Dissolution Shelf Life of Packaged Pharmaceutical Tablet by Prediction and Experiment

Jurmkwan Sangsuwan[1*] and Hugh E. Lockhart[2]

[1] *Department of Packaging Technology, Faculty of Agro-Industry, Chiang Mai University, Chiang Mai 50200, Thailand*

[2] *School of Packaging, Michigan State University, East Lansing, Michigan 48824, USA*

*Corresponding author. E-mail: jurmkwan@chiangmai.ac.th

ABSTRACT

This research was designed to find a way to estimate shelf life of packaged pharmaceutical tablets by using package permeation and dissolution as a function of moisture content and storage time. Shelf life was estimated by the amount of time required for the moisture content of the pharmaceutical product to increase until it reached an arbitrarily-selected critical moisture content (permeation time) plus the time that the product could tolerate that storage condition (exposure time) in an open dish study. Permeation time can be calculated by using information from a sorption isotherm for the product, WVTR of the package and other parameters, including product dry weight, storage conditions, initial and critical moisture content.

In this study, prednisone, a moisture-sensitive uncoated tablet, was stored in an open dish at 75%RH at 25°, 30° and 40°C to determine exposure time. To prove the validity of the calculation, the actual permeation time was determined by measuring the moisture content of prednisone packaged in PVC and PVC/0.6 mil Aclar blisters at certain intervals. The calculation provided an error of less than 10%. Therefore, this calculation is useful to select candidate packaging materials that provide enough moisture barrier to a product for the stability test. The actual dissolution shelf life was arbitrarily chosen by using as the failure point a 10% reduction in dissolution. When the predicted shelf life and the actual shelf life were compared, the predicted shelf life was from 8 to 44 percent less than the experimental result.

Key words : Dissolution, Shelf Life, Prednisone, Blister

INTRODUCTION

The shelf life of a drug is the time lapse from manufacturing to the specified expiration date during which the characteristics of the drug product will remain within the approved specifications (Chow and Shao, 1991; USP 23 <1151>). Certain physical properties that can cause failure are appearance, palatability, uniformity and suspendability (USP <1191>). Acceptability in appearance, (for example, turning yellow in tablets, stickiness in capsules or cracking in coated tablets) can be determined easily by visual or tactile means. Failure to meet these limits can result in recall of the product (Murthy and Ghebre-Sellassie, 1993). Dissolution is another physical property that is listed as a criterion for acceptable levels of stability in the monograph for every drug product listed in the United States Pharmacopoeia (USP).

In many researches, dissolution has been found to be susceptible to change (loss of ability to dissolve) during storage (Nakabayashi et al., 1981; Chowhan, 1994; Qian, 1996;

Wu, 1996; Kokitkar, 1997; Rohrs et al., 1999; Thomas, 2000; Yoon, 2000). Failure to meet the monograph dissolution requirement during, or at the end of a stability test, can result in failure to win approval of an NDA. Such failure can result in recall of an approved drug from the market.

The shelf life of a marketed drug depends on product properties, package properties and storage conditions. Shelf life of a pharmaceutical product, determined by stability testing, is expensive and time-consuming. Faster, less expensive ways to qualify a drug or its packaging are desireable.

Another way to study the dissolution shelf life of a pharmaceutical product is prediction or calculation by mathematical model (Thomas, 2000; Yoon, 2000). The model will take into account moisture content of product, permeability of package and dissolution change with change in moisture content (Qian, 1996; Wu, 1996; Kokitkar, 1997; Thomas, 2000; Yoon, 2000). The model can be represented by a computer program (Yoon, 2000) which is a tool to provide convenient calculation of (1) shelf life in a given package and (2) the barrier package required to attain a specified shelf life. The computer program is based on equation sets that include equations for permeation of packages and the moisture equilibrium isotherm for the product.

Although prediction of the shelf life of the pharmaceutical product by these equation sets cannot be used in place of stability testing, this prediction is very useful for calculating the barrier required to achieve a desired shelf life. Then the shelf life can be achieved by selecting the appropriate packaging material. Study of the product in it's package can be done in this way to minimize the trial-and-error process in package selection. The choice of barrier is then confirmed using the stability test.

