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SHELF LIFE ESTIMATION OF USP 10mg PREDNISONE CALIBRATOR TABLETS IN RELATION TO DISSOLUTION & NEW WINDOWS-BASED SHELF LIFE COMPUTER PROGRAM

presented by

SEUNG-YIL YOON

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&
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By

Seung-yil Yoon

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ABSTRACT

SHELF LIFE ESTIMATION OF USP 10mg PREDNISONE CALIBRATOR TABLETS IN RELATION TO DISSOLUTION
&
NEW WINDOWS BASED SHELF LIFE COMPUTER PROGRAM

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Dissolution is a critical parameter in determining the performance and defining quality control, regulatory compliance, and bioavailability of solid oral drug products. The US Food and Drug Administration (FDA) requires that any drug product on the market must at all times meet the requirements of the USP monograph. Otherwise, it will be recalled from the market. The monograph specifies dissolution requirements. Uncoated USP 10mg Prednisone calibrator tablets were used for dissolution shelf life estimation based on an open dish study. The tablets were stored in open dishes for 90 days at three different temperatures (25, 30, 40 °C) and five different relative humidities (50, 65, 75, 80, 90% RH). Dissolution and moisture content were measured at planned intervals. The resulting data were used to estimate dissolution failure in a variety of packages stored in 92% RH at 25, 30, and 40 °C. The same data were also used to select the barrier packages required to achieve a desired shelf life (expiration date) at the same conditions.

The Windows based shelf life computer program was used to estimate the shelf life. This program enabled computation of a barrier package requirement or an expiration date with a few keystrokes.

DEDICATION

This thesis is dedicated to my wife Youngmi Shin, my family, and my friends.

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I would like to thank Dr. H.E. Lockhart for his guidance and patience in this research. He taught me how important to write the thesis and made me cheer up always. I am also grateful to thank Dr. S. Selke and Dr. Gililland for their prompt and thoughtful discussion of this thesis. I can't imagine how many times they read my thesis. Also, I want to thank my lab partners M. Thomas and S. Adams.

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INTRODUCTION

Dissolution is one of the criteria for acceptable levels of stability, and it is used to decide the failure point of solid oral drug products. It has been accepted by the United States Pharmacopeial Convention (USPC) as a measure of bioavailability and as a stability-indicating parameter for solid oral drug products. The US Food and Drug Administration (FDA) requires that all drug products on the market must at all times meet the requirements of the United States Pharmacopeia (USP) monograph, including dissolution for solid oral drug products. Otherwise, they will be recalled from the market. Every year, 8 to 16 solid oral drug products are recalled for dissolution failure as reported by USPC in its publication USP DI (Drug Information).

When solid oral drug products are exposed to high humidities at high temperatures, the dissolution can be reduced substantially. Open dish exposure at such conditions causes greater dissolution reduction than the accelerated testing that is done with tablets in a package. Packages for drug products serve as barriers to moisture transfer, and thus they protect from the deleterious effect of high humidities. The lower the moisture permeability of the package, the smaller the effect of high humidity on dissolution, and the longer the dissolution shelf life of the drug product will be.

Every solid oral drug product on the market has an expiration date in its particular package, such as a glass bottle, plastic bottle, or blister package. To determine the expiration date before the product is introduced to the market place, the FDA requires that the manufacturer must do stability testing. The product is placed in a simulated market storage condition in the particular package which will be on the market.

Today, a wide variety of packaging materials are available for drug products. If the product fails in too short a time with a particular package, the stability testing must be done again with another package. The cost to stability test every material with every product is prohibitive. In practice, of course, drug products are put on stability test in a variety of packages simultaneously, rather than waiting for a single package to fail. Since all of these packaged drugs must be sampled, observed, and tested at every time interval, the cost of stability testing can be in the millions of dollars. Also, the product might be overpackaged with an expensive high barrier package. Therefore, the manufacturers need an estimation technique for stability testing.

Most companies use accelerated testing as an estimation technique. In this procedure, the product is stored at 40±2°C, 75±5% RH for 6 months in the intended market package. At the same time products are placed in this accelerated condition, they are also stored at an intermediate condition (30±2°C, 60±5% RH), and a representative market condition (25±2°C, 60±5% RH) known as long term testing. If products fail accelerated testing, data from the first six months of intermediate testing may be submitted in place of the failed accelerated testing data. The rate of chemical change is estimated and translated into expiration dates at various storage conditions. However, there is no mathematical or predictive relationship among accelerated testing, intermediate testing, and actual condition testing for any product parameter other than chemical change. Therefore, new estimation techniques are highly desirable to minimize experimentation in the stability test.

One such technique would be to use open dish testing to determine dissolution behavior. Dissolution is a stability indicating physical characteristic that seems to be

measurable and predictable, but not by the Arrhenius relationship. This open dish data could then be combined with package permeability data to enable the selection of the correct barrier package for the product in its market.

In the open dish method, unlike the accelerated testing which is done with the combination of product, package, and environmental condition, the product and package are tested separately. First, the product is stored in an open dish at some set of conditions and tested to find the critical dissolution points. Second, the permeability of the package is measured. Finally, the results of product and package testing are used in a shelf life prediction model to estimate the shelf life, or to estimate the barrier required to achieve a desired shelf life. The shelf life of drug products can be estimated easily for any storage condition and known permeability constant for the package by using the open dish method if there are open dish data for the product at those conditions. Since 1994, research at the School of Packaging has focused on using this method to select barrier packages and to estimate product dissolution shelf life.

A new user-friendly Windows based shelf life program has been developed for the purposes of time saving, and ease of use in a variety of applications. This program is described in Appendix C. The open dish method and the Windows based shelf life computer program will be useful in providing an effective way for the industry to select packages with good barrier and low cost for stability testing.

The main objectives of this study are to estimate the shelf life of USP 10mg Prednisone calibrator tablets by the following steps:

1. Find the critical dissolution points of USP 10mg Prednisone calibrator tablets under various storage conditions by using the open dish method.
2. Determine the permeability constant for one or more packages by experiment or from literature values.
3. Estimate the shelf life of USP 10mg Prednisone calibrator tablets in packages using the Windows based shelf life program.
4. Estimate the barrier required to achieve a particular shelf life for USP 10mg Prednisone calibrator tablets using the Windows based shelf life program.

CHAPTER 1

LITERATURE REVIEW

1.1 Shelf Life Prediction

Not many years ago, the appropriate packaging of pharmaceuticals involved nothing more than carrying out stability testing in the desired package. The package was viewed as relatively inert and hence received little attention. However, this situation has changed with new drug regulations, an increasing variety of drug products, and the development of improved packaging materials. Today, drug manufacturers must be aware of a wide range of packaging issues that relate to the stability of drug products (Liebe, 1990).

Liebe also summarizes as follows: every drug product requires stability testing in order to establish an expiration date. The traditional method of simply carrying out stability testing on combinations of package and product variables is far too costly and time consuming in today's marketplace. Therefore, it is essential to find the most cost-effective package as quickly as possible, in order that applicable stability testing begin at the earliest stage of a product. The objective of package stability testing is to match package performance with needed protection using cost-effective package materials.

To find the most cost-effective package in the shortest time, manufacturers need an estimation technique. There are two different approaches to finding the most cost-effective package. One is accelerated testing in the package which is used in most of companies and the other is the open dish method which is done at Michigan State University.

1.1.1 Stability Testing with Packaged Products

Every drug product must undergo stability testing to be sold on the market place. It is required by the US Food and Drug Administration (FDA) for determination of expiration dates. In the Code of Federal Regulations 21 CFR 211.166, the FDA says:

"There will be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine proper storage conditions and expiration dates. The written program shall be followed and shall include:

(1) sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;
(2) storage conditions for samples retained for testing;
(3) reliable, meaningful and specific test methods;
(4) testing of the drug product in the same container-closure system as that which the drug product is marketed;
(5) *testing of drug products for reconstitution at the time of dispensing."*

The stability testing procedures are becoming uniform, and storage conditions have been standardized by the International Conference on Harmonization (I.C.H.). Pharmaceutical companies use these conditions: 25±2 °C, 60±5% RH for long-term testing and 40±2 °C, 75±5% RH for accelerated testing. Minimum time periods for long-term testing and accelerated testing are 12 months and 6 months respectively. The testing will normally be every three months over the first year, every six months over the second year, and then annually (USP <1196>, 1995). If the product fails accelerated testing, then intermediate testing is used at 30±2 °C, 60±5% RH for 12 months. Data from the first six months of intermediate testing may be submitted in place of the failed accelerated testing data.

The FDA requires a full long-term stability test in the market package. Only when the drug passes this test, it is fully approved for marketing. The FDA will accept the results of testing at the accelerated or intermediate conditions as preliminary evidence

that the drug will pass the full test period. The process is time consuming and expensive.

1.1.2 Open Dish Study

Researchers (Wu, 1996; Qian, 1996; Kokitkar, 1997; Adams, 1998) at Michigan State University took a somewhat different approach to shelf life estimation. They characterized the dissolution behavior of drug products at constant temperature as a function of equilibrium moisture content (EMC), relative humidity and time. Results were obtained based on three fundamental factors that relate to the stability of the drug product: the product, the package, and the environment. The EMC of the product was determined as a function of relative humidity at 25, 30, and 40 °C. Then the dissolution was measured as a function of relative humidity or moisture content at 25, 30 and 40 °C. Two solid oral drug products, gelatin capsules and coated tablets, were placed in seven different relative humidities at 25, 30, and 40 °C for 90 days and the dissolution was measured. When critical dissolution points were determined, moisture contents were found at those points. This is the critical moisture content at which the drug products no longer met the dissolution specification and had therefore reached expiration. Separately, the third factor, the package moisture transmission rate, was characterized under known environmental conditions. From these results, a mathematical model was applied to estimate a shelf life under given environmental conditions. The shelf life calculation is, then, reduced to time factors that are determined by the package and the environment. Once the key package parameters (water vapor transmission rate), the environmental conditions (relative humidity, temperature), and the critical moisture content of the product are known, an estimation of shelf life can be made using the model.

