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Accelerated physical stability testing and long-term predictions of changes in the crushing strength of tablets stored in blister packages

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Summary

A physical model is presented which permits the amount of sorbed moisture and the crushing strength of compressed tablets stored in blister packages to be predicted based on a knowledge of: (1) tablet moisture sensitivity; (2) package moisture permeability; and (3) relative humidity storage conditions. The tendency of tablets to sorb water can be characterized in approximately one week by storing unprotected tablets at several relative humidities. This information, in combination with package moisture permeability data, permits changes in tablet crushing strength and sorbed moisture to be made under a variety of storage and packaging conditions. These predictions are useful in establishing long-term stability testing protocols. They are also useful in predicting what tablets stored in blister packages might reasonably be expected to experience in the market place where short-term and long-term oscillating conditions are likely to occur. Theoretical predictions based on the physical model indicate that, in general, tablets stored in relatively permeable blister packaging materials will be protected from large, short-term humidity fluctuations of several hours or days. Long-term fluctuations due to monthly and seasonal variations in humidity will be important. Tablets stored in relatively permeable blister packages at relative humidities representative of marketplace conditions can be expected to experience humidities varying between 30% and 70% while less permeable packages will show less variation. This suggests that oscillating unprotected tablets between 30% and 70% relative humidity every 2–3 days for a 2–3-week period may produce changes similar to those observed for tablets stored in marketed blister packages. Tablets tested using these conditions showed changes in crushing strength similar to those packaged in blister packages and used in a 3-year field study. The theoretical predictions and experimental results emphasize the importance of matching the dosage formulation characteristics to the package material and testing conditions. In this way, a more rational selection of packaging material and testing protocols can be made.

Introduction

The physical stability of solid dosage forms, and in particular compressed tablets, is of obvious importance to the formulation scientist. For example, changes in the friability, disintegration, dissolution, and crushing strength of tablets are influenced by storage conditions. A number of reports in the literature have also discussed the process of moisture penetration through packaging material and its influence on stability. Reamer et al. (1977) and Kentala et al. (1982) packaged

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commercially available desiccant pellets in unit dose repackaging materials to characterize the permeability of the packages to moisture. Mizrahi et al. (1970) combined the mass transfer characteristics of packaging materials with chemical stability information to predict the extent of browning of dehydrated cabbage. Veillard et al. (1979) used a similar model to characterize the diffusion of water vapor through polyvinylchloride blister packaging. The authors concluded that the effect of moisture sorption on tablet crushing strength is dependent on the formulation and that it is necessary to consider the characteristics of the formulation when selecting a package. Nakabayashi et al. (1980a and b) also used a similar physical model to predict the shelf-life of tablets stored in blister packaging under varying temperature and humidity conditions. Excellent agreement between predicted and observed results were obtained. Accelerated testing conducted at 45°C was proposed by Nyqvist and Lundgren (1982) as a useful tool for predicting tablet sorption and crushing strength profiles at 25°C.

This article discusses the influence of: (1) package permeability; (2) tablet moisture sensitivity; and (3) storage conditions on the crushing strength of compressed tablets stored in blister packages. These properties can be incorporated into the proposed physical model and allow useful long-term physical stability predictions to be made. This approach permits changes in tablet crushing strength to be predicted under a variety of storage conditions. With this information, suitable accelerated stability studies can be designed and packaging requirements more rationally selected.

The effects of oscillating relative humidity on the physical stability of compressed tablets are also addressed. Predictions are made and results from accelerated testing are compared with data obtained on compressed tablets stored in blisters at several locations worldwide for a 3-year period.

While not addressed specifically in this study, a similar approach may be useful for predicting other changes in tablet properties such as disintegration and dissolution. Other packages for which moisture permeation data is available, such as glass bottles, etc., may also be evaluated as can other dosage forms such as capsules.

Theory

A schematic diagram of the physical model similar to that of previous investigators (Mizrahi et al., 1970; Veillard et al., 1979; Nakabayashi et al. 1980a and b) is shown in Fig. 1. The blister packaging material surrounding the dosage form is a diffusional barrier to the movement of water vapor from one side of the package to the other. Inside the package is a compressed tablet or some other moisture sorbing material such as a capsule. It is assumed in this physical model that an instantaneous equilibrium is established between the water vapor inside the blister cavity and the dosage form and that all components are in thermal equilibrium. The direction and rate of water movement is, of course, dependent upon the concentration gradient of water across the package material. Two additional kinetic processes may be of some importance under certain situations. It is possible that a concentration gradient of water vapor could exist within the package cavity. However, this is not a serious consideration for blister packages because of the small volume and distance between the package membrane and the dosage form. It is likely to be a concern, however, if other packages such as bottles are considered since substantial volumes and distances can be involved. The rate of moisture uptake by the dosage form may also need to be considered in some cases. For the compressed tablets studied,

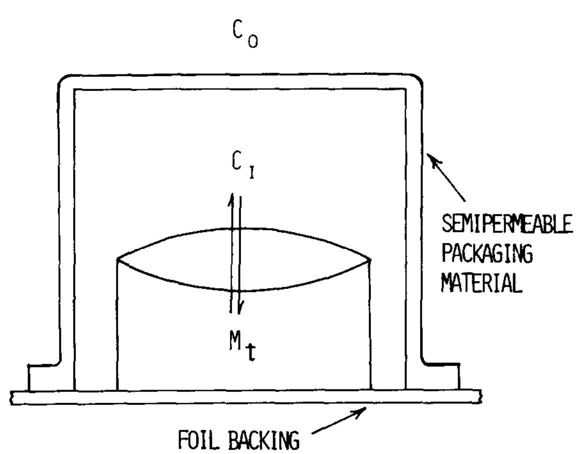

Fig. 1. Schematic diagram of physical model.

equilibrium moisture content was achieved relatively rapidly (approximately 3 days). This is considered rapid compared to the water vapor transmission through the membrane. It can therefore be assumed that the rate determining step in the overall transport of water vapor is the blister package membrane.