Dissolution behavior of a drug product is studied using an open dish method. Product is placed in a dish that is not covered, and exposed to a test environment of some specified temperature and relative humidity. Product will absorb moisture until it reaches equilibrium with the environment in which it is stored. Many researchers have reported that the dissolution is affected by moisture content (Taborsky-Urdinola et al., 1981; Akbuga et al., 1984; Rohrs et al., 1999; Thomas, 2000; Yoon, 2000).

Furthermore, a product in an open dish may meet the dissolution requirements for some time after its moisture content reaches equilibrium with the test environment, then begin to lose ability to dissolve - i.e., dissolution decreases. (Kokitkar, 1997; Thomas, 2000). Therefore, the open dish method can tell us how long the product can tolerate a specific condition after the moisture content reaches equilibrium at some humidity and moisture content level.

Barrier packages, when used for drugs, limit the inflow of water vapor to the product, thus limiting the uptake of moisture and keeping the moisture content of the product low. Under these conditions, the moisture content of a packaged product will take longer to reach any level than would the product in open dish.

The purpose of this work was to test the hypothesis that shelf life can be estimated on the basis of package permeation, product moisture isotherm and dissolution behavior of the product. This approach involves two parts: (1) determine the time for the product to reach a "critical" moisture content for dissolution failure and (2) determine the time from reaching that moisture content to dissolution failure.

MATERIALS

1. Prednisone, 5 mg, from Upjohn Lot 92DUW, Exp. 10/2004
2. Saturated salt solutions for 13, 34, 51, 75, 80, 96%RH
3. Blister packaging fabricated from

- 7.5 mil Polyvinyl chloride (PVC) film Lot#EA901
- Lamination of 0.6 mil Aclar RX 160/2 mil Polyetheylene/7.5 mil Pentapharm clear PVC Lot#EA886
- Lidding: 0.8 mil foil/1.2#C133/3.5# C11551 heat-seal coating

4. Molecular sieve desiccant tablets for permeation

EQUIPMENT

1. Temperature-controlled environmental chambers at 25°, 30° and 40°C
2. Closed polyethylene buckets to provide six storage environments
3. Humidity sensors (Newport Scientific Inc., accuracy ± (1%)
4. Metrohm Karl Fischer Titrator with Brinkman Polytron® Homogenizer (720 KFS Titrino, 703 Ti Stand)
5. Dissolution apparatus (Vankel VK6010)
6. UV/VIS spectrophotometer (Lambda 20, Perkin Elmer Corporation)
7. Computer program "Shelf life 2000" developed by Seung-yil Yoon, School of Packaging, Michigan State University

METHODS

Determination of Moisture Sorption Isotherms of Prednisone at 25°, 30° and 40°C.

Prednisone tablets were weighed before storage in six relative humidities and reweighed after storage for a period of time until no change in weight. The initial moisture content (IMC) was determined by Metrohm Karl Fischer Titrator with Brinkman Polytron® Homogenizer. The Equilibrium Moisture Content (EMC) was determined by using equation (1).

$$\%EMC = \left\{ \left[\frac{Wf}{Wi}(1+IMC) \right] - 1 \right\} x\ 100 \qquad (1)$$

Where, Wf = final weight of the samples, g
Wi = initial weight of the samples, g
IMC = initial moisture content of the samples, g water/ g dry product

Determination of WVTR for Materials Selected

PVC and PVC/0.6 mil Aclar were selected to form blister packaging for this experiment because they would provide convenient time periods for permeation of moisture into the blister cavity until moisture content of tablets reached the critical moisture content. From experience, we know that the PVC is poor barrier while PVC/0.6 mil Aclar is better.

Water Vapor Transmission Rate (WVTR) of Blister Packaging was determined according to USP <671> Container Permeation for Single-Unit Containers and Unit-Dose Containers for Capsules and Tablets, with certain changes, as follow. Two types of blister packaging were filled with molecular sieve tablets and sealed at the Packaging Laboratory, Eli Lilly. Empty blister packs were used as blanks. Packages were stored at 25°C, 30°C and 40°C at 75%RH. The weight gained was measured at the following time intervals: every day for PVC@25° and 30°C; every 12 hours for PVC@40°C and every 3 days for PVC/0.6 mil Aclar at all 3 temperatures. The slope of weight gain versus time plot can be used to calculate WVTR in gram/day•package. This WVTR can be used to calculate P' which will be used to calculate time, t, by equation (2).