1.2 Packaging and Storage Time Affecting the Dissolution of Solid Oral Dosage Forms

Factors that affect the dissolution stability of a product during aging include formulation, processing, the dissolution apparatuses, the test parameters, and packaging and storage. All factors except for packaging and storage have been explained very well in previous studies (Wu, 1996 and Adams, 1998). Therefore, package and storage factors were emphasized in this review.

In 1981, Taborsky-Urdinola et al. reported the effects of packaging and storage in multiple-unit and unit-dose containers on the dissolution rate of Prednisone tablets. USP Prednisone dissolution calibrator tablets[1] that were packaged in polyethylene bags and unpackaged (open dish) tablets were selected to compare their dissolution rate in this literature review. Both sets of tablets were placed in a tropical microenvironment of approximately 40 °C and 85% relative humidity for a three-month study. This condition is typically used to demonstrate accelerated test results. Dissolution rates were measured at pre-determined intervals during storage.

Figure 1 clearly demonstrates Tarborsky-Urdinola's finding that packaging and storage affect product integrity. Her study demonstrated a direct correlation between dissolution of the pharmaceutical product and the moisture barrier of its packaging. The dissolution reduction rate of open tablets was much larger than the reduction rate of packaged tablets. The permeability of the container was critical in this situation where the product was subjected to this condition, in excess of room conditions (22 °C, 75% RH).

[1] These calibrator tablets were of the same formulation as therapeutic tablets, different from the 10mg calibrator tablets used in this study.

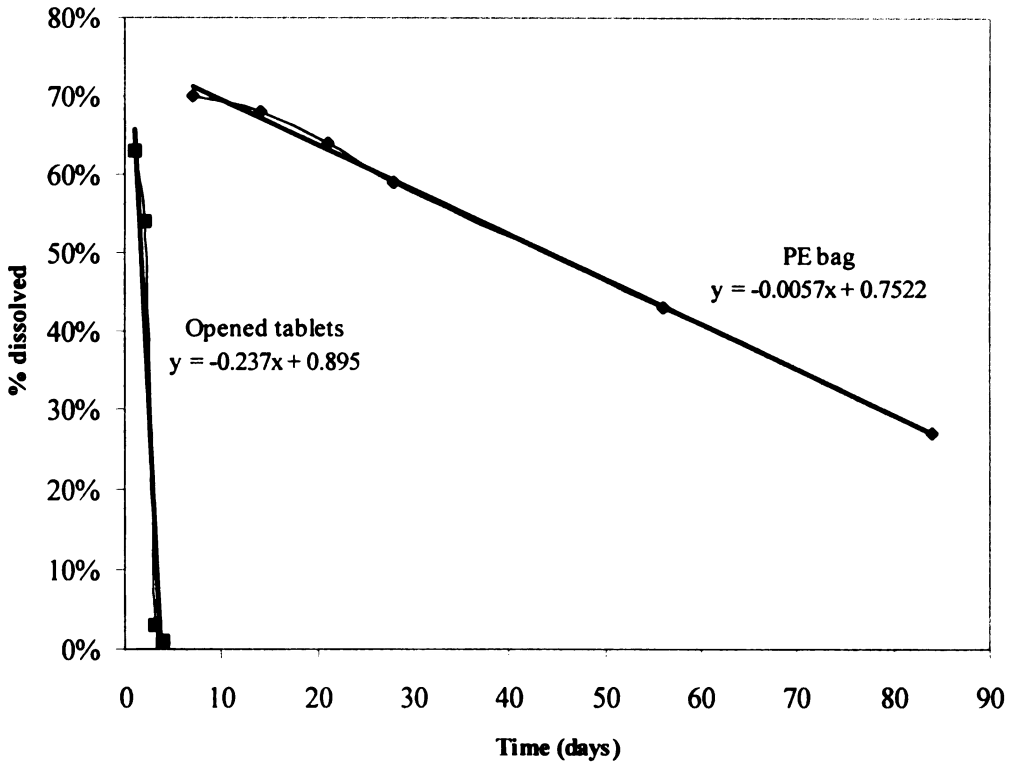


Figure 1. Dissolution of tablets packaged with PE bag and opened tablets at 40 °C, 85% RH

In 1981, Nakabayashi and coworkers examined shelf life in relation to the *in vitro* dissolution rate. Prednisolone tablets in a moisture-semipermeable package and in a glass bottle were used for stability testing. The effects of moisture and heat on the tablet dissolution rates were investigated under various temperature and humidity conditions. The dissolution rate decreased with increasing moisture content at ambient temperature. Table 1 shows the dissolution reduction rate constant decreased as moisture content increased at 40 °C. The dissolution reduction rate constant can be obtained by the relationship between the dissolution rate and time. It supported the idea that dissolution depends on moisture content.

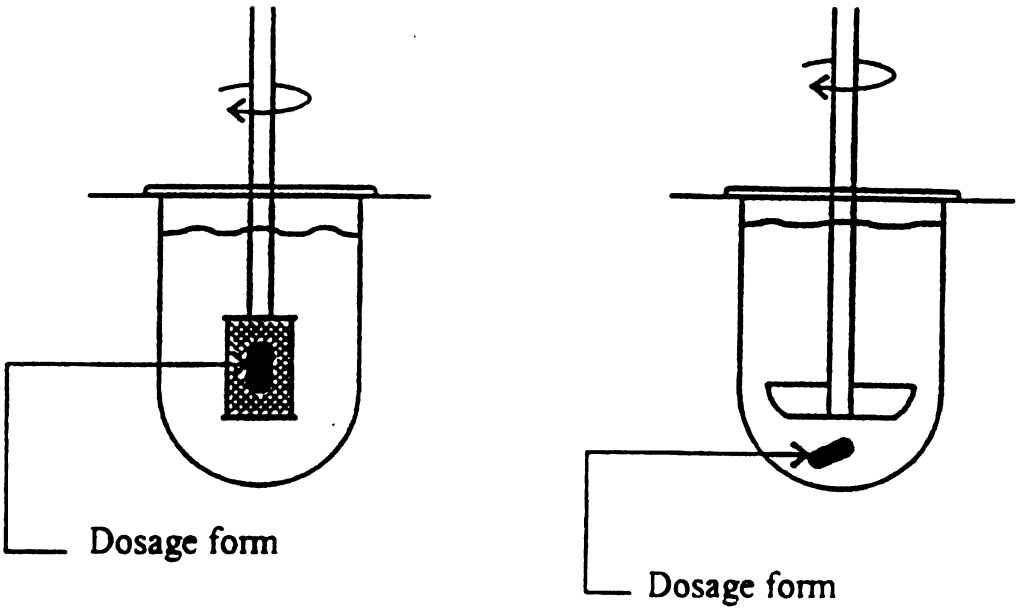
Table 1. Apparent dissolution reduction rate constant (K) of Prednisolone tablets with various moisture contents at several temperatures. (Nakabayashi et al., 1981)

Temperature, °C	Moisture Content, %	K, d^{-1}
25	5.6	0.0091
25	4.77	0.0049
40	5.41	0.0165
40	4.64	0.0092
40	4.12	0.0055
40	3.54	0.0037
50	3.1	0.0038

1.3 In Vitro Dissolution Tester

In-vitro dissolution testers represent in-vivo conditions. In-vitro conditions are different for different products. To represent in-vivo conditions, in-vitro dissolution testers usually use deionized water at 37±0.5 °C for the medium. The drug product is immersed in the medium with agitation for a period of time up to an hour. The amount and kind of agitation, and the length of time, are specific to the product. Under these conditions, the drug should have sufficient water solubility to dissolve in the aqueous phase. This will demonstrate its availability to penetrate through the surfaces of the gastrointestinal tract and into the blood stream (Abdou, 1989). Any significant change in the in-vitro release profiles of a drug during storage may indicate a change in bioavailability.

There are two official USP dissolution methods that are the most widely used for testing immediate release dosage forms. Apparatus 1 is the rotating basket model (Figure 2-(a)) and apparatus 2 is the rotating paddle method (Figure 2-(b)).



(a) Apparatus 1, rotating basket (b) Apparatus 2, rotating paddle

Figure 2. U.S.P. Dissolution Methods

1.4 General Idea of Dissolution for Tablets Stored in High Humidity

The dissolution behavior of dry solid oral drug products might be explained by the action of the disintegrant. The particles of disintegrant take up water into the porous network of a tablet. If wetting of the disintegrant particles slows, disintegration of the tablets also slows (Bolhuis et al., 1981). Then, the tablet that takes up water swells. In the swollen tablet, there might be stronger intermolecular hydrogen bonding among excipients than in the fresh tablet. The intermolecular hydrogen bonding affects the dissolution of the tablet. If the intermolecular hydrogen bonding is strong, the dissolution rate is low. Also, the crystallinity of an active ingredient might be changed by moisture uptake and storage time. If the crystallinity is low, the dissolution rate tends to be high (Hirasawa et al., 1998).

1.5 Prednisone Tablets & USP Dissolution <711>

In the USP monographs, Prednisone tablets and the dissolution method are described well. The USP monograph says that for tablets labeled to contain 10 mg Prednisone or less, the dissolution test should use 500 ml of the water medium (37±0.5 °C), in apparatus 2 at 50 rpm for 30 minutes. The amount of Prednisone dissolved is determined from ultraviolet absorbance at the wavelength of maximum absorbance at about 242 nm of filtered portions of the solution under test.