For this physical model, the flux of water through the membrane can be written:

$$J = P_m(C_o - C_i) \quad (1)$$

where J is the steady-state flux of water vapor through the package membrane, P_m is the permeability of the membrane, C_o is the concentration of water vapor outside the package, and C_i is the concentration of water vapor inside the package.

Because thermal equilibrium is assumed, the water vapor concentration is directly proportional to the percent relative humidity. Simple interconversion is therefore possible. Water vapor concentration is used in all calculations but, for convenience, much of the discussion will use % relative humidity (RH). Mass balance considerations lead to the following relationship for the flux:

$$J = (1/A)(\mathrm{d}M/\mathrm{d}t) \quad (2)$$

where A is the area of the membrane and $\mathrm{d}M/\mathrm{d}t$ is the rate of change of mass with respect to time.

The total mass of water, M, in the inner cavity of the package is equal to the mass of water in the vapor phase plus that sorbed to the tablet. In general, however, the mass of water sorbed to the dosage form is much greater than that in the vapor phase so that the total mass of water inside the cavity is essentially equal to that sorbed to the tablet.

A relationship between water vapor concentration, C_i, and tablet weight, W_t, can be determined experimentally and can take a variety of forms. In general:

$$W_t = f(C_i) \quad (3)$$

where $f(C_i)$ can be a complex function.

In this study a linear relationship is assumed to exist:

$$W_t = KC_i + W_o \quad (4)$$

where K is a measure of the capacity of the dosage form to sorb moisture, and W_o is the predicted tablet weight at 0% relative humidity.

The moisture content of the compressed tablet is given by:

$$M_t = W_t - W_o \quad (5)$$

and:

$$M \approx M_t = KC_i \quad (6)$$

Combining Eqns. 1, 2 and 6 yields the following differential equation:

$$\mathrm{d}M/\mathrm{d}t = AP_m(C_o - M/K) \quad (7)$$

which relates the rate of moisture change, $\mathrm{d}M/\mathrm{d}t$, to the tablet moisture sensitivity, K; the package permeability, P_m; and the storage conditions, C_o.

Transport under constant humidity conditions

Eqn. 7 can be integrated assuming that the external water concentration, C_o, is maintained constant. The moisture content of the dosage forms as a function of time, t, is then given by:

$$M = KC_o - (KC_o - M_o)\,\mathrm{e}^{-AP_m t/K} \quad (8)$$

where M_o is the moisture content of the dosage form at $t = 0$. From Equation 8, the moisture content of the dosage form, M, can be calculated a priori if the package permeability, P_m, the external water concentration, C_o, the area of the package, A, and the moisture characteristics of the dosage form, M_o and K are known.

Transport with varying humidity storage conditions

When the external relative humidity, i.e. water vapor concentration, outside the package varies as a function of time, C_o can be written in the general form:

$$C_o = g(t) \quad (9)$$

where $g(t)$ describes the water concentration over the time interval of interest. Eqn. 7 can then be written in the form of a linear first-order differential equation:

$$dM/dt + (AP_m/K)M = (AP_m)g(t) \qquad (10)$$

In these studies, Eqn. 9 is written in the form of a polynomial:

$$C_o = A_0 + A_1 t + A_2 t^2 + A_3 t^3 \qquad (11)$$

The solution to Eqn 10 is then:

$$M = (B_1 + B_2 t + B_3 t^2 + B_4 t^3) + (M_o - B_1)\,e^{-at} \qquad (12)$$

where $a = AP_m/K$ (13)

$$B_1 = A \cdot P_m \left\{ \frac{A_0}{a} - \frac{A_1}{a^2} + \frac{2A_2}{a^3} + \frac{6A_3}{a^4} \right\} \qquad (14)$$

$$B_2 = A \cdot P_m \left\{ \frac{A_1}{a} - \frac{2A_2}{a^2} + \frac{6A_3}{a^3} \right\} \qquad (15)$$

$$B_3 = A \cdot P_m \left\{ \frac{A_2}{a} - \frac{2A_3}{a^2} \right\} \qquad (16)$$

$$B_4 = A \cdot P_m \left\{ \frac{A_3}{a} \right\} \qquad (17)$$

Using Eqn. 12, it is possible to calculate the moisture sorbed to a tablet when the external environment changes according to Eqn. 11.