Calculation Barrier Permeation (P') Required to Provide the Specific Time to Achieve Critical Moisture Content

$$t = \frac{W_D \beta}{P' ps} \ln \left[\frac{Aw_0 - Aw_{t=0}}{Aw_0 - Aw_{t=t}} \right] \quad (2)$$

Where, t = Time during which the product in the package gains moisture until it reaches equilibrium

W_D = Product dry weight, grams
β = Slope of sorption isotherm
p_s = Saturation partial pressure, mmHg
Aw_0 = Water activity of storage condition = $\frac{RH_0}{100}$
RH_0 = Relative humidity of storage condition
$Aw_{t=0}$ = Water activity of product when it is fresh
$Aw_{t=t}$ = Water activity of product at the critical moisture content.

Table 1 shows the comparison between calculated from 2.2 and actual from 2.1. The actual must be no greater than the required. An actual less than required is preferred.

Table 1. Comparison of Required Calculated and of Material Chosen.

Time to achieve 6% moisture content (equilibrium)	Temperature	P' Required, g/day. mmHg•package	Actual P' of PVC/0.6 mil Aclar, g/day. mmHg•package
65 days	25°C	3.2061E-06	3.115E-06
20 days	30°C	9.1615E-06	7.1208E-06
9 days	40°C	6.5856E-06	6.736E-06

Determination of Moisture Content

By Metrohm Karl Fischer Titrator with Brinkman Polytron(Homogenizer

Determination of Dissolution

The dissolution test was performed according to USP <711>Dissolution and Official monographs of prednisone.

RESULTS AND DISCUSSION

Sorption Isotherm of Prednisone at 25°, 30° and 40°C

In general, the sorption isotherm at higher temperature lies below that of the lower temperature because the water holding capacity decreases as temperature increases. However, in Figure 1, sorption isotherms of prednisone at the three temperatures appeared not to be separated from each other, but this was a result of the vertical scale used. The water holding capacities of prednisone at 25°, 30° and 40°C tended to be lower with increasing temperature, but the differences may be negligible.

Figure 1 shows the shape of the whole isotherms of prednisone from the relative humidity of 13% up to almost 100% at 25°, 30° and 40°C. Because the failure of prednisone was at 75% relative humidity, it was unnecessary to utilize the whole isotherm. The regions of 13% to 80% relative humidity in the sorption isotherms were of interest because the initial points and critical points were within this range. The useful regions of sorption isotherms of

prednisone at three temperatures were straight lines. Therefore, the linear model or equation (2) was appropriate to be used to calculate the time to reach equilibrium moisture content, t.

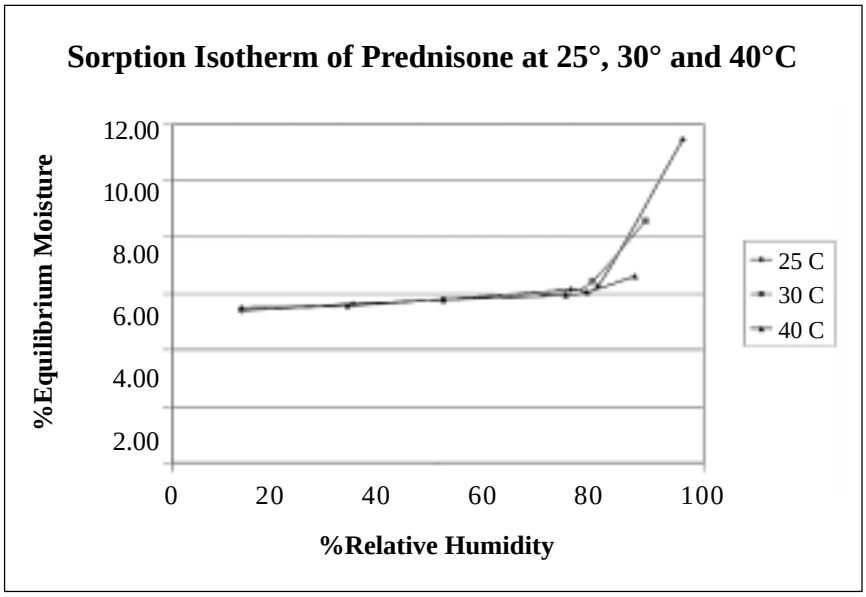


Figure 1. Sorption Isotherm of Prednisone at 25°, 30° and 40°C.