1.6 Definition of Prednisone

Prednisone is a crystalline or amorphous glucocorticoid drug $C_{12}H_{26}O_5$ that is a dehydrogenated analogue of cortisone. It is more active biologically than cortisone, and is used similarly. Glucocorticoids are adrenocortical steroids, both naturally occurring and synthetic, which are readily absorbed from the gastrointestinal tract. Prednisone is a white, odorless, crystalline powder. It is very slightly soluble in water and slightly soluble in alcohol, chloroform, dioxane, and methanol. The chemical name for Prednisone is 17,21-dihydroxypregna-1,4-diene-3,11,20-trione and its molecular weight is 358.43 (The MERCK Index, 1989). The structural formula is shown in Figure 3.

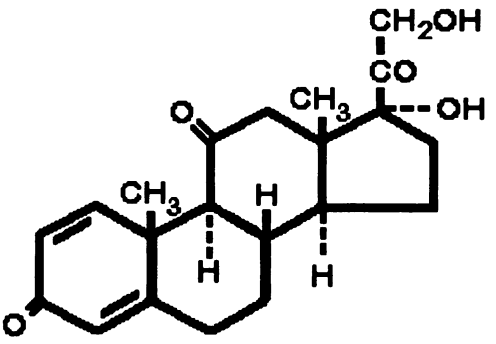


Figure 3. Structural formula of Prednisone

Naturally occurring glucocorticoids (hydrocortisone and cortisone), which also have salt-retaining properties, are used as replacement therapy in adrenocortical deficiency states. Their synthetic analogs are primarily used for their potent anti-inflammatory effects in disorders of many organ systems (Nobile et al., 1955). Glucocorticoids cause profound and varied metabolic effects. In addition, they modify the body's immune responses to diverse stimuli.

1.7 History of Dissolution Calibrator Tablets

The dissolution test is not a precise, reproducible and well-defined test. When it was introduced, there were no standards on which to rely, no guidelines for statistical treatment of the data, and no indisputable evidence of the viability of the dissolution test (Abdou, 1989). Therefore, a calibrator tablet was needed to standardize the dissolution tester. Prednisone therapeutic tablets are now used for calibration. Originally, a therapeutic dosage form was chosen by USP, and special lots of this formulation were

supplied by the manufacturer. USP would then perform dissolution tests with tablets from this lot. Then tablets from this lot were supplied with a USP certification of the dissolution (Lockhart, 1999). These tablets, with their certified dissolution, became the calibrator standard. However, these calibration standards had shortcomings. The Food and Drug Administration's Division of Drug Analysis (DDA) published articles in 1983 and 1995 showing that USP Prednisone therapeutic tablets were not entirely suitable for calibrating dissolution apparatuses or for detecting dissolved gases in the medium (Moore et al., 1996).

In 1979, DDA found a commercial 10mg Prednisone tablet, which was called NCDA #2. NCDA #2 was extremely sensitive to dissolved gases in the medium and was more sensitive to system alignment than the USP Prednisone therapeutic tablets being used for calibration. FDA formulated a new tablet with characteristics similar to NCDA #2 for use as a USP 10mg Prednisone calibrator. The new tablet was made at the University of Maryland at Baltimore (UMAB) with various combinations of disintegrant, blending times, and compression force. The USP 10mg Prednisone calibrator tablets were a significant achievement in the effort to improve the repeatability of the dissolution test because they are highly sensitive to dissolved gases in the dissolution medium. The new USP 10mg Prednisone calibrator tablets were used in this study.

1.8 Formulation of Prednisone Calibrator Tablets

The dissolution behaviors of Prednisone calibrator tablets and Prednisone therapeutic tablets are very different because they use different formulations and different manufacturing processes. The Prednisone therapeutic tablets are formulated and

manufactured to dissolve well in the stomach. However, Prednisone calibrator tablets are especially designed to not dissolve rapidly because they should be stable for a long time. They were also designed to be sensitive to dissolved gasses and other process variables in the dissolution procedure and apparatus. They can be called robust. Table 2 shows the formulations of Prednisone therapeutic tablets and Prednisone calibrator tablets, and illustrates the function of each excipient.

Table 2. Formulations of Prednisone therapeutic tablets and calibrator tablets

Upjohn[1)] **5 mg Prednisone therapeutic tablet**	**USP[2)]** **10 mg Prednisone calibrator tablet**
Calcium Stearate (lubricant)	Microcrystalline Cellulose (binder, disintegrant)
Corn Starch (binder, disintegrant)	Dibasic Calcium Phosphate (disintegrant)
Lactose (binder, disintegrant)	Sodium Starch Glycolate (binder, disintegrant)
Mineral Oil (lubricant)	Stearic Acid (insoluble lubricant)
Sorbic Acid (preservative)	Magnesium Stearate (hydrophobic disintegrant, insoluble lubricant)
Sucrose (binder, disintegrant)	

1) The formulation was obtained from http://www.druginfonet.com/deltason.htm
2) The formulation was obtained from William Brown (researcher in USP)

Marshall and Rudinic (1989) give a general description of excipients for solid oral tablets. The excipients perform multiple functions as shown in Table 2. The organic materials used as filler are primarily carbohydrates (starch, lactose, sucrose) because of their general ability to enhance the products' mechanical strength as well as their freedom from toxicity, acceptable taste and reasonable solubility profiles.

Microcrystalline cellulose (up to 20%) used as a binder is normally added to enhance compression characteristics because of its high binding property in compression

(Nakai et al., 1977). Dissolution performance may be adversely affected at higher compressional forces. Sodium starch glycolate propagates capillary effects but also swells and/or dissolves to further enhance disintegration behavior. Mineral oil, stearic acid, calcium stearate, and magnesium stearate used as lubricants act by interposing an intermediate layer between the tablet constituents and the die wall, which yields preferentially when the tablet surface moves relative to the die on compression and on ejection. The smaller the amount of stress needed to shear the material, the better its lubricant properties will be. Also, the magnesium stearate is a hydrophobic disintegrant. The Prednisone calibrator tablets that contain hydrophobic disintegrant are wetted slowly; thus disintegration of the tablets is also slowed (Bolhuis et al., 1984). Dicalcium phosphate dihydrate is a comparatively low cost insoluble diluent with good powder flow potential but inherently poor compression characteristics. Sorbic acid is used as a preservative.

1.9 G.A.B. Model

The G.A.B. (from Guggenheim – Anderson – De Boer) sorption model is a three-parameter equation with physically meaningful coefficients which fits data very well up to 0.9 a_w in many cases (Bizot, 1991). The G.A.B. model is a good method for construction of sorption isotherm curves. The G.A.B. equation can be written in quadratic form as:

$$\left(\frac{a_w}{M}\right) = \alpha a_w^2 + \beta a_w + \gamma$$

where,

α, β, γ: Constants
M: Moisture Content
a_w: Water Activity

The quality of the fit is judged from the value of the relative percent root mean square (% RMS). The lower the RMS, the better is the quality of the fit. If the RMS is zero, it means the quality of the fit is perfect.

$$\%RMS = \sqrt{\frac{\sum_i^N \left[\frac{M_{exp} - M_{calc}}{M_{exp}}\right]^2}{N}} \times 100$$

where,

M_{exp} is experimental moisture content

M_{calc} is calculated moisture content

N is number of observations

The G.A.B. sorption model can be plotted with experimental sorption data and the quadratic equation can be obtained by a polynomial regression method or a spreadsheet computer program (see Appendix B).

The G.A.B. quadratic equation can be modified as follows:

$$M = \frac{a_w}{\alpha a_w^2 + \beta a_w + \gamma} \quad (1)$$

$$(\alpha M)a_w^2 + (\beta M - 1)a_w + \gamma M = 0 \quad (2)$$

If the a_w value is put into equation (1), then M can be calculated. By using the quadratic formula, the a_w can be calculated from equation (2). This is used to determine the equilibrium moisture content (EMC) at a relative humidity (RH, RH = $a_w \times 100$) and the RH at an EMC.

CHAPTER 2

MATERIALS, EQUIPMENT, AND EXPERIMENTAL PROCEDURES

2.1 Materials and Equipment

1. USP 10mg Prednisone calibrator tablets (USP Rockville, MD) formulated with microcrystalline cellulose, dibasic calcium phosphate, sodium starch glycolate, stearic acid, and magnesium stearate.

2. USP Reference Standard (Prednisone 250 mg, U.S.P.C., Inc. Rockville, MD), Lot K

3. Three environmental chambers (25, 30, 40°C) in which temperature and relative humidity are controlled automatically.

4. Saturated salt solutions for 12, 33, 50, 65, 75, 80, 90% RH (see experimental procedure)

5. Aluminum weighing pans used when measuring moisture contents.

6. Plastic petri dishes used to hold the tablets in the open dish study.

7. 21 plastic 5-gallon polyethylene buckets used to maintain relative humidities.