Materials and Methods

Tablet formulations

Three direct compression tablet formulations were tested for moisture sensitivity. Two formulations are given in detail in Table 1. Formulation A is a 2:1 mixture of lactose and microcrystalline cellulose. Formulation B is a dibasic calcium phosphate dihydrate based formulation. Both formulations were compressed to an initial tablet crushing strength of approximately 9 Strong-Cobb Units (SCU). Formulation C is a proprietary lactose–microcrystalline cellulose based direct compression formulation for which 3 years of physical stability data obtained under several environmental conditions is available. Tablet crushing strength was determined using a hardness tester (Heberlein and Co.) and tablet weight was determined using a calibrated electronic laboratory balance. Desiccant pellets (Grade 944 indicating pellets, Davison Chemicals) were used to determine the moisture permeability of the blister packages.

TABLE 1

Formulation A	
mg/tab	
199	Lactose NF – Hydrous spray process
99.5	Microcrystalline cellulose NF (AVICEL PH 101, FMC)
1.5	Magnesium stearate NF – powder
300.0	
Formulation B	
mg/tab	
482.5	Dibasic calcium phosphate dihydrate USP (Emcompress, Edward Mendell)
12.5	Sodium starch glycolate NF (Explotab, Edward Mendell)
5.0	Magnesium stearate NF – powder
500.0	

Package materials

Two types of blister packaging material were tested: (1) 0.0075 inch polyvinyl chloride (PVC) film (Klockner-Pentaplast) and (2) 0.0075 inch polyvinyl chloride with a 0.0015 inch laminate of polymonochlorotrifluoroethyene (PCTFE) (ACLAR, Techni-Plex). The blisters used in this study were backed with an impermeable foil. The circular blister cavities containing compressed tablets were 0.45 cm high with a diameter of 1.2 cm and a total surface area of approximately 2.8 cm^2. The dimensions of the circular cavities containing desiccant pellets were 0.85 cm high with a diameter of 1.5 cm and a total surface area of approximately 5.8 cm^2.

Tablet characterization

Equilibrium moisture sorption isotherms were obtained at relative humidities ranging from approximately 25% to 95% using chambers containing water saturated with different salts. The chambers were stored at room temperature (21–22 °C). The relative humidity was checked periodically with a calibrated hygrometer and deviated by no more than 3% relative humidity over the course of the study. A sufficient number of tablets were placed in disposable plastic Petri dishes and stored in the chambers. Periodically, 5 tablets were removed and the crushing strength determined. To determine weight changes due to moisture sorption, 10 tablets were weighed and placed in a separate Petri dish. These tablets were periodically weighed and the results recorded. This procedure measures the additional moisture sorbed to the tablet when exposed to a given relative humidity. It does not take into account the initial moisture content of the tablet and measures only that water which is easily exchanged with the vapor phase.

Formulation C was subjected to oscillating relative humidity conditions by alternating tablets between 70% RH and 30% RH every 2–3 days at room temperature. The crushing strength of 5 tablets was determined as described above at each time point.

Compressed tablets in blister packages were stored at 25 °C and 93% RH. Ten tablets, each in a separate cavity, were removed periodically and the crushing strength immediately determined. Data was collected over a 5-week period.

Package permeability studies

To determine the permeability of the packaging material to moisture vapor, desiccant pellets were sealed into blister cavities. Packages were stored at 25 °C and 93% RH. Periodically, the weight of the desiccant pellets and package were determined. At the same time, the weight of a similar blister package without pellets was determined. In this way, a correction for the weight gain of the packaging material could be made and an accurate determination of desiccant weight gain obtained.

Field study

The proprietary direct compression formulation (Formulation C) was packaged in PVC and PCTFE laminated material and placed on stability at 5 locations worldwide; (1) Barceloneta, Puerto Rico, (2) Mexico City, Mexico, (3) Tokyo, Japan, (4) Jakarta, Indonesia, and (5) Crawley, U.K. Personnel at each location were asked to store the packages in a convenient place which would best represent normal indoor temperature and humidity conditions for products stored in their respective geographic areas. Samples were returned to Kalamazoo periodically for testing.

Results and Discussion

The average amount of water taken up by a single desiccant pellet stored in a blister cavity at 25 °C and 93% RH is shown in Fig. 2. The slope of the line, dM/dt, is a measure of the permeability of the blister package material. For the PVC package, approximately 1.06 mg of water vapor diffuses through a 5.8 cm^2 package per day. The PCTFE laminated package material has a permeability of approximately 0.11 mg per day per 5.8 cm^2. The membrane permeability, P_m, can be calculated from Eqn. 7 assuming $C_o = 2.141 \times 10^{-2}$ mg/cm^3 (93% RH at 25 °C), a package area of 5.8 cm^2, and a water vapor concentration inside, C_i, equal to zero due to the presence of the desiccant pellet. The permeability for PVC is 9.91 $\times 10^{-5}$ cm/s and for the PCTFE laminate, P_m is

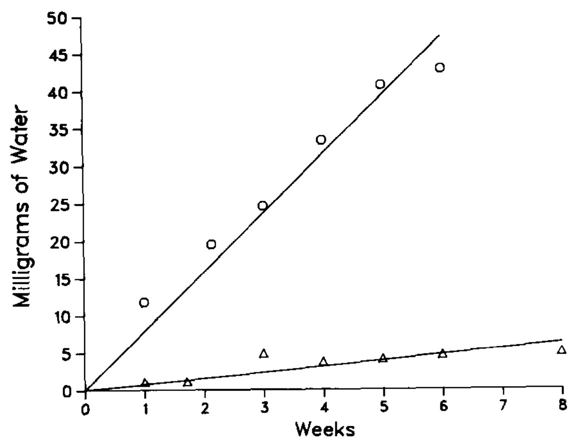

Fig. 2. Moisture transmission through PVC (○) and PCTFE laminated (△) blister packages stored at 25 °C and 93% relative humidity. Package area = 5.8 cm^2.