Figures 2 shows linear trend line and its equation of isotherms at 25°C. Percent relative humidity could be predicted from % moisture content. Since the initial moisture content in dry basis of fresh prednisone was 5.45%, the relative humidity of prednisone inside the bottle was 19% at 25°C. Because the isotherms were so close, the relative humidity inside the bottle was probably around 19% throughout this range of temperature.

The equilibrium moisture content of prednisone at 75%RH was 6.15%, 6.04% and 5.94% at 25°, 30° and 40°C respectively. Since the difference of initial and equilibrium moisture content was small (less than 1%), the time it took to achieve equilibrium moisture content, t, was short.

The slope of each sorption isotherm was necessary to calculate the time needed to achieve equilibrium moisture content, t, for each storage condition.

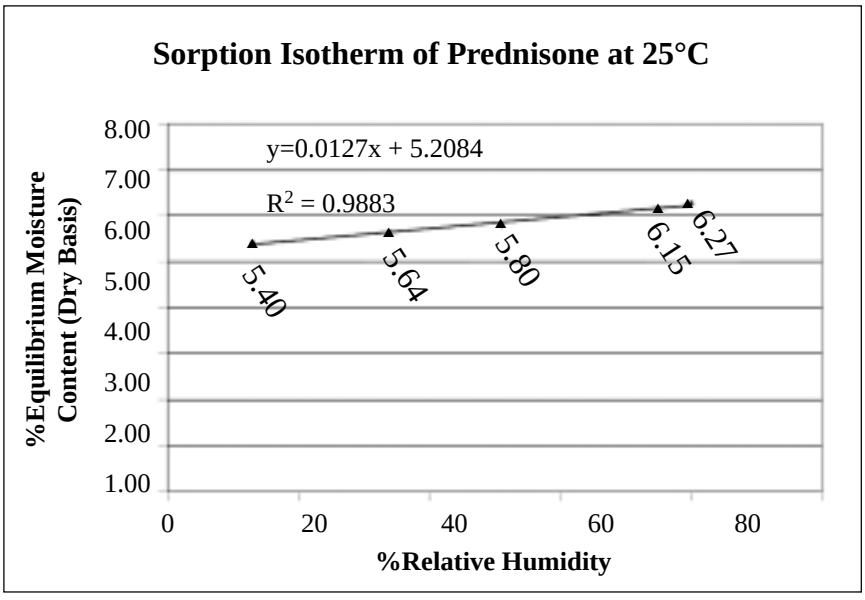


Figure 2. Sorption Isotherm of Prednisone at 25°C.

Water Vapor Transmission Rate (WVTR) Determination

Table 2 shows WVTR and the permeance of each cavity of PVC and PVC/0.6 mil Aclar blister. The values in these tables will be used to calculate the time required to achieve equilibrium moisture content, t.

The higher the WVTR, the less the time to reach equilibrium moisture content and the shorter the shelf life. PVC/0.6 mil Aclar has low WVTR compared with PVC at all 3 temperatures. This means Aclar allowed permeation of water at a slower rate than PVC. As a result, it provided better protection to the prednisone than PVC.

Table 2. Water Vapor Transmission Rate (WVTR) and Permeance () of PVC and PVC/0.6 mil Aclar Blister Cavity.

Blisters	Temperature	WVTR (g/day•cavity)	P' (g/day•cavity•mmHg)
PVC	25°C	1.1489E-3	6.4483E-5
	30°C	1.5787E-3	6.6143E-5
	40°C	2.5900E-3	6.2420E-5
PVC/0.6 mil Aclar	25°C	5.5515E-5	3.1158E-6
	30°C	1.6996E-4	7.1208E-6
	40°C	2.8064E-4	6.736E-6

Moisture Content

Initial Moisture Content

Initial moisture content is the moisture content of tablets fresh from the bottle. It shows the initial condition of the product. Relative humidity inside the bottle, which is necessary to calculate the time required to achieve equilibrium moisture content, can be determined by projecting from the initial moisture content in the isotherm. Karl Fisher equipment reports the percent of moisture content in wet basis which is 5.17±0.104. It is necessary to convert to moisture content in dry basis, 5.45±0.114, to be compatible with the result of equilibrium moisture content in the sorption isotherm.