8. 7 humidity sensors (Newport Scientific Inc.) – narrow range hygrosensor (accuracy: ±1%)

9. Mettler AE 160 scale (Mettler Inc.)

10. Pipetman (Model No. P1000, P5000, Rainin Instrument Co. Inc.)

11. Pipette tips (Rainin Instrument Co. Inc.)

12. Ultrasonic Cleaner (Branson Cleaning Equipment Company) used in dissolving the reference standard (Prednisone).

13. Vacuum oven (Precision Scientific Model 524) used to dry the reference standard (Prednisone)

14. Metrohm Karl Fischer Titrator with Brinkman Polytron® Homogenizer (720 KFS Titrino, 703 Ti Stand)

15. Six vessel dissolution tester (Vankel VK6010)

16. UV/VIS-spectrophotometer (Lambda 20, Perkin Elmer Corporation)

17. Thermometer (-1 ~ 51 °C, 1/10, Fisher Scientific)

18. 5 ml plastic syringes (Becton Dickinson and Company) for sampling

19. Filter (0.45 μm, MILLEX®– HV) for sampling

20. Disposable tubes (12×75 mm, VWR Scientific®) for sampling

2.2 Experimental Procedures

The USP 10mg Prednisone calibrator tablets are round, smooth, non-coated tablets. The test tablets were all taken from the same lot which was packaged in amber glass bottles.

First, a spectrophotometer calibration curve was made to calculate the concentration of Prednisone in all the dissolution experiments. This was determined from ultraviolet absorbance measurements at the wavelength of maximum absorbance, at 242 nm, using a filtered portion of the solution under test. The solution was diluted with water and was compared with a standard solution having a known concentration of USP Prednisone reference standard in the same medium. If the 10mg Prednisone dissolves completely in the 500ml medium, the concentration is 0.02mg Prednisone/1ml medium (100%). Based on this, stock solution was made first, and then it was diluted as 100%, 75%, 50%, and 25%. This dissolution calibration curve was used to calculate the concentration of Prednisone in the dissolution medium at each interval.

$$\textbf{Stock Solution} = \frac{25 \text{ mg prednisone}}{100 \text{ ml water}} = 0.25 \text{ mg/ml}$$

Dilution

100% 2 ml (0.25 mg/ml) stock solution diluted to 25 ml distilled water = 0.02 mg/ml

$$\frac{0.25 \frac{\text{mg}}{\text{ml}} \times 2 \text{ ml}}{25 \text{ ml}} = 0.02 \text{ mg/ml}$$

75% 1.5 ml (0.25 mg/ml) stock solution diluted to 25 ml distilled water = 0.015 mg/ml

$$\frac{0.25 \frac{\text{mg}}{\text{ml}} \times 1.5 \text{ ml}}{25 \text{ ml}} = 0.015 \text{ mg/ml}$$

50% 1 ml (0.25 mg/ml) stock solution diluted to 25 ml distilled water = 0.01 mg/ml

$$\frac{0.25\ \frac{mg}{ml} \times 1\ ml}{25\ ml} = 0.01\ mg/ml$$

25% 0.5 ml (0.25 mg/ml) stock solution diluted to 25 ml distilled water = 0.005 mg/ml

$$\frac{0.25\ \frac{mg}{ml} \times 2\ ml}{25\ ml} = 0.005\ mg/ml$$

The stock solution to construct the calibration curve was made twice as shown in Table 3. Figure 4 shows that the two dissolution calibration curves were almost identical. The R^2 of the first curve was 1 and the second was 0.9998. Therefore, the first calibration curve was used to calculate the dissolution concentration of Prednisone.

Table 3. Dissolution Calibration Curve of 10mg Prednisone

Concentration	%	1st solution	2nd solution
		Absorbance	Absorbance
0.02	100%	0.905	0.89
0.015	75%	0.685	0.6825
0.01	50%	0.463	0.465
0.005	25%	0.248	0.243

Calculation

1st calibration curve: $y = 0.8772x + 0.027$

$$x = \frac{y - 0.027}{0.8772}$$

y: Absorbance

x: % Dissolution or % Concentration

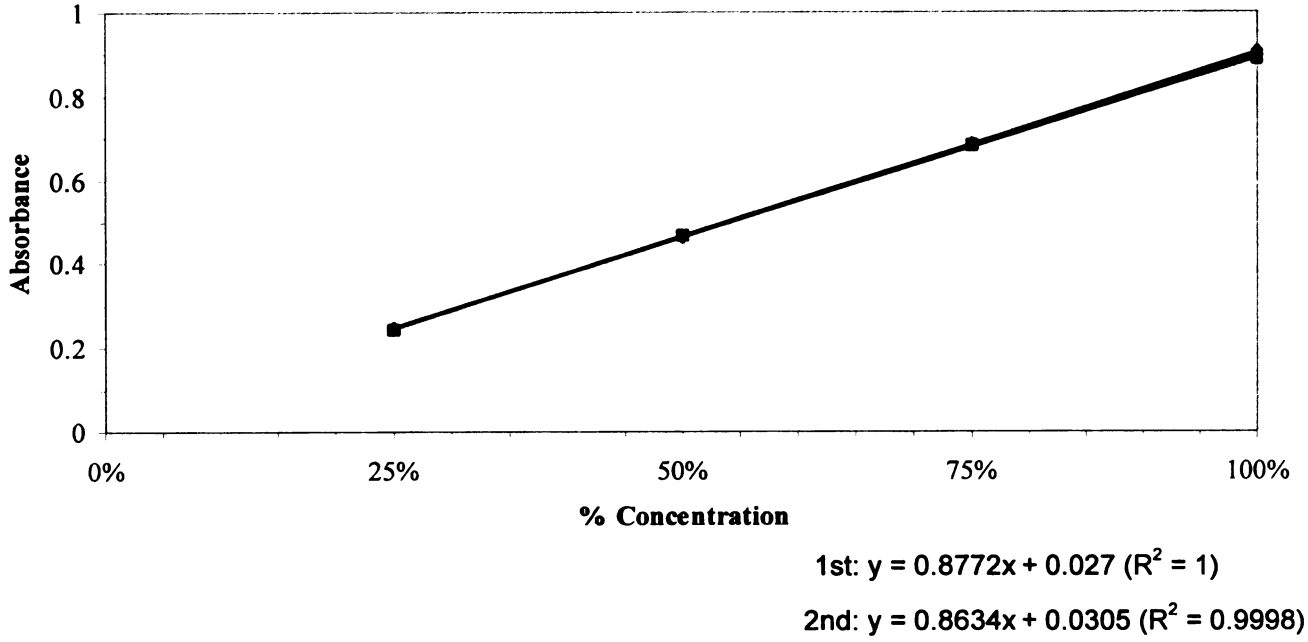


Figure 4. Calibration curve for the spectrophotometer using USP 10mg Prednisone

The initial dissolution profile, weight, and initial moisture content were measured with tablets taken from a fresh bottle. The tablets were stored in 5-gallon buckets with tight fitting lids. Before the samples were stored in open dishes in the buckets, the relative humidity inside each bucket was measured during opening and closing. These measurements demonstrated the time required to reach equilibrium after the lid was closed. See Table 4.

Table 5 shows the list of saturated salt solutions used to provide the required range of relative humidities. The RH in the buckets varied about ±1.5% over a one month period, indicating good control. The RH at low temperature (25 °C) was more stable than the RH at high temperature (40 °C). Table 4 shows that the greater the difference in relative humidity between the chamber and bucket, the more time was needed to reach equilibrium conditions after opening and closing. Low RH needed more time than high RH to reach equilibrium. Based on this, a sampling schedule was chosen which provided sufficiently long time intervals. For example, the 12% RH bucket needs about 6 hours to reach equilibrium conditions. Therefore, the moisture content of the tablet is best measured at time intervals greater than one day.

Table 4. Relative humidity equilibrium time inside buckets at each temperature

Chamber Conditions		Nominal RH						
		12%	33%	50%	65%	75%	80%	90%
Equilibrium Time	25°C 75% RH	7 hrs	6 hrs	5 hrs	3 hrs	0 hrs	1 hrs	2.5 hrs
	30°C 65% RH	6 hrs	4 hrs	1 hrs	0 hrs	1 hrs	2 hrs	3 hrs
	40°C 75% RH	6 hrs	5 hrs	3 hrs	2 hrs	0 hrs	0.5 hrs	2 hrs

Table 5. Salt solutions used to prepare the humidity buckets and their respective relative humidities.

Saturated Salt Solution	RH (%)					
	25 °C		30 °C		40 °C	
	1/9/1999	2/9/1999	1/9/1999	2/9/1999	1/9/1999	2/9/1999
Lithium Chloride	*	16.0	*	15.2	*	12.8
Magnesium Chloride	34.0	34.0	33.8	35.3	32.3	32.8
Magnesium Nitrate	53.5	53.3	51.3	51.3	48.0	49.5
Sodium Nitrite	66.0	66.3	64.8	64.8	64.8	64.6
Sodium Chloride	76.5	76.8	75.8	76.3	76.0	76.1
Ammonium Sulfate	81.0	80.5	80.0	79.8	79.0	79.0
Potassium Nitrate	91.5	92.0	89.7	91.2	87.2	87.5

*The sensor for 12% was not available.

To determine the initial moisture content (IMC) of tablets, the Brinkmann Karl Fischer titrator was used. In the Karl Fisher titrator, the titrimetric determination of water is based upon the quantitative reaction of water with an anhydrous solution of sulfur dioxide and iodine in the presence of a buffer which reacts with hydrogen ions. The determination of water is achieved by detecting an electrometric change in the solution when all available water is consumed. The amount can be calculated from the amount of titrating reagent needed to reach the endpoint.

The Karl Fischer titrator was standardized three times using deionized water. If the standardization values are in the range of ±2% standard deviation (SD), the IMC of tablets can be measured. The tablets were dropped in the vessel without powdering with a mortar and pestle because the tablets can be homogenized by the Brinkmann Karl Fischer titrator. The resulting wet-weight-based moisture content was converted to a dry-weight-based moisture content.