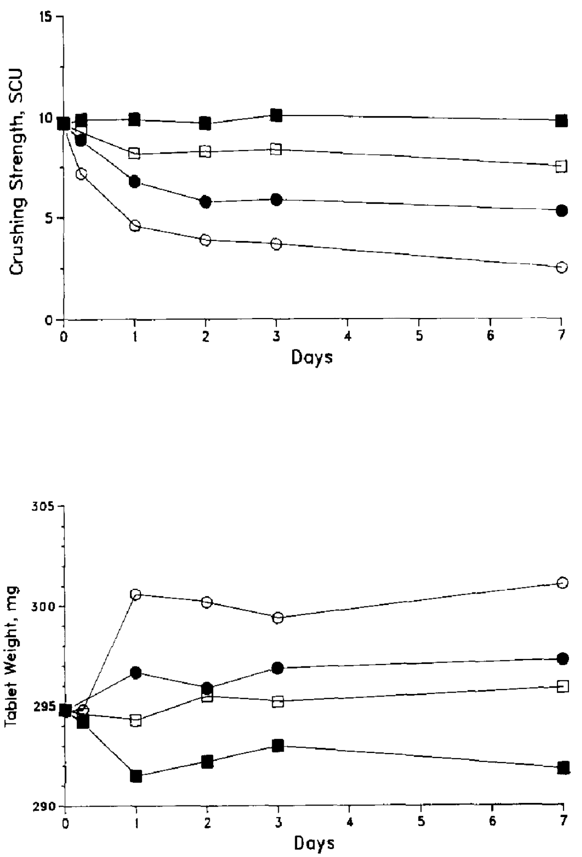

Fig. 3. Change in tablet crushing strength and tablet weight of Formulation A stored at different relative humidities: ■, 25%, □, 65%; ●, 75%; ○, 95%.

1.03×10^{-5} cm/s. These results are approximately 2 times lower than the water vapor transmission rates reported by the manufacturers for PVC and PCTFE and determined by ASTM procedures. The difference may, in part, be due to the differences in the test conditions: ASTM procedures require testing at 37.8° C and 90% RH.

The changes in crushing strength and tablet weight of compressed tablets of Formulations A and B exposed to various relative humidities at room temperature are shown in Figs. 3 and 4. The crushing strength decreased at high humidities for the two formulations. The equilibrium tablet weight of the two formulations increased when exposed to humidities greater than 60%. For the lowest humidity, both formulations lost weight, they were essentially being dried at 25% RH. The tablets reached constant weight and crushing strength after 1–3 days.

Fig. 5A and 5B show the linear relationship between tablet weight and relative humidity for the two formulations. The slope is related to the capacity factor, K, given in Eqn. 4: for Formulation A, $K = 558$; for Formulation B, $K = 382$.

A linear relationship also exists between crushing strength, CS, and relative humidity for these formulations at equilibrium (Fig. 6A and B).
For Formulation A:

$$CS = 13.37 - 493C_i \tag{18}$$

For Formulation B:

$$CS = 12.06 - 318C_i \tag{19}$$

Changes in the crushing strength of compressed tablets stored in blister packages at 25° C and 93%

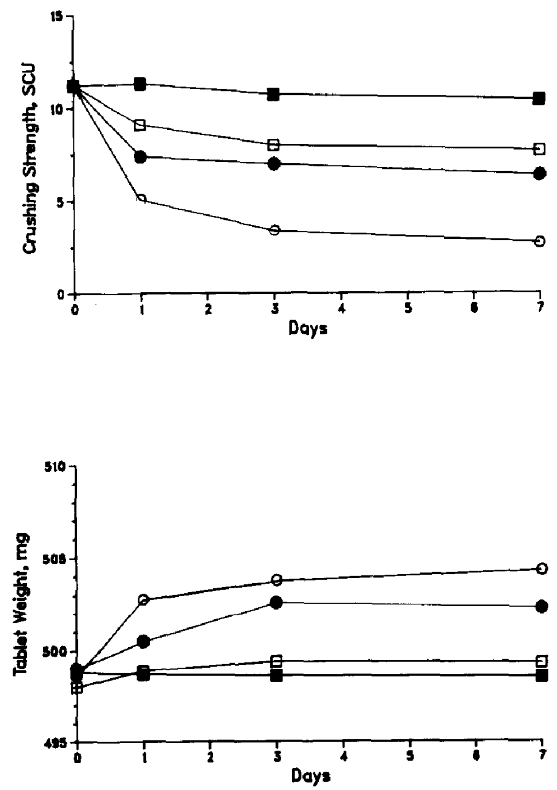

Fig. 4. Change in tablet crushing strength and tablet weight of Formulation B stored at different relative humidities: ■, 25%; □, 60%; ●, 70%; ○, 95%.