Moisture Content of Prednisone in Open Dish, PVC and PVC/0.6 mil Aclar Blister

In Table 3, the moisture content of prednisone in the open dish achieved equilibrium within a day. Times to achieve equilibrium moisture content of prednisone packaged in PVC/0.6 mil Aclar were longer than those in PVC at the same temperature. Therefore, the higher the barrier of packaging material, the longer time to reach equilibrium moisture content at the same storage condition. Regardless of the packaging material, as the temperature increased, the time to reach equilibrium decreased.

Table 3. Time to Achieve Equilibrium Moisture Content of Prednisone from the Experiment.

Temperature	25°C	30°C	40°C
Open dish	1 day	1 day	1 day
PVC	3 days	2 days	1 day
PVC/0.6 mil Aclar	65 days	20 days	9 days

Dissolution

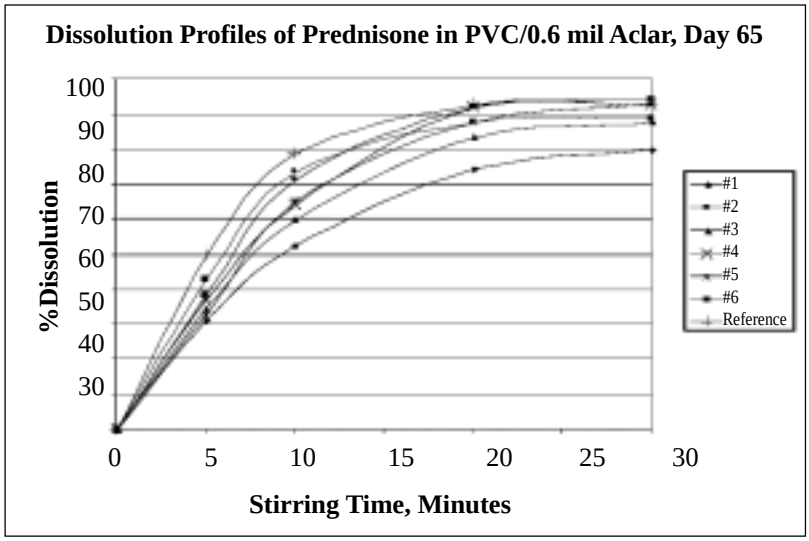
Dissolution Profiles of Prednisone Fresh from the Bottle

The dissolution profile shows the dissolution characteristic of an individual product. Profile changes under the conditions of heat, moisture and aging.

The average dissolution value of the prednisone fresh from the bottle at 30 minutes was 93.0%. The standard deviation of dissolution value at 30 minute stirring time of six tablets was 0.972.

Dissolution Profiles of Prednisone after Aging

Dissolution of prednisone changed considerably after aging at all storage conditions. As time passed, the dissolution curve shifted well below that of fresh prednisone. Even though the tablets meet the monograph requirement of 80% dissolution at 30 minutes stirring time, the profile has moved steadily downward. Profiles of prednisone packaged in PVC and PVC/0.6 mil Aclar shifted in the same way as those in open dish. Figure 3 shows dissolution profiles of prednisone tablets in PVC/0.6 mil Aclar stored at 25°C, 75%RH at day 65. Compared with the profiles of 6 tablets of prednisone fresh from the bottle, the gaps between profiles of six tablets at day 65 were wider than the closely-packed profiles of fresh prednisone. Therefore, the variability of profiles which become greater as time went on was an early warning of deterioration of tablets, so increased standard deviation can be used as an early warning indication.



Note: Reference profile is an average profile of 6 tablets of prednisone fresh from the bottle.

Figure 3. Dissolution Profiles of Prednisone in PVC/0.6 mil Aclar after Storage at 25°C, Day 65.