To determine the moisture sorption isotherms, the tablets were placed in open petri dishes in the humidity buckets at 25, 30, and 40 °C. The moisture contents were

determined gravimetrically. The difference in the moisture content (MC) of the tablet and the external environment acts as a driving force. If the moisture content in an external environment is higher than that in the tablet, the moisture in the external environment drives for the tablet. Therefore, the tablet absorbs moisture till the MC reaches equilibrium with the moisture content of the external environment. To decide the equilibrium moisture content of the tablets, a moisture gain vs. time graph was made as shown in Figure 5. After the moisture content reached some point, the moisture content began to fluctuate. The equilibrium moisture content was averaged from the fluctuating moisture content.

After the moisture equilibrium sorption isotherm data were obtained, the G.A.B. model was used to construct sorption isotherm curves at each temperature. Also, sorption isotherm curves at 35 and 20 °C were interpolated within and extrapolated from the three sorption isotherms (25, 30, 40 °C) constructed by the G.A.B. model.

To determine the critical point for dissolution and to observe the physical condition of the tablets, six tablets per petri dish were placed for 90 days in 50, 65, 75, 80, 90 %RH at 25, 30, and 40 °C. Tablets were removed according to the sampling schedule just before testing dissolution. Table 6 gives the storage plan. The inside RH of the fresh bottle was determined from the sorption isotherm curve to be about 50%. Therefore, tablets were stored only above 50% RH.

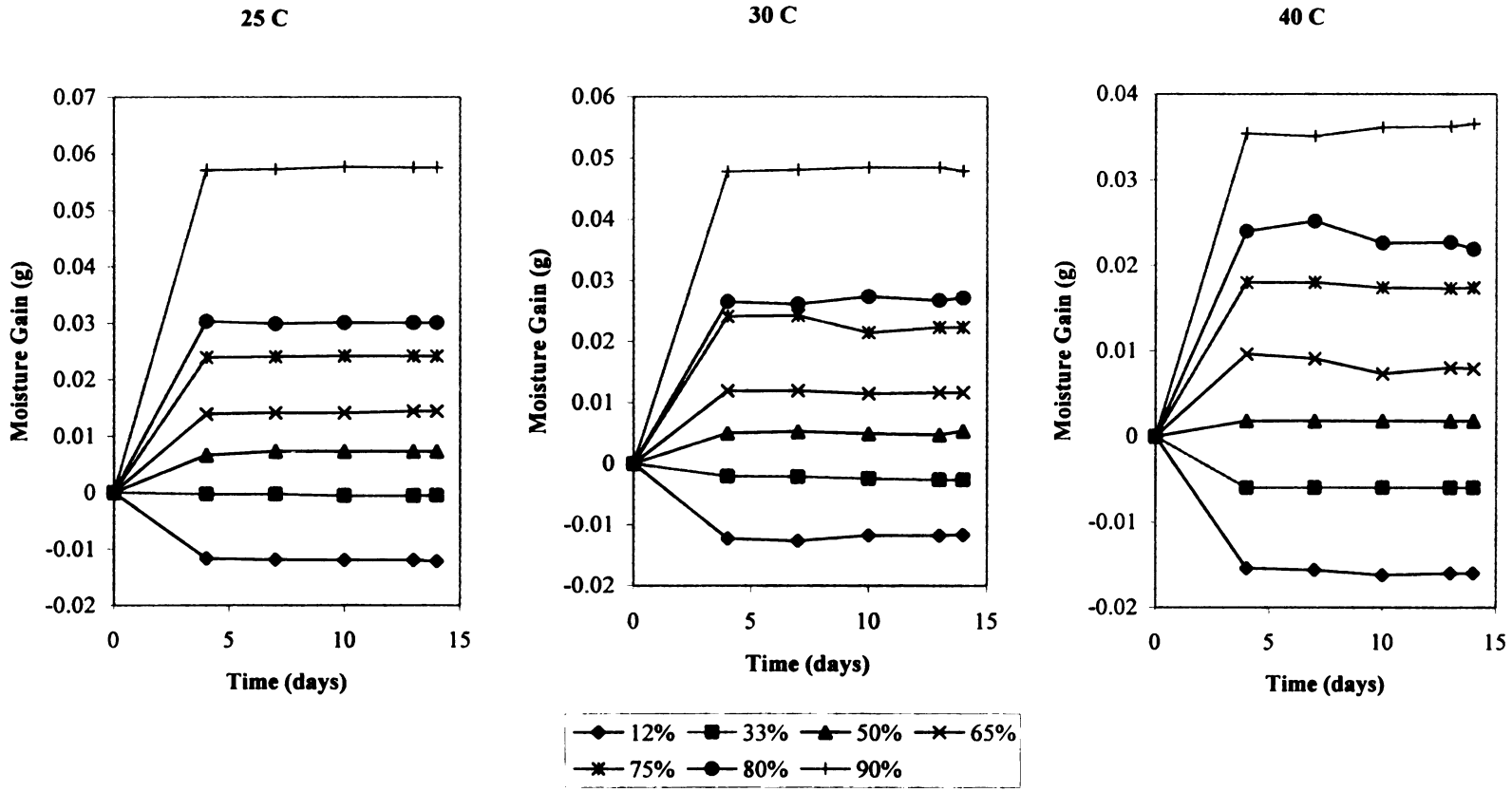


Figure 5. Equilibrium points of USP 10mg Prednisone Calibrator Tablets at 25, 30, 40 °C.

Table 6. The Dissolution testing storage plan of USP 10mg Prednisone calibrator tablets.

Temp. (°C)	Time (days)	Nominal RH (%)						
		12	33	50	65	75	80	90
25 °C	15			X	X	X	X	X
	30			X	X	X	X	X
	45			X	X	X	X	X
	60			X	X	X	X	X
	75			X	X	X	X	X
	90			X	X	X	X	X
30 °C	15			X	X	X	X	X
	30			X	X	X	X	X
	45			X	X	X	X	X
	60			X	X	X	X	X
	75			X	X	X	X	X
	90			X	X	X	X	X
40 °C	15			X	X	X	X	X
	30			X	X	X	X	X
	45			X	X	X	X	X
	60			X	X	X	X	X
	75			X	X	X	X	X
	90			X	X	X	X	X

Dissolution of tablets was measured for 90 days by using a USP dissolution instrument, Apparatus 2 (paddle method) as described in USP <711> Dissolution. The dissolution medium used for the procedure was 500 ml of deionized water. The deionized water was boiled to degas for 1 hour at the boiling point and cooled to 37 °C. The paddle rotated at 50 rpm. After 30 minutes dissolving, 5ml samples were withdrawn from the dissolution medium and absorption was read at 242 nm in the uv spectrophotometer. One tablet was used per vessel and six vessels were used for each storage humidity and temperature combination. The absorbance was calculated to percent dissolution using the dissolution calibration curve.

CHAPTER 3

DATA AND RESULTS

3.1 Initial Dissolution Profile of USP 10mg Prednisone Calibrator Tablets

In accordance with the USP monograph for 10mg Prednisone, experiments were carried out with 500 mL of the dissolution medium and 50 rpm speed for the stirrer. The initial dissolution profile (Table 7 and Figure 6) shows how a USP 10mg Prednisone calibrator tablet dissolves over 60 minutes at 50 rpm. As shown in Table 7, dissolution of six tablets was measured for 60 minutes. The initial dissolution average value of six tablets was 29% at 30 minutes. This is a very low initial value compared to therapeutic tablets, since most therapeutic tablets have more than 95% initial dissolution at 30 minutes. Figure 6 shows also the unusual shape of the initial dissolution profile. This profile shows a gradual rise to 29% at 60 minutes. Most therapeutic tablets dissolve quickly, reaching the initial value at or near 95% in 15 minutes. The unusual shape of this profile and low initial value of dissolution are probably because the tablets are formulated to be robust.

These new USP 10mg Prednisone calibrator tablets are not on the market yet, and there is no monograph to show dissolution limits. Since these are not a therapeutic dosage form, there will probably not be a monograph. However, USP staff member William Brown[1] reports that a 10% change from initial dissolution can be used as a dissolution failure point. Therefore, about 26% was used as the dissolution failure point.

[1] Personal communication by an e-mail (04/13/1999).

Table 7. Initial dissolution profile data for the USP 10 mg Prednisone calibrator tablets

Dissolution Conditions	Time (min)	Apparatus Position						Avg. (6)	SD (6)
		1	2	3	4	5	6		
Paddle at 50 rpm	0	0%	0%	0%	0%	0%	0%	0%	0%
	10	13%	17%	15%	16%	16%	14%	15%	2%
	20	19%	26%	23%	24%	24%	22%	23%	2%
	30	**25%**	**33%**	**30%**	**29%**	**29%**	**28%**	**29%**	**3%**
	40	29%	38%	34%	34%	33%	33%	34%	3%
	50	33%	42%	38%	38%	38%	37%	38%	3%
	60	35%	46%	41%	40%	40%	40%	40%	3%

