bricant. Concentrations of 1% or more of magnesium stearate, polyethylene glycol 4000, or talc were effective in lowering the accumulation of static charge by ascorbic acid to the lowest range while concentrations of 0.1% gave only partial reduction.

The antistatic properties of the lubricant were not altered by the materials to which they were added. The addition of magnesium stearate, polyethylene glycol 4000, or talc in 5.0% concentrations to either acetaminophen, ascorbic acid, or anhydrous citric acid resulted in a significantly lower static charge, whereas the addition of 5% stearic acid to the same materials did not alter the magnitude of their charge.

## REFERENCES

(1) Gold, G., and Palermo, B. T., *J. Pharm. Sci.*, **54**, 310(1965).
(2) Nelson, E., *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, **43**, 596(1954).
(3) Strickland, W. A., Jr., Higuchi, T., and Busse, L. W., *ibid.*, **49**, 35(1960).
(4) "Encyclopedia of Chemical Technology," 2nd ed., Interscience Publishers, Inc., New York, N. Y., 1963, p. 654

# Physical and Chemical Stability Testing of Tablet Dosage Forms

By LEON LACHMAN

**The influence of excipients and lubricants on the chemical and physical stability of tablets is demonstrated. Tablet color stability and its measurement is reviewed. The applicability of chemical kinetic principles and the Arrhenius relationship to stability data for tablet systems is illustrated. The importance of the package to product stability is shown. The utility of exaggerated temperature, light, and humidity conditions in the stability testing of tablet dosage forms is demonstrated. The importance and significance of a well-organized stability testing program for evaluating the physical and chemical stability of solid dosage forms are discussed.**

FOR MOST pharmaceutical manufacturers, the tablet dosage form accounts for a major portion of their product line. This dosage form is well accepted in the United States by both patient and physician for use in the oral administration of drugs.

Generally, in solid heterogeneous systems, the active ingredient tends to decompose at a slower rate than in liquid heterogeneous or homogeneous systems. However, this does not mean that it can be assumed that a drug in a tablet dosage will not exhibit stability problems. In fact, it is possible to encounter considerable instability of the drug in the tablet, as well as change in the physical properties of the tablet form.

In the subsequent sections of this paper, the factors contributing to the chemical and physical instability of tablet dosage forms, the feasibility of employing chemical kinetic principles to predict stability at shelf conditions from accelerated data, the influence of the package on product stability, and the significance and importance of a well-organized stability testing program for evaluating the physical and chemical stability of tablet dosage forms will be reviewed.

Received June 1, 1965, from the Research Department, Ciba Pharmaceutical Co., Summit, N. J.
Accepted for publication July 30, 1965.
Presented to the Fourth Texas Industrial Pharmacy Seminar, Austin, February 1965.

## CHEMICAL AND PHYSICAL STABILITY

**Influence of Inert Ingredients.**—It is only within recent years that considerably more attention has been paid to the influence that tablet diluents, lubricants, and granulating systems have on the stability of the active ingredient in the tablet and on the physical properties of the tablet dosage form. These materials, once regarded as inert fillers, have been found to potentiate the chemical degradation of the active ingredient, cause the disintegration time and dissolution rate of tablets to change with storage, influence the therapeutic effectiveness of the medicament in the tablet by modifying its absorption characteristics, cause changes in the color of the tablet, and affect other physical properties, such as friability and hardness.

In a recent study (1), a number of common tablet diluents were evaluated as to their influence on the stability of vitamins A and $B_1$ and ascorbic acid. One-gram disks were compressed of the diluent, vitamin, and 0.5% magnesium stearate to simulate conditions of storage for a tablet dosage form of the vitamins. The disks of the various diluents and vitamins were stored in amber bottles at room temperature and 45°, assayed at intervals for residual vitamin content, and observed for changes in physical appearance.

The data in Table I show that vitamin A is most stable in the presence of mannitol and lactose, while in the presence of diluents containing high initial moisture, the worst stability is obtained.

The data in Table II show that vitamin $B_1$ exhibits excellent stability in the presence of mannitol, sucrose, lactose, and kaolin. However, as

TABLE I.—STABILITY OF VITAMIN A IN SOLID VEHICLE MATRICES

| Vehicle | Moisture, % | Activity Retained After Storage: 30 Days at 45°C., % | 90 Days at 45°C., % | 90 Days at RT, % | Color After Storage |
|---|---|---|---|---|---|
| Mannitol | 0.2 | 90 | *74* | ... | White |
| Sucrose | 0.2 | 80 | 67 | ... | White |
| Lactose | 1.0 | 89 | *76* | 85 | White |
| Calcium sulfate | 2.7 | 75 | 66 | 80 | White |
| Aluminum hydroxide | 15.0 | 73 | 56 | ... | Brown |
| Starch | 8.0 | 59 | 50 | 85 | Yellow |
| Kaolin | 1.0 | 75 | 67 | ... | Brown |
| Dextrose | 8.0 | 81 | 67 | ... | Buff |
| Mannitol and sucrose | 0.2 | 88 | 72 | 90 | White |
| Mannitol and aluminum hydroxide | 2.9 | 60 | 60 | 88 | Brown |
| Mannitol and starch | 1.8 | 70 | 62 | 84 | Buff |
| Mannitol and dextrose | 1.6 | 83 | 72 | ... | Buff |