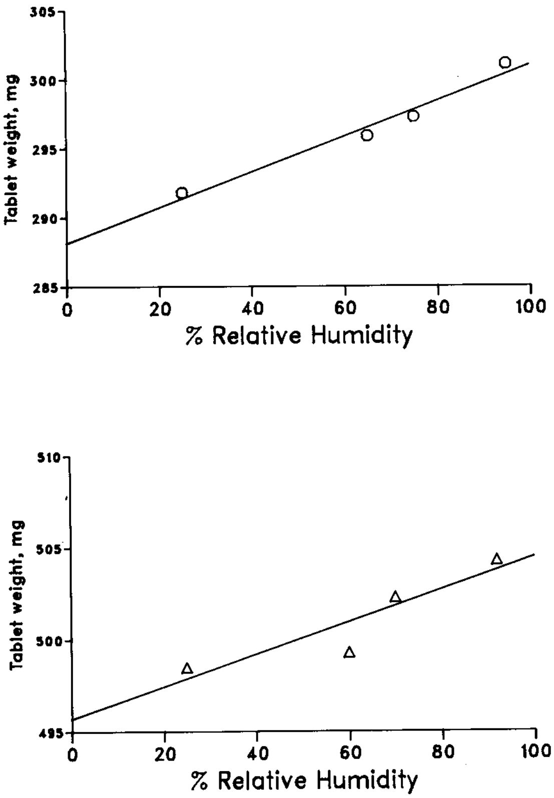

Fig. 5. A: tablet weight of Formulation A as a function of relative humidity. B: tablet weight of Formulation B as a function of relative humidity.

RH have also been determined and are shown in Fig. 7A for Formulation A and in Fig. 7B for Formulation B. A priori theoretical predictions are shown by the solid lines in these figures. The theoretical predictions are based on the membrane permeability, tablet properties, and storage conditions as given in Eqn. 8. The moisture content, M, of the dosage form is calculated and the corresponding crushing strength calculated from Eqns. 6, 18 and 19. In general, there is good agreement between theory and experimental results although the changes in crushing strength decreased somewhat more rapidly than predicted for Formulation A in PVC blisters.

Fig. 7A and 7B also demonstrate the interplay between package permeability and tablet moisture sensitivity. For example, the crushing strength of Formulation B is less sensitive to moisture and this shows up in Fig. 7B as a less drastic change in crushing strength for tablets in PVC blisters. The effect of different package permeabilities is also apparent. The selection of appropriate sample times for stability studies must take these factors into account. For the formulations packaged in PVC blisters at 25°C and 93% RH, a stability study longer than 6–8 weeks will yield little additional information. The predictions based on Eqn. 8 provide excellent guidance in setting up an appropriate physical stability testing program for this type of constant humidity study.

Careful inspection of Eqn 8 shows that the internal relative humidity, C_i, changes slowly even for the permeable PVC material. For example, rearranging Eqn. 8 and assuming $M_o = 0$, the time it takes a tablet to reach 90% of the new moisture equilibrium condition is:

$$t_{90\%} = 2.3K/(AP_m) \qquad (20)$$

For Formulation A in PVC packaging $t_{90\%} = 57$ days while for the PCTFE laminate packaging

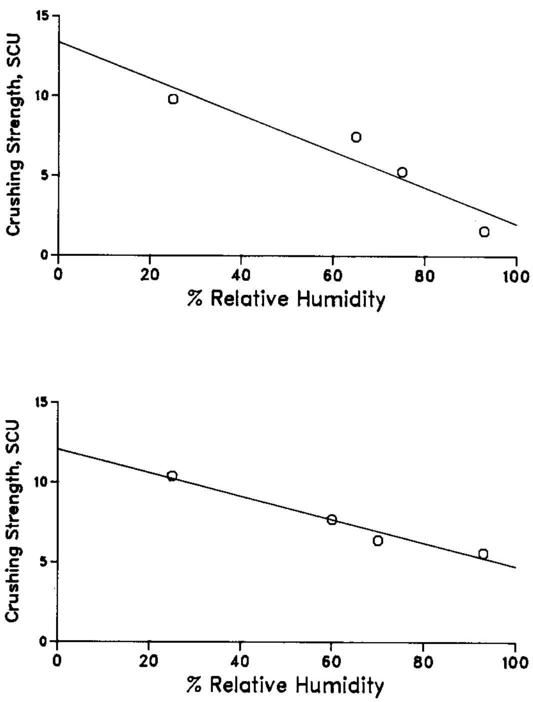

Fig. 6. A: tablet crushing strength of Formulation A as a function of relative humidity. B: tablet crushing strength of Formulation B as a function of relative humidity.