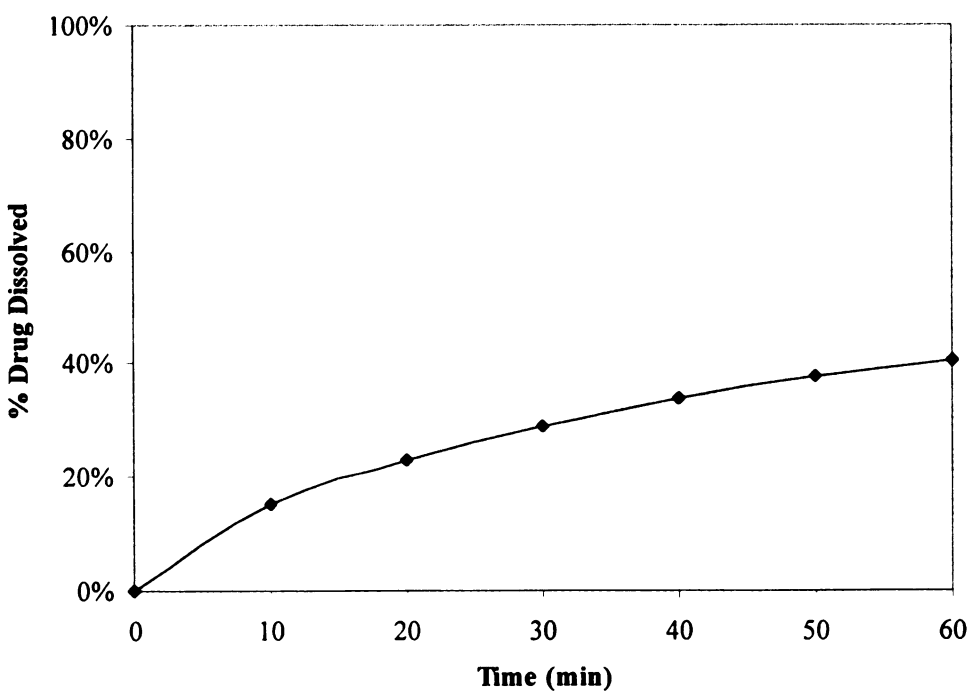


Figure 6. USP 10mg Prednisone Initial Dissolution Profile

3.2 Weight & Initial Moisture Content (IMC)

The average weight of 10mg Prednisone calibrator tablets was measured to be about 220mg.

The average moisture content based on wet weight, converted to a dry weight basis is shown in Table 8. The average was 3.24%.

Table 8. Initial Moisture Content (IMC) of USP 10mg Prednisone calibrator tablets

	Standardization	Wet based MC	Dry based MC
1	99.05%	3.35%	3.47%
2	100.07%	3.05%	3.15%
3	98.68%	3.02%	3.11%
4		3.23%	3.34%
5		3.18%	3.28%
6		3.02%	3.11%
Average (6)	99.27%	3.14%	3.24%
SD (6)	0.72%	0.13%	0.14%

Calculation

$$\%\ dry\ weight\ based\ moisture\ content = \frac{\%\ wet\ weight\ based\ moisture\ content}{100 - \%\ wet\ weight\ based\ moisture\ content} \times 100$$

$$= \frac{3.35\%}{100 - 3.35\%} \times 100 = 3.47\%$$

3.3 Equilibrium Moisture Sorption Isotherm

The equilibrium moisture content (EMC) of the tablets was calculated with the following formula. The EMC is expressed on a dry product weight basis.

$$EMC = \left[\frac{P_f \cdot (1 + \frac{IMC}{100})}{P_i} - 1 \right] \times 100$$

where,

P_f: Final product weight, g

P_i: Initial product weight, g

IMC: Initial Moisture Content (g water/100g dry product)

EMC: Equilibrium Moisture Content (g water/100g dry product)

Table 9 shows equilibrium moisture contents at 25, 30, 40 °C and in Figure 8, the EMC at each RH was plotted to construct the equilibrium moisture sorption isotherm curve by using the G.A.B. model. The sorption isotherm curve is usually constructed with 7 to 9 data points (Figure 7). However, if it is constructed by the G.A.B. model, unlimited data points can be used. Therefore, a very smooth sorption isotherm curve can be made. The G.A.B. model was used to construct the smooth curves in Figure 8 using the data in Table 9 that produced the sorption isotherm curve in Figure 7. The G.A.B. quadratic regressions that were used to construct sorption isotherm curves are given in Appendix B.

There are two methods to determine the expected EMC at known RH or the expected RH at known EMC using a sorption isotherm curve. The first method reads the

value for EMC or RH directly from the sorption isotherm curve. The second method uses the G.A.B. quadratic equation as explained below. If the G.A.B. model fits the experimental sorption isotherm data very well, the EMC or the RH can be calculated by using the G.A.B. quadratic equation.

For example, the G.A.B. quadratic equation at 40 °C;

$$\left(\frac{a_w}{M}\right) = -39.272a_w^2 + 48.938a_w + 0.6014,$$

is modified to the following:

$$M = \frac{a_w}{-39.272a_w^2 + 48.938a_w + 0.6014} \quad (1)$$

$$(-39.272 \cdot M) \cdot a_w^2 + (48.938 \cdot M - 1) \cdot a_w + 0.6014 \cdot M = 0 \quad (2)$$

If any a_w value from 0 to 1 is put into equation (1), the moisture content (M) can be calculated. Also, if any moisture content between 0 and the highest EMC is put into equation (2), the a_w can be calculated by the quadratic formula. Therefore, the G.A.B. quadratic equation can be used to determine the critical moisture content at a critical storage condition (RH = 100 × a_w). The critical storage condition was determined by measuring the dissolution of stored tablets. If the 10% dissolution changed tablets were found at a condition, the condition can be used as the critical storage condition. Also, this can be used to determine the inside relative humidity of the fresh bottle with the initial moisture content of tablets. To provide a safety factor, one might choose as critical, a storage condition of lower relative humidity than that at which 10% change in dissolution was found.

Table 9. Equilibrium Moisture Sorption Isotherm of 10mg Prednisone calibrator tablets at 25, 30 40 °C.

40 °C	Actual Relative Humidity						
Days	**12.80%**	**32.80%**	**49.50%**	**64.55%**	**76.05%**	**79%**	**87.45%**
Initial wt. (t=0)	1.1007	1.1052	1.101	1.0993	1.1033	1.1089	1.1022
4	1.0853	1.0992	1.1028	1.1089	1.1213	1.1329	1.1376
7	1.0851	1.0992	1.1028	1.1084	1.1213	1.1341	1.1373
10	1.0845	1.0992	1.1028	1.1066	1.1207	1.1315	1.1383
13	1.0847	1.0992	1.1028	1.1073	1.1206	1.1316	1.1384
14	1.0847	1.0992	1.1028	1.1072	1.1207	1.1308	1.1387
Final wt. (t=t)	1.08486	1.0992	1.1028	1.10768	1.12092	1.13218	1.13806
EMC	**1.7543**	**2.6795**	**3.4088**	**4.0270**	**4.8888**	**5.4074**	**6.5989**
30 °C							
Days	**15.20%**	**35.30%**	**51.25%**	**64.80%**	**76.25%**	**79.80%**	**91.20%**
Initial wt. (t=0)	1.1056	1.1127	1.1168	1.1005	1.1048	1.0976	1.0969
4	1.0933	1.1106	1.1218	1.1124	1.1289	1.1241	1.1447
7	1.0929	1.1105	1.122	1.1124	1.129	1.1237	1.145
10	1.0938	1.1102	1.1217	1.1119	1.1262	1.1249	1.1454
13	1.0938	1.11	1.1215	1.1121	1.1271	1.1243	1.1454
14	1.0939	1.11	1.1221	1.1121	1.1271	1.1247	1.1448
Final wt. (t=t)	1.09354	1.11026	1.12182	1.11218	1.12766	1.12434	1.14506
EMC	**2.1138**	**3.0136**	**3.7041**	**4.3357**	**5.3762**	**5.7552**	**7.7728**
25 °C							
Days	**16%**	**34.05%**	**53.25%**	**66.30%**	**76.75%**	**80.05%**	**91.95%**
Initial wt. (t=0)	1.1095	1.1063	1.0986	1.0977	1.1176	1.1109	1.1115
4	1.0978	1.106	1.1052	1.1116	1.1415	1.1412	1.1686
7	1.0976	1.106	1.1059	1.1118	1.1416	1.1408	1.1688
10	1.0975	1.1057	1.1059	1.1118	1.1418	1.141	1.1692
13	1.0975	1.1057	1.1059	1.1121	1.1418	1.141	1.1691
14	1.0973	1.1058	1.1059	1.1121	1.1418	1.141	1.1691
Final wt. (t=t)	1.09754	1.10584	1.10576	1.11188	1.1417	1.141	1.16896
EMC	**2.1271**	**3.1971**	**3.9129**	**4.5736**	**5.4663**	**6.0373**	**8.5771**