TABLE II.—STABILITY OF VITAMIN $B_1$ (U.S.P. POWDER) IN SOLID VEHICLE MATRICES

| Vehicle | Moisture, % | Activity After Storage: 30 Days at 45°C., % | 90 Days at RT, % | Color After Storage |
|---|---|---|---|---|
| Mannitol | 0.2 | *100* | 98 | White |
| Sucrose | 0.2 | *100* | 99 | White |
| Lactose | 1.0 | *100* | ... | White |
| Calcium sulfate | 2.7 | 88 | 99 | White |
| Aluminum hydroxide | 15.0 | 46 | 98 | White |
| Starch | 8.0 | 18 | 98 | White |
| Kaolin | 1.0 | *100* | 100 | Brown |
| Dextrose | 8.0 | 13 | 87 | White |
| Mannitol and sucrose | 0.2 | 96 | 94 | White |
| Mannitol and aluminum hydroxide | 2.9 | 29 | 93 | White |
| Mannitol and starch | 1.8 | 32 | 91 | White |
| Mannitol and dextrose | 1.6 | 20 | 88 | White |
| Mannitol (and coated vitamin $B_1$) | | 100 | ... | White |

observed for vitamin A, the diluents of high initial moisture cause the greatest degradation of vitamin $B_1$.

As seen from the results tabulated in Table III, ascorbic acid appeared to have good stability in all diluents with the exception of aluminum hydroxide. Most of the ascorbic acid preparations, however, changed color during the storage period. The color change was not directly related to loss of vitamin potency in all cases. Mannitol, sucrose, and lactose were the only three diluents in which no color change was observed.

Yamamoto and co-workers (2, 3) investigated the influence of the hygroscopicity of different diluents on the stability of ascorbic acid and sodium ascorbate when stored under varying humidity conditions and in the presence of the diluents of varying moisture content. It was found that, in the case of non-hygroscopic diluents, the influence of the diluent is almost negligible since the moisture is absorbed only by the ascorbic acid or sodium ascorbate. With diluents such as calcium carbonate or lactose, which are poorly soluble in water and have high critical relative humidities, again little influence was observed on the degradation. However, in the case of diluents such as sucrose, glucose, or sodium chloride, which are readily water soluble and have a critical relative humidity lower than that of the active agent, the active agent dissolves

TABLE III.—STABILITY OF ASCORBIC ACID (U.S.P. GRANULAR) IN SOLID VEHICLE MATRICES

| Vehicle | Moisture, % | Activity After Storage for 90 Days at 45°C., % | Color After Storage for 90 Days at 45°C. |
|---|---|---|---|
| Mannitol | 0.2 | 100 | White |
| Sucrose | 0.2 | 99 | White |
| | | 100 | White |
| Lactose | 1.0 | 97 | White |
| | | 99 | White |
| Aluminum hydroxide | 15.0 | 66 | Brown |
| | | 74 | Brown |
| Starch | 8.0 | 100 | Yellow |
| | | 99 | Yellow |
| Calcium sulfate | 2.7 | 99 | Buff |
| | | 100 | Buff |
| Kaolin | 1.0 | 100 | Brown |
| | | 95 | Brown |
| Dextrose | 8.0 | 100 | Straw |
| | | 95 | Straw |
| Mannitol and sucrose | 0.2 | 96 | White |
| Mannitol and aluminum hydroxide | 2.9 | 99 | Brown |
| Mannitol and starch | 1.8 | 98 | Buff |
| Mannitol and dextrose | 1.6 | 100 | Yellow |

TABLE IV.—STABILITY OF ASPIRIN WITH DILUENT

| Diluent | Storage Temp. | % Free Salicylic Acid After Storage Time, Wk. 4 | 12 | 24 | 36 | 52 |
|---|---|---|---|---|---|---|
| Aluminum hydroxide dried gel | RT | 0.53 | 1.2 | 2.3 | 3.0 | 3.9 |
| | 37.5° | 1.5 | 2.0 | 2.3 | 5.1 | 6.9 |
| Calcium carbonate | RT | 0.20 | 0.61 | 0.96 | 2.2 | 4.4 |
| | 37.5° | 0.39 | 1.3 | 1.3 | 5.2 | 11.3 |
| Calcium gluconate | RT | 0.15 | 0.19 | 0.52 | 0.55 | 0.80 |
| | 37.5° | 0.10 | 0.22 | 0.27 | 0.44 | 0.78 |
| Calcium lactate · $5H_2O$ | RT | 0.09 | 0.10 | 0.30 | 3.0 | 71.0 |
| | 37.5° | 0.09 | 36.4 | 65.0 | 83.0 | 100.0 |
| Dihydroxyaluminum aminoacetate | RT | 0.08 | 0.16 | 0.30 | 0.69 | 0.65 |
| | 37.5° | 0.20 | 0.25 | 0.59 | 0.63 | 0.70 |
| Magnesium carbonate | RT | 0.57 | 1.0 | 2.2 | 4.1 | 11.0 |
| | 37.5° | 2.0 | 2.2 | 2.6 | 25.0 | 42.9 |
| Magnesium hydroxide | RT | 1.2 | 2.2 | 5.3 | 15.6 | 19.5 |
| | 37.5° | 5.5 | 12.5 | 19.7 | 29.8 | 38.6 |
| Magnesium oxide | RT | 1.4 | 2.1 | 6.5 | 15.2 | 18.0 |
| | 37.5° | 4.8 | 4.9 | 6.5 | 18.2 | 24.0 |
| Magnesium trisilicate | RT | 3.9 | 6.6 | 31.2 | 54.6 | 100.0 |
| | 37.5° | 18.3 | 20.8 | 67.6 | 88.4 | 100.0 |
| Sodium bicarbonate | RT | 3.8 | 5.5 | 17.2 | 74.1 | 100.0 |
| | 37.5° | 27.8 | 72.8 | 85.8 | 100.0 | 100.0 |
| Sodium phosphate dibasic, anhyd. | RT | 0.36 | 0.83 | 14.8 | 83.2 | 100.0 |
| | 37.5° | 13.9 | 71.5 | 73.0 | 92.3 | 100.0 |