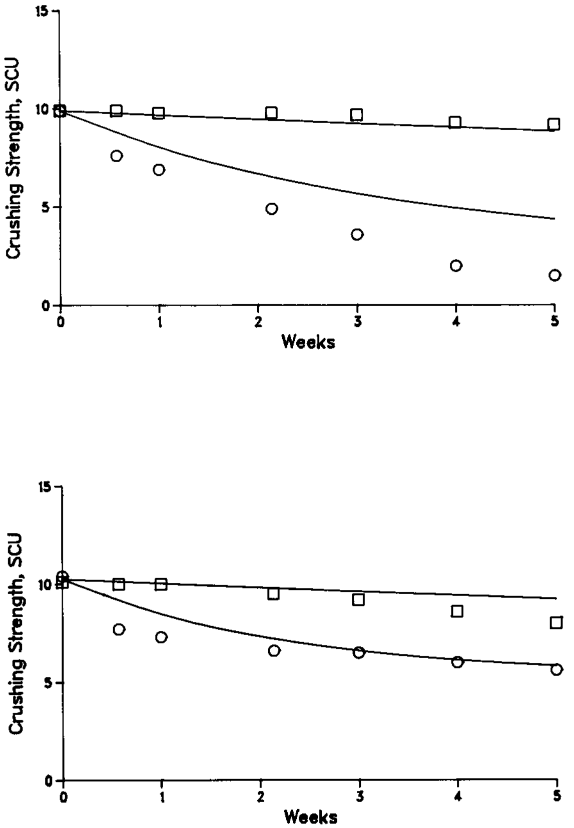

Fig. 7. A: tablet crushing strength changes of Formulation A as a function of time for tablets stored in PVC (○) and PCTFE laminate (□) blister packages. Solid line is theoretical prediction. B: tablet crushing strength changes of Formulation B as a function of time for tablets stored in PVC (○) and PCTFE laminate (□) blister packages. Solid line is theoretical prediction.

$t_{90\%} = 547$ days. Clearly, short-term fluctuations of several hours or days duration would have little effect on the formulations in the packages tested here.

The physical model is also useful in predicting the effects of varying the outside relative humidity, C_o. Exposure to normal environmental conditions such as those likely to be experienced in the marketplace is a relatively complicated situation. Large short-term daily fluctuations can be expected and are superimposed on more gradual seasonal variations. Eqns. 12 and 20 provide a way of determining the importance of these rapid short term fluctuations and longer seasonal variations.

Long-term theoretical predictions under conditions of oscillating outside relative humidity can be made based on Eqn. 12 assuming that the equations relating moisture content and humidity apply under oscillating conditions. Fig. 8 shows the average daily relative humidity in New Orleans, LA for 1980 (U.S. Department of Commerce, 1980) corrected to a temperature of 25°C. New Orleans was chosen for this study because it appeared to have the most "hostile" environment of the United States cities considered. The humidity was corrected by assuming that cool outside air was warmed to 25°C without the addition of additional water vapor. No cooling (air conditioning) was assumed to occur in the summer period, although this would likely reduce the humidity. The humidity rarely exceeded 80% in the summer months and was substantially lower in the winter when corrected for warming. In fact, the outside relative humidity is generally higher in the winter months in New Orleans; the average daily relative humidity was often in the 80–100% range during the winter in 1980. The solid curve in Fig. 8 shows a polynomial regression line. The following polynomial describes the daily variation in relative humidity:

$$\%RH = 31 + 0.143t + 1.3 \times 10^{-3}t^2 - 4.86 \times 10^{-6}t^3 \quad (21)$$

where t is day of the year (January 1 = 1; December 31 = 365) and % RH is the percent relative humidity. Other periodic functions could equally well describe the humidity conditions.

Theoretical predictions using Eqns. 21 and 12 provide insight into what realistic variations in tablet moisture content and crushing strengths might be. Figs. 9 and 10 show predictions over a several year period for Formulation A assuming that the relative humidity, and hence C_o, outside the package is represented by Eqn. 21. For convenience, the relative humidity inside the package is shown in the figures and not tablet moisture content or crushing strength values. It is clear from Fig. 10 that the PCTFE laminate offers superior package protection compared to the PVC material for Formulation A (Fig. 9). In PVC, the

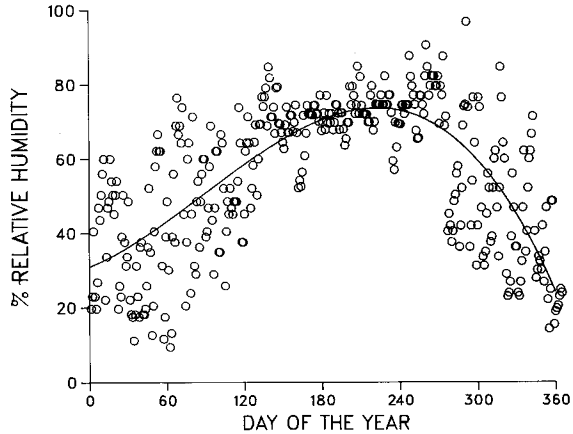

Fig. 8. Relative humidity as a function of day of the year (January 1 = 1; December 31 = 365) in New Orleans, LA for 1980. Relative humidity in the winter months corrected to 25 ° C. Solid line is least-squares regression line given in Eqn. 21.

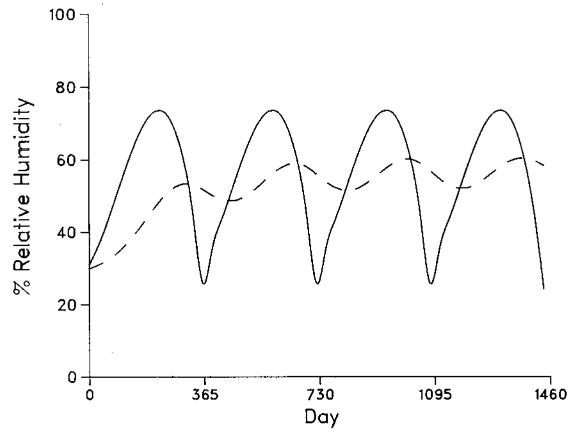

Fig. 10. Predicted relative humidity inside a PCTFE laminated blister package with oscillating outside relative humidity for Formulation A. Solid line is external humidity given by Eqn. 21; dashed line is predicted relative humidity inside package.

relative humidity inside the package mirrors the outside humidity quite closely. Note, however, that realistically it appears that variations from about 30% RH to 70% RH can be expected even in the permeable PVC package under the conditions specified. For the PCTFE laminate material, the relative humidity inside the package shows the same oscillation pattern but the range is from a high of about 60% RH to a low of about 50% RH. Obviously the PCTFE laminate provides increased protection in this case. Similar predictions can be made for Formulation B and similar profiles are obtained. Based on Eqn. 20, short-term fluctuations of several hours or days can be ignored even for PVC packaging.

