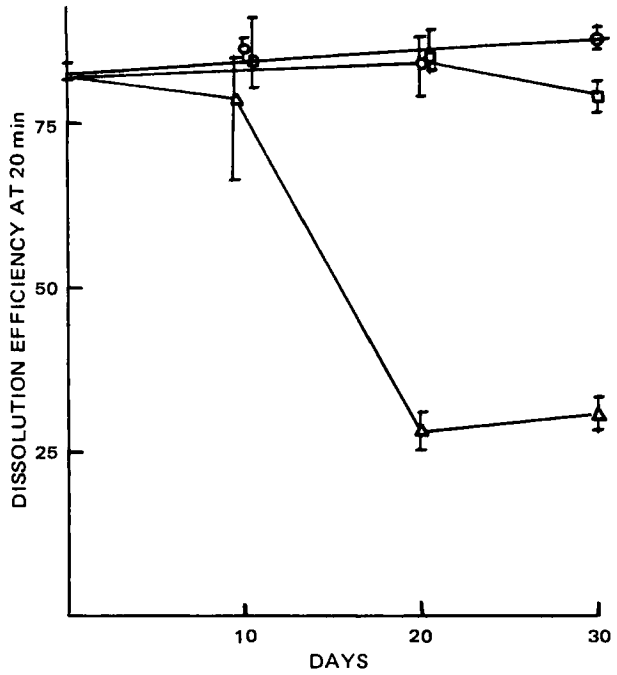


**Figure 2**—*Effect of storage time on the dissolution efficiency of I-A tablets. Key: ○, 23° and 75% R.H.; □, 45° and 75% R.H.; and △, 65° and 40% R.H.*

differed from that at the end of the storage stress period. Thus, those who rely upon hardness values as an indication of changes in dissolution may be following an unreliable practice.

Second, the reported data cast considerable doubt on the use of accelerated stability-type tests to predict changes at room temperature. Predictions of behavior at room temperature from data obtained at 45 and 65° would lead to unreliable results for the investigated systems.

It is interesting to speculate on the reasons for these results. The direct effect of water vapor on the disintegrant, as described by Khan and Rhodes (4), is probably involved. Also, in the case of povidone, it is reasonable to postulate a direct interaction between the dye and disintegrant. Fung *et al.* (5) made use of the stabilizing effect of the interaction between povidone and nitroglycerin for the formulation of that drug. More than one mechanism probably underlies the reported data, and further work in various tablet matrixes would be valuable to elucidate the principles operating in such systems.

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# Disaggregation of Compressed Tablets

**MICHAEL H. RUBINSTEIN ˣ and DOROTHY M. BODEY**

**Abstract** □ Tablets of dibasic calcium phosphate containing varying proportions of intra- to extragranular maize starch were prepared at three compaction pressures. The surface area generated per tablet after 10 and 30 min of disintegration was measured with an automated counter by a new technique. The optimum starch combination that produced the maximum surface area in a tablet formulation was either 2.5% intra–12.5% extragranular or 15% intragranular starch alone. The distribution of starch did not affect the resultant strength of the tablets, and maximum generation of surface area was achieved by compacting the tablets at as low a pressure as practical.

**Keyphrases** □ Disaggregation—compressed tablets of dibasic calcium phosphate, with varying proportions of intra- to extragranular starch, effect of compaction pressure □ Dosage forms—compressed tablets, dibasic calcium phosphate with varying proportions of intra- to extragranular starch, disaggregation, effect of compaction pressure □ Tablets, compressed—dibasic calcium phosphate with varying proportions of intra- to extragranular starch, disaggregation, effect of compaction pressure □ Calcium phosphate, dibasic—compressed tablets with varying proportions of intra- to extragranular starch, disaggregation, effect of compaction pressure □ Starch, intra- and extragranular—varying proportions in dibasic calcium phosphate compressed tablets, disaggregation, effect of compaction pressure

Disintegration of a compressed tablet is the process by which a whole tablet breaks up into small pieces when in contact with fluid. If the process is considered to be a zero- or first-order reaction, the specific rate constant is inversely proportional to the disintegration time, as measured by the USP disintegration test. This official test is concerned solely with the breakdown of tablets to particles that pass the 10-mesh screen. No indication is given as to whether the undermesh material consists of coarse aggregates or fine particles, even though, as long ago as 1945, Kelly and Green (1) reported that it was clinically important that tablets disintegrated beyond the size of the original granules.

## BACKGROUND

The official disintegration tests assume that two tablets with the same disintegration times disintegrate in the same manner to produce fragments that, for all intents and purposes, have similar size distri-