TABLE V.—FORMULAS IN GRAMS FOR 1,000 ASPIRIN TABLETS

| Ingredients | I | II | III | IV |
|---|---|---|---|---|
| Aspirin | 240.0 | 240.0 | 240.0 | 240.0 |
| Calcium succinate[a] | ... | ... | 182.0 | 182.0 |
| Calcium carbonate | ... | 72.5 | ... | 72.5 |
| Starch | 25.0 | 31.5 | 43.0 | 49.5 |
| Talc | ... | 11.0 | 14.0 | 26.0 |
| Total | 265.0 | 355.0 | 479.0 | 570.0 |

[a] Furnished through the courtesy of S. B. Penick and Co., New York, N. Y.

in a saturated solution of the diluent resulting in considerable reduction of the stability of the active compound. In a mixture prepared with a diluent which is insoluble, but absorbs moisture, generally the stability of the active compound decreases rapidly when the moisture content becomes higher than a certain level.

The influence of antacid compounds and other diluents on the stability of aspirin (4) is illustrated by the data in Table IV. The results in this table were obtained from mixtures containing two parts of aspirin and one of diluent stored in amber screw-capped bottles at room temperature and 37.5°. These results show that calcium gluconate and dihydroxyaluminum aminoacetate cause the least deleterious effect on aspirin stability after 1 year of storage at room temperature and 37.5°.

Nazareth and Huyck (5) studied the effect of calcium carbonate and calcium succinate separately and in combination on the stability of aspirin tablets. The relative stability of the aspirin tablet formulations presented in Table V is summarized by the data in Fig. 1, where tablets were stored at 45° up to 8 weeks. It is evident from the curves in this figure that calcium succinate has a considerable deleterious effect on the stability of aspirin, while calcium carbonate has only slight effect on the stability of aspirin.

The influence of lubricant type and concentration

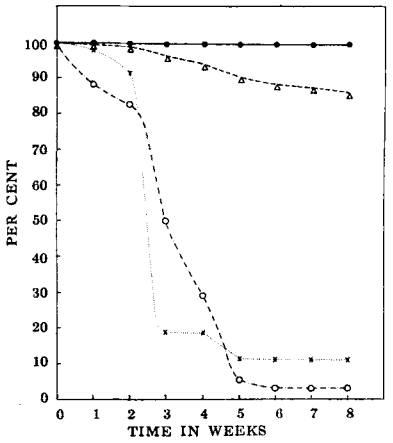


Fig. 1.—Stability of aspirin at 45°. Key: ●, formula I; △, formula II; ×, formula III; ○, formula IV.

of lubricant in aspirin decomposition in tablets containing aspirin, phenacetin, and caffeine (6) is illustrated by the data in Table VI. In most cases, an increase in lubricant concentration caused a corresponding increase in decomposition of aspirin; the most striking effect resulted when the lubricant

TABLE VI.—TYPES OF LUBRICANT AND LEVELS OF LUBRICANT

| Lubricant | High Level, % | Low Level, % | Mean Dec., % High | Low |
|---|---|---|---|---|
| Glyceryl esters[a] | 2 | 0.5 | 2.90 | 0.81 |
| Magnesium stearate | 2 | 0.5 | 9.51 | 2.60 |
| Talc | 4 | 1.0 | 0.99 | 0.90 |
| Calcium stearate | 2 | 0.5 | 19.25 | 5.68 |
| Stearic acid | 2 | 0.5 | 5.98 | 1.74 |
| Mineral oil | 4 | 1.0 | 1.97 | 1.36 |
| Talc plus mineral oil | 4 | 1.0 | 1.31 | 0.65 |

[a] Marketed as Aldo 33 by Glycol Chemicals, Inc., New York, N. Y.

type was one causing a large effect at the lower concentration—for example, calcium stearate, stearic acid, and magnesium stearate.