Failure of Prednisone

According to its USP monograph, prednisone that dissolves less than 80% at 30 minutes stirring time is unacceptable. In order to detect the failure point as early as possible, a 10% reduction in dissolution was designated to be a failure point for this research. For this prednisone product, a dissolution at 10% decrease from initial dissolution was 93.0 x 0.90 = 83.7%. At each time interval, six tablets of prednisone were sampled to measure the dissolution. If one or more tablets dissolved less than 83.7%, this indicated the dissolution failure. Table 4 summarizes the first day that failure was found after storage. The deterioration or 10% change in dissolution of prednisone at all three temperatures can be found earlier in open dish than that in PVC and PVC/0.6 mil Aclar because of the protection provided by the package. Since PVC/0.6 mil Aclar provided better moisture protection than PVC, the failure of prednisone packaged in PVC/0.6 mil Aclar occured later than that in PVC. Prednisone in open dish at 30°C failed earlier than that at 40°C because not only heat causes the failure of prednisone but also moisture content. Moisture content of the tablets at 30°C is higher than at 40°C. Therefore, the combination of heat and moisture content might have caused the prednisone stored at 30°C to fail earlier than at 40°C. This was also found in aspirin tablets in a previous study; first dissolution failure of aspirin found on day 45 at 30°C but not until day 75 at 40°C (Adams, 1998).

Table 4. The First Day that Failure was Found.

Prednisone in	The first day that failure was found		
	25°C	30°C	40°C
Open dish	30	12	18
PVC blister	38	25	24
PVC/0.6 mil Aclar blister	65	37	32

Verification of Calculation

Moisture Content

Table 5 shows the results of using equation (2) to predict the time to achieve equilibrium moisture content. Predicted moisture contents were compared with the actual moisture contents of the prednisone tablets from the experiment. The only difference between actual and predicted time to achieve equilibrium moisture content was found in prednisone packaged in PVC/0.6 mil Aclar and stored at 30°C which was 20 days instead of 22, less than 10% difference.

Table 5. Time to Achieve Equilibrium Moisture Content of Prednisone by Prediction and Experiment.

Packaging	Storage Condition	Prediction	Experiment
PVC	25°C	3 days	3 days
	30°C	2 days	2 days
	40°C	1 day	1 day
PVC/0.6 mil Aclar	25°C	65 days	65 days
	30°C	22 days	20 days
	40°C	9 days	9 days

Shelf Life

Table 6 shows the predicted shelf life or failure time resulting from calculation of permeation time plus exposure time. Exposure time is the time required to produce 10% change in dissolution of prednisone as found in the open dish study. Predicted failure times were less than the actual failure times for prednisone packaged in PVC stored at all 3 temperatures and PVC/0.6 mil Aclar at 30° and 40°C. Therefore, it was safe to use this prediction for the packaging that provided low barrier. For higher barrier packaging, the time to achieve the equilibrium moisture content was long. The permeation time shown in Table 6 of prednisone packaged in PVC/0.6 mil Aclar was 65 days. The mechanism of failure was in fact operating before equilibrium moisture content was established.

Table 6. Shelf life by Prediction and Experiment by Using a 10% Decrease in Dissolution as a Critical Point.

Blister Packaging	Storage Condition	Permeation time, day	Exposure time, day	Predicted failure time, day	Actual failure time, day
PVC	25°C	3	30	33	38
	30°C	2	12	14	25
	40°C	1	18	19	24
PVC/0.6 mil Aclar	25°C	65	30	95	65
	30°C	22	12	34	37
	40°C	9	18	27	32

Since the experiment was continued after the 10% change in dissolution had been found, we have an additional result of failure by using the dissolution of less than 80%, according to individual monograph of prednisone, as a failure point. The validity of prediction agreed with that using a 10% change in dissolution as a failure point. The prediction reasonably and correctly predicted the failure of prednisone packaged in PVC. Prednisone in PVC/0.6 mil Aclar failed earlier at 25°C than predicted using both criteria as the failure points. Failure at the other two temperatures was about the same as or later than predicted.

CONCLUSION

Since the difference of initial and critical moisture content of prednisone was small (less than 1%), the time it took to achieve equilibrium moisture content was short. PVC did not provide enough moisture protection to a moisture-sensitive tablet such as prednisone which has a narrow range of initial and critical moisture content. However, PVC might be suitable for other products which have a broad range of initial and critical moisture content. Equation (2) reasonably and accurately predicted the time it took to achieve equilibrium moisture content with an error less than 10%. It is useful to apply this equation in order to select the packaging material that provides an adequate moisture barrier for pharmaceutical products.