Fig. 11 depicts the profile for a formulation with a capacity factor 1/4 that of Formulation A stored in the PCTFE laminate blister. The oscilla-

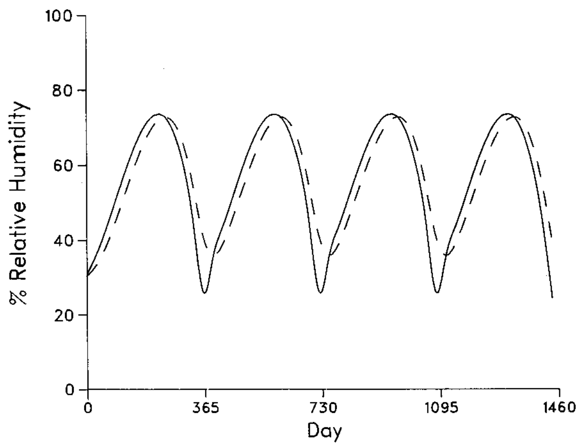

Fig 9. Predicted relative humidity inside a PVC blister package with oscillating outside relative humidity for Formulation A. Solid line is external humidity given by Eqn. 21; dashed line is predicted relative humidity inside package.

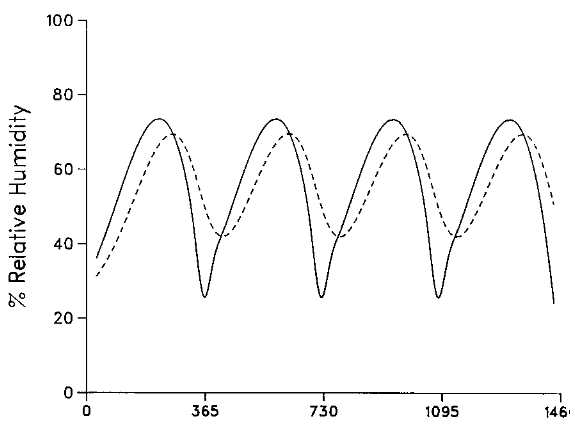

Fig. 11. Predicted relative humidity inside a PCTFE laminated blister package with oscillating outside relative humidity for a formulation with 1/4 the moisture capacity of Formulation A. Solid line is external humidity given by Eqn. 21; dashed line is predicted relative humidity inside package.

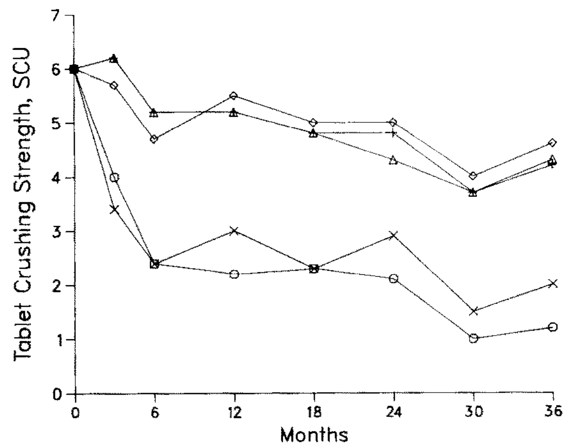

Fig. 12. Variation in tablet crushing strength of Formulation C as a function of time for tablets stored in PVC blister packages; ○, Puerto Rico; △, Mexico; +, Japan; ×, Indonesia; ◇, England.

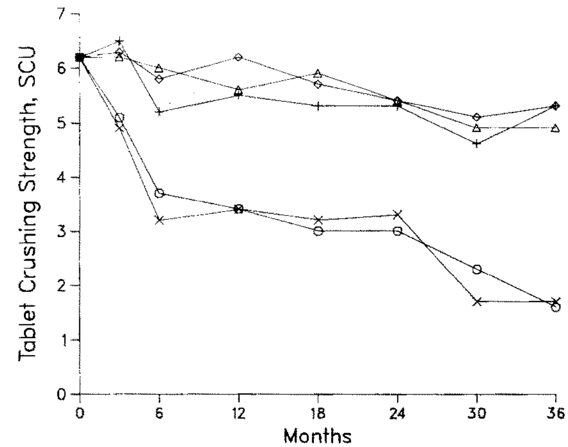

Fig. 13. Variation in tablet crushing strength of Formulation C as a function of time for tablets stored in PCTFE laminated blister packages: ○, Puerto Rico; △, Mexico; +, Japan; ×, Indonesia; ◇, England.

tion in relative humidity inside the package is more dramatic than is seen in Fig. 10. The profile in PVC blisters would deviate only slightly from that seen in Fig. 9. For this hypothetical case the PCTFE laminate may offer no substantial improvement in protection. Clearly package permeability and dosage form moisture characteristics must be considered together in choosing a suitable package material.