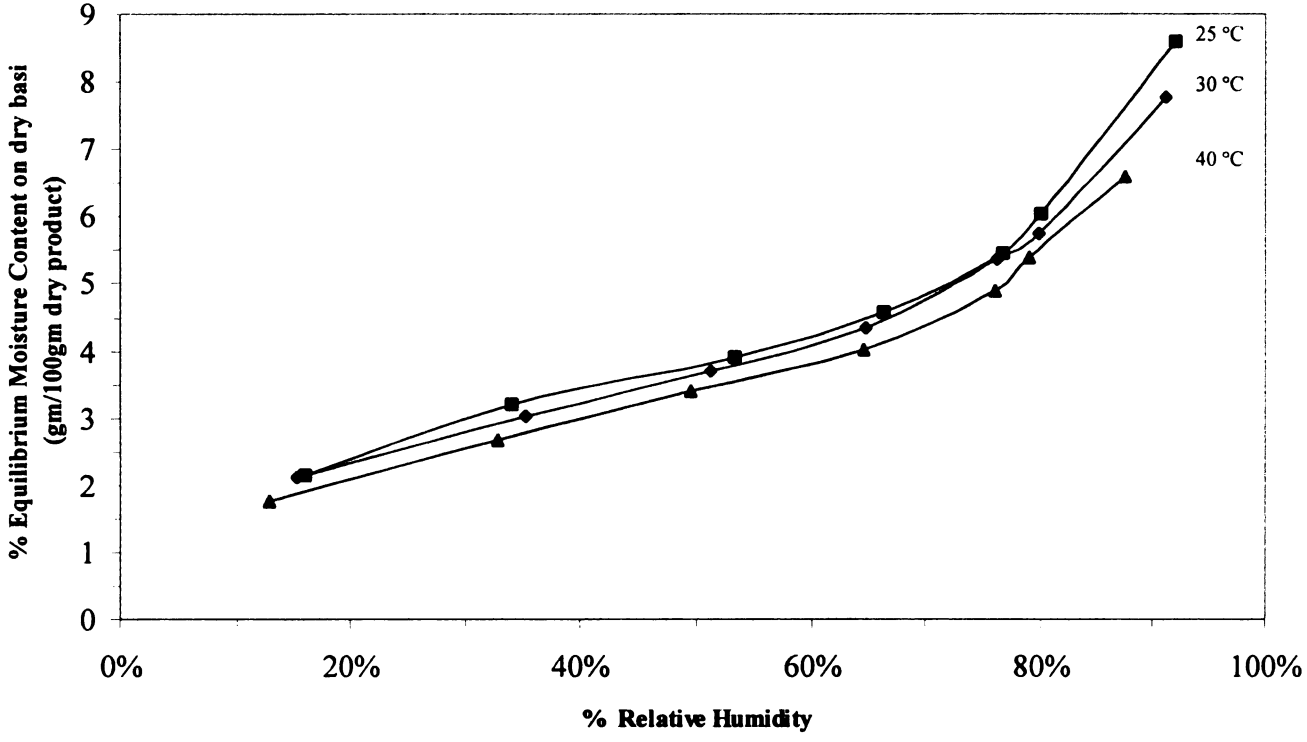


Figure 7. Moisture sorption isotherm curves of USP 10mg Prednisone calibrator tablets constructed by using 7 experimental data points at 25, 30, and 40 °

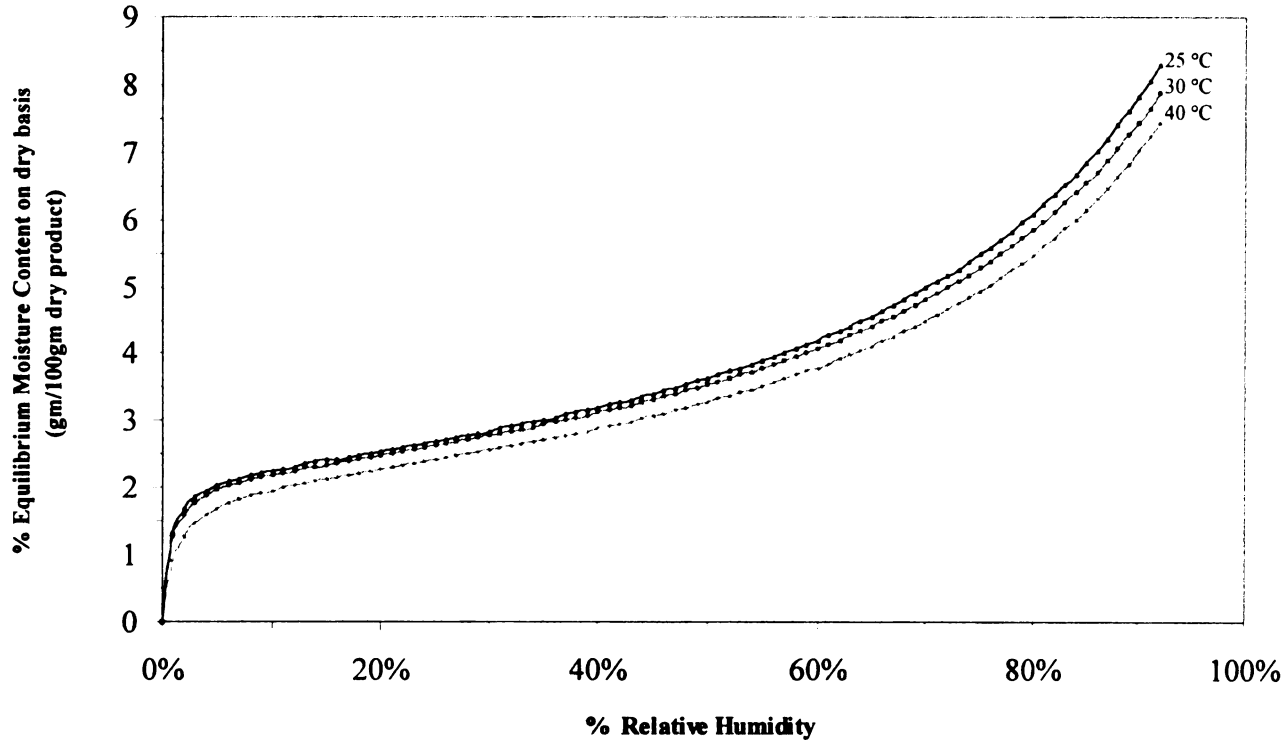


Figure 8. Moisture sorption isotherm curves of USP 10mg Prednisone calibrator tablets constructed by using the G.A.B. model at 25, 30, and 40 °C

3.4 Arrhenius Relationship

In this study, the researchers chose to compute shelf life and to determine barrier properties to meet conditions specified by International Conference on Harmonization (ICH). In other applications it would be important to estimate shelf life and determine barrier properties at a variety of conditions with data obtained from open dish studies.

To estimate the shelf life of a product in a package at any temperature, the moisture equilibrium sorption isotherm and the permeability must be calculated for the same temperature. The permeability and the moisture sorption isotherm are calculated using an Arrhenius relationship.

For the sorption isotherm, three moisture equilibrium sorption isotherms at 25, 30, and 40 °C were obtained in this work. This means that the shelf lives of the tablets can be estimated only at those conditions. However, if sorption isotherms are interpolated or extrapolated, sorption isotherms at other conditions can be constructed. The relationship between the equilibrium moisture content and the temperature can be plotted as a linear equation. With this linear equation, the equilibrium moisture contents can be interpolated or extrapolated to a desired temperature. Figure 9 shows the interpolated sorption isotherm curve at 35 °C and the extrapolated sorption isotherm curve at 20 °C.

For the permeability, there are also three sets of permeability data (25, 30, 40 °C) that were obtained from previous work at the School of Packaging (Table 10). By using the Arrhenius equation, permeabilities at 20 and 35 °C can be calculated. Table 10 shows the permeabilities calculated at 20 and 35 °C by using the Arrhenius equation. Figure 10 shows the Arrhenius relationship between temperature and permeability.

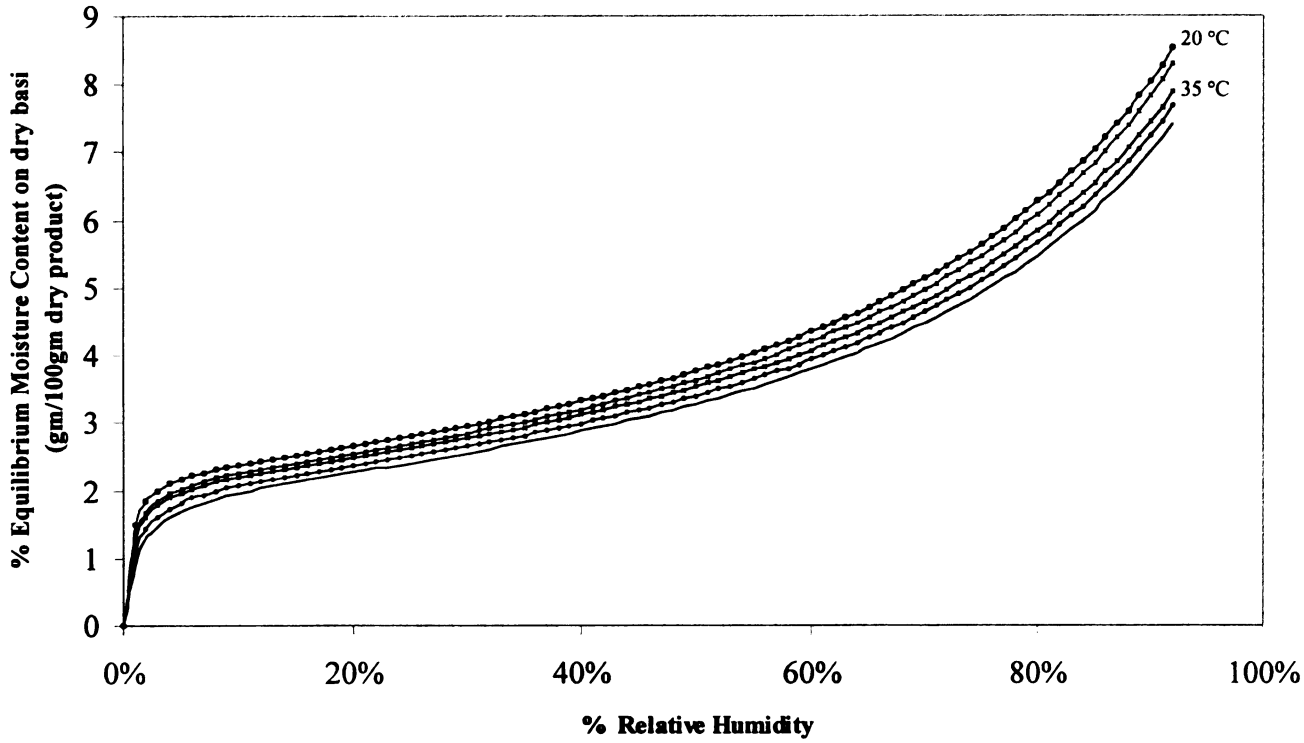


Figure 9. Moisture sorption isotherm curves of USP 10mg Prednisone calibrator tablets interpolated to 35 °C and extrapolated to 20 °C.