Nazareth and Huyck (7), in their study on the stability of aspirin in aspirin, phenacetin, and caffeine tablets, substantiate the findings of Ribeiro *et al.* (6) in that they found magnesium stearate in the tablet formula to cause considerable degradation of aspirin, while talc hardly influences the stability of aspirin in the tablet formulation.

It has been shown that alkaline lubricants cause discoloration of tablets containing amphetamine sulfate in a spray-dried lactose base (8). This is illustrated in Table VII, where data are presented on the discoloration of tablets after storage for 48 hr. at 40° and 85% relative humidity. The alkalinity of the lubricant converts some of the sulfate salt of amphetamine to the free base, which then reacts with the lactose, resulting in discolored tablets.

In our laboratories, it has been found that when stearic acid was used as a lubricant in tablet formulations for certain of the rauwolfia alkaloids, considerable degradation of the medicament took place. For example, after 2 weeks of storage at 50°, only 47% residual drug remained in the tablet formulation. Replacement of the stearic acid with magnesium stearate resulted in a stable tablet formulation. A particular rauwolfia alkaloid was found to be extremely sensitive toward granulation by either water or alcohol systems, as well as diluents containing bound water. Considerable degradation was found after granulating the tablet formula; for example, 14% loss was obtained when syrup was used as the granulating medium, and 8% when ethanol was used.

Table VII.—Discoloration of Amine–Lactose Tablets After 48 hr. at 40° and 85% Relative Humidity

| Amine | Lubricant | Visual Observation |
|---|---|---|
| Amphetamine $SO_4$, 10% | Mg stearate, 1% | Discoloration |
| Amphetamine $SO_4$, 10% | Na stearate, 1% | Discoloration |
| Amphetamine $SO_4$, 10% | Talc, 2% | Discoloration |
| Amphetamine $SO_4$, 10% | Stearic acid, 1% | No discoloration |
| Amphetamine $SO_4$, 10% | Glyceryl monostearate | No discoloration |
| Amphetamine $SO_4$, 10% | None | No discoloration |
| Amphetamine base, 10% | None | Strong discoloration |

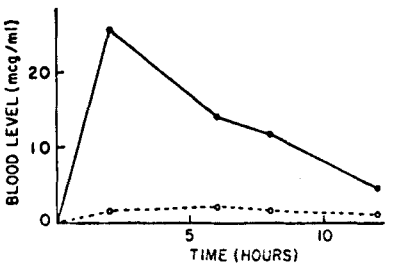


Fig. 2.—Decrease in blood levels when an aged tablet (---------) was administered orally to humans rather than a fresh tablet (———).

Of considerable importance are the physical changes that can be caused by tablet diluents, granulating agents, and lubricants. Probably the most important one from a therapeutic standpoint is an increase in disintegration time or dissolution rate. This can cause a reduction or loss in therapeutic effectiveness of the medication because the active ingredient would be less readily available for absorption. The plots in Fig. 2 show the blood levels obtained after oral administration of a tablet formulation when it was first prepared and the same tablet formulation after it was stored for a period of time. The tablet formulation in *in vitro* testing showed increased disintegration time and dissolution rate from that obtained when initially tested.

In the formulation of glutethimide tablets, it was found that certain granulating agents caused the tablets to *set up* and have longer disintegration

Table VIII.—Influence of Granulating System on Disintegration Time of Glutethimide Tablets

| Granulating System | Initial D. T. | Storage Cond. Temp. | Storage Cond. Time | D. T. |
|---|---|---|---|---|
| Rice starch paste | 1 min. 30 sec. | 65° | 1 wk. | 8 min. 10 sec. |
| Acacia soln., 1% | 1 min. | 60° | 1 wk. | 13.5 min. |
| Gelatin soln. | 10 min. | 50° | 1 wk. | 34.5 min. |
| Cornstarch + alginic acid | 45 sec. | RT | 6 wk. | 40 min. |
| Gelatin + wheat starch | 30 sec. | 50° | 3 mo. | 8 min. |
| PEG 6000 + wheat starch | 3 min. | 50° | 1 wk | >40 min. |

Table IX.—Rate Constants for the Fading of FD&C Red No. 3

| Diluent | Nature of Colorant | Dye Dispersion Method | $k \times 10^5$ (f.-c. hr.)$^{-1}$ |
|---|---|---|---|
| $CaSO_4 \cdot 2H_2O$ | Dye | Comminuted[a] | 11.3 ± 1.1 |
| $CaSO_4 \cdot 2H_2O$ | Dye | Micropulverized[a] | 11.4 ± 0.8 |
| $CaSO_4 \cdot 2H_2O$ | Lake | Comminuted or ball milled[b] | 7.4 ± 0.8 |
| $CaHPO_4$ | Dye | Micropulverized[a] | 6.7 ± 0.6 |
| $CaHPO_4$ | Lake | Comminuted or ball milled[b] | 7.8 ± 0.3 |
| Lactose | Dye | Micropulverized[a] | 6.1 ± 0.3 |
| Lactose | Lake | Micropulverized[b] | 4.6 ± 0.9 |

[a] Average of three slopes, each a different dye concentration. [b] Average of two slopes, each the same dye concentration.

times. This is illustrated by the data summarized in Table VIII.