The results of a 3-year field study using Formulation C are shown in Figs. 12 and 13 for tablets stored in PVC and PCTFE laminated packaging. One can see a periodic oscillation in the crushing strength of the tablets in both types of packaging. Once again, the PCTFE laminate offers somewhat better protection than the PVC. The crushing strength is frequently about 1 SCU greater for tablets in the PCTFE laminated package. Also of interest is the fact that two of the most humid locations (Puerto Rico and Indonesia) show substantial reductions in crushing strength compared to the other locations. Furthermore, there is an overall continual decrease in crushing strength at all locations. This suggests that, as tablets are exposed to oscillating humidity, changes in crushing strength may not be completely reversible – leading to an overall drop in crushing strength with time.

To investigate the effect of oscillating relative humidity on the crushing strength of Formulation C, unprotected tablets were oscillated between 30% and 70% RH at room temperature every 2–3 days. The results are shown in Fig. 14. Oscillating between 30% and 70% relative humidity was done since these conditions were predicted to be challenging yet reasonable conditions for Formulation C tablets stored in PVC blister packages. A pattern representative of that seen for tablets stored in Puerto Rico and Indonesia was observed. There was some oscillation of crushing strength and a

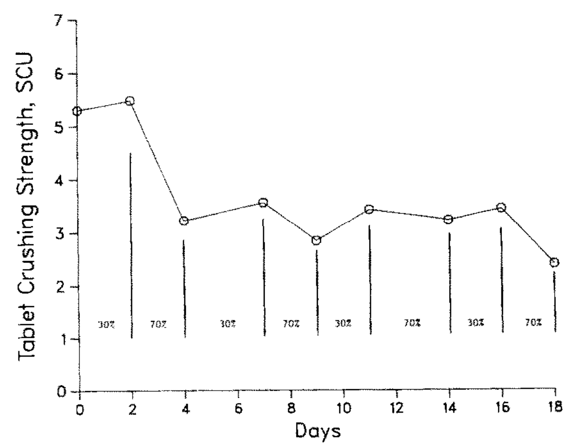

Fig. 14. Changes in the crushing strength of unprotected Formulation C tablets as a function of time and exposed to oscillating relative humidity conditions.

general trend toward decreasing hardness. A limiting value of the crushing strength of approximately 2–3 SCU was obtained in the accelerated conditions and a similar value was seen in the field study. Humidity variations between 45% and 65% RH were predicted for these tablets in PCTFE laminated packages and, in general, tablets in this type of package showed less of a drop in crushing strength.

Conclusions

This study has demonstrated that the tablet moisture sensitivity of compressed tablets can be characterized in approximately one week by storing unprotected tablets at several relative humidities. Using the simple physical model described here, this information, in combination with package moisture permeability information, permits changes in tablet crushing strength to be predicted under a variety of storage and packaging conditions. These predictions are useful in establishing long-term stability testing protocols and also in predicting what tablets stored in blister packages might reasonably be expected to experience in the market place where short-term and long-term oscillating conditions are likely to occur. Theoretical predictions based on the physical model indicate that tablets stored in relatively permeable, PVC blister packages can be expected to experience humidities between 30% and 70% RH. Accelerated testing under these conditions using tablets not protected by packaging materials yielded results consistent with those obtained from a 3-year field study. Tablets in less permeable PCTFE laminated packages are predicted to experience smaller variations and smaller changes in tablet crushing strength. These results suggest that meaningful accelerated testing conditions can be predicted using a simple physical model. It is possible to match the dosage formulation characteristics to the package material and testing conditions. In this way, a more rational selection of packaging material and testing protocols can be made.

References

Kentala, M.D., Lockhart, H.E., Giacin, J.R. and Adams, R., Computer-aided simulation of quality degradation of oral solid drugs following repackaging. *Pharm. Technol.*, 6 (1982)46, 48, 50, 52–53.

Mizrahi, S., Labuza, T.P. and Karel, M., Computer-aided predictions of extent of browning in dehydrated cabbage. *J. Food Sci.*, 35 (1970) 799–803.

Nakabayashi, K., Shimamoto, T. and Mima, H., Stability of packaged solid dosage forms. I. Shelf-life predictions for packaged tablets liable to moisture damage. *Chem. Pharm. Bull.*, 28 (1980a) 1090–1098.

Nakabayashi, K., Shimamoto, T. and Mima, H., Stability of packaged solid dosage forms. II. Shelf-life predictions for packaged sugar-coated tablets liable to moisture and heat damage. *Chem. Pharm. Bull.*, 28 (1980b) 1099–1106.

Nyqvist, H. and Lundgren, P., Studies on the physical properties of tablets and tablet excipients. *Acta Pharm. Suec.*, 19 (1982) 401–412.

Reamer, J.T., Grady, L.T., Shangraw, R.F. and Mehta, A.M., Moisture permeation of typical unit dose repackaging materials. *Am. J. Hosp. Pharm.*, 34 (1977) 35–42.

U.S. Department of Commerce, NOAA, *Local Climatological Data, Monthly Summary for New Orleans*, LA (1980).

Veillard, M., Bentejac, R., Duchene, D. and Carstensen, J.T., Moisture transfer tests in blister package testing. *Drug Dev. Ind. Pharm.*, 5 (1979) 227–244.