Dissolution decreased as temperature increased or storage time passed. In order to use this testing and calculation for finding packaging for drugs, we needed to consider that the shelf life ended when there was an important change, not necessarily the complete failure of the drug. The critical point for the drug occurred sooner than actual failure. It was appro-

priate to show specific changes such as high standard deviation, greater variability of dissolution profiles or a 10% change from initial dissolution, which is 83.7%, to indicate the failure.

The hypothesis predicted correctly the shelf life of prednisone packaged in low barrier packaging such as PVC that provided a short permeation time. For prednisone packaged in PVC/0.6 mil Aclar and stored at 25°C, the experimental shelf life was shorter than the predicted one. Because the permeation time was a long term, dissolution deterioration may have begun before tablets even reached equilibrium moisture content; permeation was slow enough to lag behind the dissolution rate change. However, the permeation times at higher temperature (30° and 40°C) were shorter, this caused the predicted shelf life of prednisone packaged in PVC/0.6 mil Aclar to be acceptable.

However, the prediction is useful to avoid a costly trial-and-error process to select the barrier for the stability test. A barrier that provides a calculated shelf life less than the desired shelf life can be removed from consideration as a barrier package for stability test.

REFERENCES

Adams, S.P. 1998. Dissolution shelf life of hydroxypropyl methyl cellulose coated aspirin tablets at I.C.H. temperatures and various relative humidities. M.S. Thesis, Michigan State University.

Akbuga, J., A. Ari-Ulubelen, and G. Bayraktar-Alpmen. 1984. Effect of relative humidity on drug release from Phenytoin sodium tablets and capsules. Pharmazie 39:560–561.

Chowhan, Z.T. 1994. Factors affecting dissolution of drugs and their stability upon aging in solid dosage form. Pharmaceutical Technology 18:60–73.

Chow, S.C., and J. Shao. 1991. Estimating drug shelf-life with random batches. Biometrics 47:1071–1079.

Kokitkar, M.P. 1997. Prediction of shelf life of a moisture sensitive drug at high relative humidity and temperature using dissolution as a function of moisture content. M.S. Thesis, Michigan State University.

Murthy, K.S., and I. Ghebre-Sellassie. 1993. Current perspectives on the dissolution stability of solid oral dosage forms. J. Pharm. Sci., 82(2):113–126, February.

Nakabayashi, K., T. Shimamoto, H. Mima, and J. Okada. 1981. Stability of packaged solid dosage forms. V. Prediction of the effect of aging on the disintegration of packaged tablets influenced by moisture and heat. Chem. Pharm. Bull. 29(7):2051–2056.

Qian, X. 1996. Dissolution stability for packaging application. M.S. Thesis, Michigan State University.

Rohrs, B.R., T.J. Thamann, P. Gao, D.J. Stelzer, M.S. Bergren, and R.S. Chao. 1999. Tablet dissolution affected by a moisture mediated solid-state interaction between drug and disintegrant. Pharmaceutical Research 16(12):1850–1856.

Suemag, J. 2001. Dissolution shelf life of packaged pharmaceutical tablets by prediction and experiment. M. S. Thesis, Michigan State University.

Taborsky-Urdinola, C.J., V.A. Gray, and L.T. Grady. 1981. Effects of packaging on the dissolution of model prednisone tablets. American Society of Hospital Pharmacists 38:1322–1327.

Thomas, M. 2000. Dissolution shelf life of prednisone theraputic dosage form tablet. M.S. Thesis, Michigan State University.

U.S. Pharmacopeia-NF, USP 23<671> Containers-Permeation: Single-Unit containers and Unit-Dose containers for capsules and tablets, p. 1788. (1995).

U.S. Pharmacopeia-NF, USP 23<711> Dissolution, p. 1791. (1995).

U.S. Pharmacopeia-NF, USP 23<1151> Pharmaceutical dosage form, p. 1940. (1995).
U.S. Pharmacopeia-NF, USP 23<1191> Stability considerations in dispensing practice, p. 1957. (1995).
Wu, S. 1996. Dissolution shelf life of unpackaged solid oral drug products. M.S. Thesis, Michigan State University.
Yoon, S. 2000. Shelf life estimation of USP 10 mg prednisone calibrator tablets in relation to dissolution. M.S. Thesis, Michigan State University.
Yoon, S. 2000. Shelf Life 2000 Computer Program. Michigan State University.