The influence of tablet diluents on the rate of color fading in tablets was recently demonstrated (9). The data in Table IX summarize the relative stability of FD&C Red No. 3 against fading when used in tablet formulations containing lactose, calcium sulfate dihydrate, and anhydrous dibasic calcium phosphate as diluents. Of these three materials, it can be seen that the tablets containing calcium sulfate dihydrate cause the most rapid fading of the color.

In addition to influencing the color stability of tablet formulations containing a certified dye, diluents can also influence the rate of discoloration of white tablets. This was shown in Tables I and III when the effect of diluents on vitamin A and ascorbic acid stability was discussed. This effect is also observed in tablet formulations containing sulfonamides as their active ingredient, as will be shown in a subsequent section of this paper when the influence of amber and flint glass on the stability of tablets is discussed.

It is also desirable to follow the friability and hardness of a tablet formulation during stability testing to insure that the friability does not become too great or that the hardness decreases to an extent where the tablet may crumble in the bottle during normal use.

**Application of Chemical Kinetic Principles.**—Although it is more difficult to apply chemical kinetics and the Arrhenius relationship to stability data for tablet systems, it can, however, be employed as long as it is possible to linearize a property of the degradation with time in accordance with chemical kinetic reaction orders. By plotting the slopes of these curves *versus* the reciprocal of the absolute temperature, Arrhenius plots are obtained; if a linear relationship exists, it can be employed to predict the stability of a constituent in the tablets at room temperature from exaggerated temperature storage data. This will now be illustrated with examples reported in the literature.

It has been shown that vitamin A acetate and palmitate encased in gelatin, acacia, and similar substances, when tableted into uncoated or chewable tablets, follow a pseudo first-order degradation scheme (10). The plot in Fig. 3 represents an Arrhenius curve of the pseudo first-order rate constants for the degradation of vitamin A palmitate beadlets in a dry-slugged mannitol base, multivitamin chewable tablet. The linearity of the plot permits the extrapolation of the degradation rate constant from the elevated temperatures to 25° thereby permitting a prediction of shelf life of the vitamin in this tablet formulation.

An interesting relationship was found by this investigator for degradations that have taken place in systems where moisture is readily available.

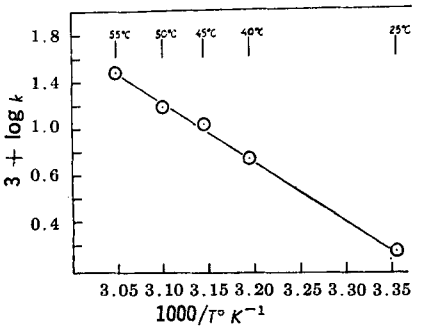


Fig. 3.—Rate constants ($k$ = week$^{-1}$) for pseudo first-order rate constants of vitamin A palmitate beadlets in a dry-slugged, mannitol-base, multivitamin chewable tablet. Log $k$ is plotted against reciprocal absolute temperature.

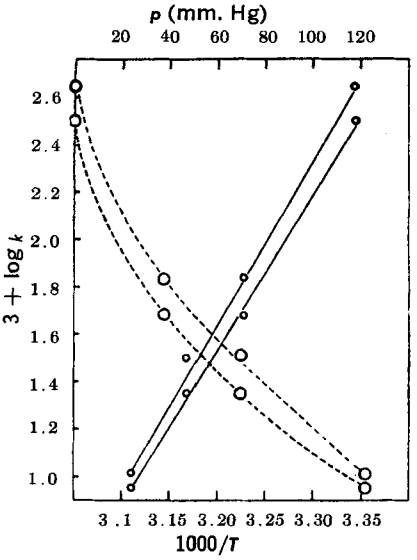


Fig. 4.—Plots of the pseudo first-order rate constant ($k$ = month$^{-1}$) for vitamin A palmitate beadlets in sugar-coated tablets. Key: ---------, regular Arrhenius plots ($1/T$ scale); ———, log $k$ *vs.* water vapor pressure ($p$-scale).

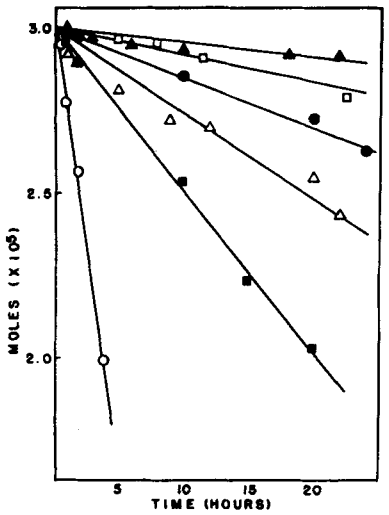


Fig. 5.—Solid state degradation of vitamin A compounds at 50°. Key: ▲, vitamin A benzhydrazone, m.p. 181–182°; □, vitamin A succinate triphenylguanidine salt, m.p. 140–140.5°; ●, vitamin A 3,4,5-trimethoxybenzoate, m.p. 85–86°; △, vitamin A nicotinate, m.p. 93–94°; ■, vitamin A phthalimido-*N*-acetate, m.p1. 11–112°; ○, vitamin A acetate, m.p. 57–58°.

For example, a plot of the pseudo first-order rate constant for the degradation of vitamin A palmitate beadlets in sugar-coated tablets gave a linear relationship when plotted against vapor pressure as shown in Fig. 4.

The above phenomenon may not be too surprising since it is known that certain reactions, such as hydrolytic ones, require the presence of an aqueous interface in which the reaction is to take place. The existence of this interface can result from the presence of pharmaceutical tablet diluents which may bind water by adsorption on surfaces, such as in the case of lactose, by capillary condensation, such as in starch, by absorption on tablet granules and by water of crystallization in certain other materials.

In a recent investigation (11), it was shown that several vitamin A derivatives degrade in accordance with zero-order kinetics as depicted by the curves in Fig. 5. It was postulated that the degradation occurs almost exclusively in a liquid film at the surface of the crystal. The relative amount of material in the liquid state may be expected in these instances to determine, in some large measure, the rate of degradation. The fraction of material in the liquid state is related to the melting point of the pure crystalline solid by the following equation:

$$\ln X_1 = -Lf/R\left(\frac{1}{T} - \frac{1}{Tm}\right)$$

where

$X_1$ = mole fraction of solvent
$Lf$ = molar heat of fusion of the liquid phase
$R$ = gas constant
$Tm$ = melting point of pure solid

On the basis of the findings of these investigators it would appear that, in a series of vitamin A derivatives, the compound having the higher melting point will be the most stable, all other factors being equal. Consequently, the suggested approach of using chemical alteration to provide derivatives having high melting points, and hence greater stability, should prove a useful tool to the pharmaceutical formulator of solid dosage forms where drug degradation poses a serious problem.

Several investigators (12) recently reported on the use of a color coder to measure the $X$, $Y$, and $Z$ components of tristimulus reflectance values in studying the darkening of tablets exposed to elevated temperature storage. Using zero- and first-order kinetic principles, these investigators were able to linearize the degree of darkening with time, and by use of Arrhenius plots were able to extrapolate the rate of darkening to that which would be expected under extended storage at shelf conditions. The straight-line plot in Fig. 6 illustrates the first-order plot of the data, and the plot in Fig. 7 illustrates the Arrhenius relationship of the rate constants with temperature.

During the past few years, there have been several investigations (13, 14), relative to the light-catalyzed fading of colored tablets in which attempts were made to apply chemical kinetic principles to this reaction. Recently, Everhard and Goodhart (14) using certain relationships developed by Kubelka and Munk as a basis (15), proceeded to quantitate the relationship of dye fading as a function of time and light intensity. Since the fading is proportional to the product of time, $t$, and intensity of light, $I$, these investigators proceeded to plot the fading function, $\theta_t$, *versus* the product of time and intensity as illustrated in Fig. 8. The consistency of the slopes at three different concentrations shows that the fading of the dye at the surface of the tablet is first order. By using the product of time and intensity, each intensity condition was found to be on the same straight line for any given concentration of dye. The general first-order equation for the straight line plots in Fig. 8 is

$$\ln \theta_t = ktI + \ln \theta' t$$

where

$\theta_t$ = (Kubelka-Munk function of the tablet) $\theta$ calculated at time $t$
$\theta' t$ = $\theta_t$ at $t = 0$
$I$ = intensity of light

By determining the times at which objectionable fading took place under high intensity, it is possible to calculate the time for objectionable fading to occur under normal storage conditions.

## INFLUENCE OF THE PACKAGE ON TABLET STABILITY

The choice of the container materials for any particular tablet product must be done only after a thorough evaluation of the influence of these materials on the stability of the product and the effectiveness of the container in protecting the product during extended storage under varying environmental conditions of temperature, humidity, and light.

Atmospheric humidity can have serious deleterious effects on the product if the container does not afford an impervious barrier between the product and environmental conditions. If moisture were to be absorbed by a product in a container, it could influence the stability of a solid dosage form, such

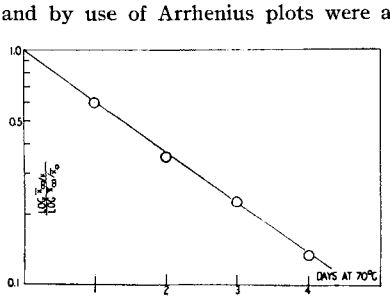


Fig. 6.—Compound C tablets. Degradation at 70° expressed as logarithm of per cent retained *vs.* days stored at 70°.

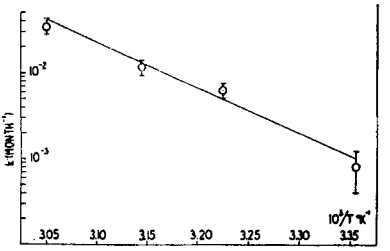


Fig. 7.—Logarithm of apparent rate constants $k$ of drug A taken from Table VI plotted as a function of reciprocal absolute temperature.

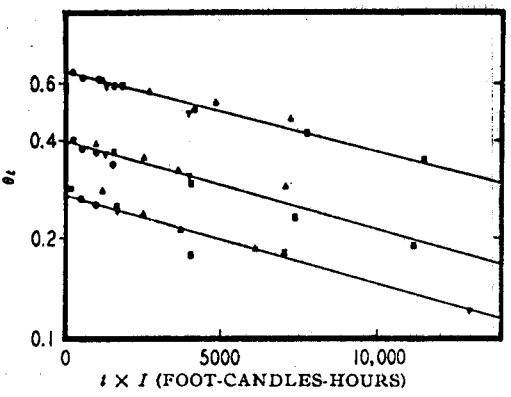


Fig. 8.—Plots of $\theta_t$ *vs.* the product of time and intensity. Key: ●, 11 f.-c.; ▲, 50 f.-c.; ■, 80 f.-c; ▼, 655 f.-c.; top line, 0.06% dye; middle line, 0.03% dye; bottom line, 0.015% dye.

TABLE X.—AMOUNT OF DYE FADED PER DAY WHEN IRRADIATED UNDER EXAGGERATED INTENSITY

| Glass Sample | FD&C Blue No. 1 | D&C Yellow No. 10 |
|---|---|---|
| Flint | 12.9 | 38.1 |
| Amber | 4.6 | 6.2 |

TABLE XI.—INFLUENCE OF LIGHT ON THE PHOTOSENSITIVITY OF A SULFONAMIDE TABLET FORMULATION

| Time, Wk. | % Reflectance at 450 mμ Open Dish | Amber Bottle |
|---|---|---|
| 0 | 52.6 | 52.6 |
| 2 | 41.3 | 52.3 |
| 4 | 35.6 | 53.6 |
| 6 | 31.7 | 53.8 |
| 8 | 28.9 | 52.9 |
| 10 | 25.4 | ... |
| 12 | 23.8 | 51.5 |

as tablets, to a considerable degree since the velocity of degradation generally increases as the product absorbs water.

In recent years, plastic containers of varying polymer composition have been evaluated as a replacement for glass for packaging tablet medications. At the present time, there are several tablet products on the market which are packaged in plastic bottles. However, because of the tendency of plastic containers to be permeable to the water vapor and other gases in the atmosphere, the chemical and physical stability of tablets stored in plastic bottles can be affected considerably. Penicillin tablets were found to degrade in polystyrene containers due to the permeation of water vapor (16). Consequently, it is essential, when evaluating the stability of a tablet product to be packaged in a plastic container, to perform the stability tests on tablets stored in the plastic container.

Most deterioration reactions are temperature dependent. Generally, as the temperature increases, so does the rate of degradation. However, in certain instances, the reverse could be true. An example of such a case is a solid dosage form. By storing tablets under elevated temperatures, moisture in the tablets is driven off into the atmosphere within the container. In the event the container is not completely impermeable, water vapor can pass from the container into the atmosphere, thereby causing the tablets to exhibit enhanced stability. Unless the temperature is reduced, vapor pressure conditions in the container will prevent the entrance of atmospheric moisture into the container.

An example of such a situation was found for a capsule product containing an antihistamine resin adsorbate, aspirin, and sodium ascorbate packaged in glass vials sealed with bakelite screw caps and polyethylene snap caps (17). Due to the permeability of the polyethylene closure, the escape of moisture from the formulation is allowed, thereby effectively removing the component responsible for the hydrolytic degradation of aspirin. In addition, the permeable polyethylene cap closure permits the escape of the acidic gaseous degradation products resulting from aspirin hydrolysis. This would further reduce the autocatalytic degradation of aspirin due to the presence of acidic degradation products.

It is often important for the container to protect a product from environmental light radiations. Many pharmaceutical preparations exhibit physical or chemical changes due to the radiant energy of light. Light radiations can cause color development or color fading and potentiate oxidation–reduction degradation of an active ingredient in a tablet formulation.

Products exhibiting physical and chemical changes from the effects of radiant energy can be adequately protected in most instances by the use of special glass containers. Flint glass, which is the most widely used multipurpose container material, has the disadvantage of being transparent to light rays above 300 mμ. As a result, amber glass, which essentially shuts out the light rays up to 470 mμ, has been used extensively.

Since it is known that the photochemical activity of the light radiations drops off with increasing wavelength, it would be expected that the amber container would afford better protection to a product against light than the flint glass. That this is the case will now be illustrated.

The data in Table X show that the rates of fading of colored tablets stored in amber bottles are substantially less than those in the flint glass bottles.

Sulfonamides are known to be affected by light. The data in Table XI show the protective effect of amber glass against tablet darkening as measured by the change in reflectance at the surface of the sulfonamide tablets.

As can be seen by the substantial decrease in reflectance values of the tablets exposed to light in the open dish, the tablets darken considerably. Visual observations of these tablets indicated that they had taken on a yellow-tan color. However, for the tablet stored in amber bottles, no significant change in reflectance took place, and visual observation showed no apparent darkening.

## STABILITY TESTING LABORATORY

In order to perform chemical and physical stability testing of tablet dosage forms adequately, it

is essential for a pharmaceutical manufacturer to invest in specialized laboratory equipment and skilled personnel. Although constant-temperature baths may be ideal for kinetic studies on a small scale, they are not practical for testing preparations which are packaged in their final containers. This is due to the fact that, in most cases, the packages are of such size that the baths are not of adequate capacity, nor are the packages generally of such a type that can be immersed in a bath. Since the most significant tests, from a practical point of view, must be conducted on the final formulation with due consideration for the influence of the container on stability, space and equipment must be adequate for a large number of samples. For milder conditions of storage, the retention periods will be longer, and space requirements will be greater than for severe conditions of storage. Because rates of change in a property of a tablet preparation are dependent upon environmental conditions, it is essential to obtain equipment capable of operating within narrow limits of temperature, humidity, and light intensity. This will result in an increase in the accuracy of the extrapolated data.

As illustrated in the previous sections of this paper, the stability of tablet formulations can be affected by temperature, light, and humidity. Consequently, it is essential to have adequate equipment available which would permit the performance of stability tests under exaggerated conditions of temperature, humidity, and light. With the availability of such equipment and the application of certain physical chemical principles to the data collected under exaggerated test conditions, it should be possible, in most cases, to predict the chemical and physical stability of tablet dosage forms in a relatively short period of time.

It is hoped that, as a result of the foregoing information, a better insight into the factors that can affect the chemical and physical stability of tablet dosage forms and the utility of employing chemical kinetic principles to assist in predicting the stability under extended shelf conditions from exaggerated test data has been gained.

## REFERENCES

(1) Wai, K. N., DeKay, H. G., and Banker, G. S., *J. Pharm. Sci.*, **51**, 1076(1962).
(2) Yamamoto, R., and Kawai, S., *Arch. Pract. Pharm.*, **19** (No. 1), March 1959.
(3) Yamamoto, R., *ibid.*
(4) Bandelin, F. J., and Malesh, W., *J. Am. Pharm. Assoc., Pract. Pharm. Ed.*, **19**, 152(1958).
(5) Nazareth, M. R., and Huyck, C. L., *J. Pharm. Sci.*, **50**, 608(1961).
(6) Ribeiro, D., *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, **44**, 226(1955).
(7) Nazareth, M. R., and Huyck, C. L., *J. Pharm. Sci.*, **50**, 620(1961).
(8) Castello, R. A., and Mattocks, A. M., *ibid.*, **51**, 106 (1962).
(9) Goodhart, F. W., Everhard, M. E., and Dickcius, D. A., *ibid.*, **53**, 338(1964).
(10) Carstensen, J. T., *ibid.*, **53**, 839(1964).
(11) Guillory, J. K., and Higuchi, T., *ibid.*, **51**, 100(1962).
(12) Carstensen, J. T., *et al.*, *ibid.*, **53**, 1050(1964)
(13) Lachman, L., *et al.*, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 165(1960).
(14) Everhard, M. E., and Goodhart, F. W., *J. Pharm. Sci.*, **52**, 281(1963).
(15) Kubelka, P., *J. Opt. Soc. Am.*, **38**, 448(1948).
(16) Bull, A. W., *J. Pharm. Pharmacol.*, **7**, 806(1955).
(17) Siegel, S., *et al.*, *J. Pharm. Sci.*, **51**, 1068(1962).

# Notes

## Incorporation of Hydroxyproline-$^{14}$C into the Principal Alkaloids of *Datura innoxia* Miller

By MELVIN R. GIBSON and GERALD A. DANQUIST

***Datura innoxia*** **root cultures absorb *dl*-hydroxyproline-2-$^{14}$C and distribute it to hyoscyamine and scopolamine as well as other alkaloids. The low level of incorporation suggests an indirect route and not a direct incorporation from an exogenous amino acid pool.**

A GREAT deal of interest has been engendered recently in proline–hydroxyproline relationships in animals and plants. The high content of hydroxyproline in collagen and its strikingly reduced quantity in collagen in rheumatoid states in man has been largely responsible for this interest. The wide variance in hyoscyamine–scopolamine ratios in different species of *Datura* has long been of interest and the cause for much study. In view of the obvious proline moiety in the hyoscyamine molecule and the relationship of oxidized hydroxyproline to the scopolamine molecule, attempts were begun some time ago in this laboratory to relate hyoscyamine–proline and scopolamine–hydroxyproline.

Work in this laboratory (1) showed that both growth and alkaloid content were affected in *Datura stramonium* variety *tatula*. More recent work in this laboratory (2) showed that *l*-proline-$^{14}$C was readily incorporated into the hyoscyamine and scopolamine of both *D. stramonium* var. *tatula* and

Received April 1, 1965, from the College of Pharmacy, Washington State University, Pullman.
Accepted for publication July 14, 1965.
Presented to the Scientific Section, A.PH.A., Detroit meeting, March 1965.
This investigation was supported in part by research grant GM-08564 from the National Institutes of Health, U. S. Public Health Service, Bethesda, Md., and by funds provided for medical and biological research by the State of Washington, Initiative 171.