Table 10. Permeabilities of blister packages.

	Permeability in g/days.cavity.mmHg				
Materials	40 °C 75% RH	35 °C[1)]	30 °C 60% RH	25 °C 60% RH	20 °C[1)]
PVC/PVDC 250/40(1)	3.0879×10^{-5}	2.48×10^{-5}	1.9615×10^{-5}	1.5605×10^{-5}	1.2233×10^{-5}
PVC/PVDC 250/40(2)	2.4517×10^{-5}	1.9628×10^{-5}	1.6735×10^{-5}	1.2593×10^{-5}	9.9730×10^{-6}
250/25/90	1.2524×10^{-5}	9.3161×10^{-6}	7.4550×10^{-6}	5.1420×10^{-6}	3.7625×10^{-6}
PVC/0.002 PE/0.0006 Aclar	1.0548×10^{-5}	8.9644×10^{-6}	7.9250×10^{-6}	6.4649×10^{-6}	5.4444×10^{-6}
0.0075 PVC/PE/Aclar 22A	8.1498×10^{-6}	6.7861×10^{-6}	6.3600×10^{-6}	4.8132×10^{-6}	4.0181×10^{-6}

1) calculated by Arrhenius equation.

Table 11. Descriptions of blister packages.

No.	Materials	Supplier	Code	Foil	Supplier	Code
1	PVC/PVDC 250/40[1)]	VKW	V30408-37	0.001 Hard Push-Thru	Reynolds	R80108-00
2	PVC/PVDC 250/40[1)]	VKW	V30408-37	263 Push-Thru	Reynolds	R26308-12
3	250/25/90[2)]	Klockner		205 Peel-Push equip.	LawsonMarden	
4	PVC/0.002[3)] PE/0.0006[3)] Aclar	Mirrex	T61008-25	205 Peel-Push equiv.	LawsonMarden	
5	0.0075[3)] PVC/PE/Aclar 22A	Mirrex		0.001 Hard Push-Thru	LawsonMarden	

1) g/m^2 PVDC coated duplex
2) g/m^2 PVDC coated triplex
3) thickness (inch)

Arrhenius Equation

$$P_2 = P_1 \cdot e^{\frac{Ep}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right)}$$

$$\left(\begin{array}{l} \ln P = \ln P_0 - \frac{Ep}{R}\left(\frac{1}{T}\right) \\ \text{slope} : \frac{Ep}{R} \end{array} \right)$$

where,

P_2 : Expected Permeability

P_1 : Known Permeability

R : Gas Constant

E_p : Avtivation Energy

To obtain permeabilities of PVC/PVDC 250/40 at 35 °C and 20 °C

$$P_{35°C} = P_{40°C} \cdot e^{4251.7\left(\frac{1}{313} - \frac{1}{308}\right)} = 3.0879 \times 10^{-5} \times 0.8021 = 2.48 \times 10^{-5} \ \frac{g}{\text{days.cavity.mmHg}}$$

$$P_{20°C} = P_{40°C} \cdot e^{4251.7\left(\frac{1}{313} - \frac{1}{293}\right)} = 3.0879 \times 10^{-5} \times 0.3957 = 1.22 \times 10^{-5} \ \frac{g}{\text{days.cavity.mmHg}}$$

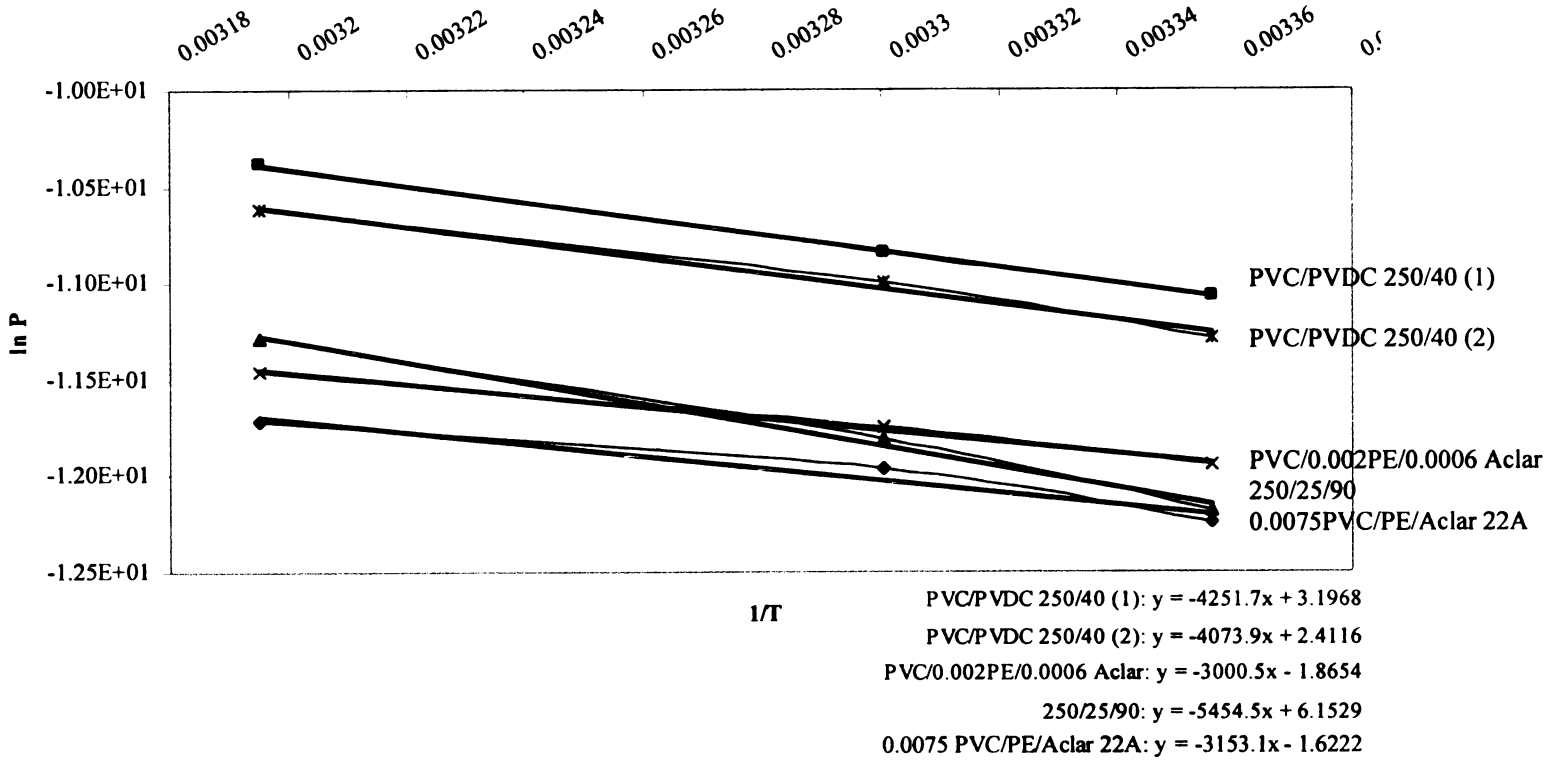


Figure 10. Arrhenius relationships for 5 blister packages

3.5 Dissolution Isotherm of USP 10mg Prednisone Calibrator Tablets

The 30-minute dissolutions over time at 25, 30, and 40 °C are given in Table 12. It reports the mean values of the readings from six vessels, which are plotted in Figure 11 (25 °C), Figure 12 (30 °C), and Figure 13 (40 °C).

As shown in Figures 11, 12, and 13, the tablets were very robust. The dissolution of stored tablets did not change over the 90 day testing period except for tablets stored at 25, 30, and 40 °C, 90% RH. The dissolution of tablets stored in 90% RH at 40 °C dropped from 29% to 25% in 15 days. The dissolution was significantly changed compared to other conditions. Therefore, this condition was used as the critical dissolution point to estimate the shelf life.

Also, the dissolution of tablets stored in 90% RH at 25 and 30 °C decreased to 23% and 24% in 15 days. In addition to that, the tablets got moldy. Therefore, the tablets failed in dissolution and by physical condition. These conditions were used as the critical dissolution points to estimate the shelf life. After the mold was found, the dissolution testing stopped.

When the package is designed, the USP 10mg calibrator tablets should be protected from high relative humidity based on these open dish results of dissolution failure and microorganism failure.

The moisture content of the tablets was measured when the dissolution was tested (Table 13). The moisture content of tablets did not change during the 90 day test period. The dissolution of the tablets was changed after reaching their equilibrium moisture content and kept changing without any moisture gain.

Table 12. 30 minutes dissolution isotherm of USP 10mg Prednisone calibrator tablets at 25, 30, 40°C

Temp.	Time (days)	Nominal RH (%)				
		50%	65%	75%	80%	90%
25°C	0	29%	29%	29%	29%	29%
	15	31%	28%	27%	31%	*23%
	30	28%	28%	28%	28%	*26%
	45	**	30%	28%	29%	***
	60	31%	29%	29%	28%	***
	90	29%	27%	28%	29%	***
30°C	0	29%	29%	29%	29%	29%
	15	30%	31%	30%	29%	*24%
	30	29%	29%	29%	27%	*26%
	45	**	31%	29%	29%	*27%
	60	32%	29%	26%	29%	***
	90	30%	31%	26%	29%	***
40°C	0	29%	29%	29%	29%	29%
	15	31%	28%	29%	30%	25%
	30	29%	30%	28%	30%	23%
	45	30%	31%	27%	26%	26%
	60	31%	29%	29%	30%	23%
	90	29%	27%	28%	30%	19%

*Tablets became moldy. The mold was not identified.
**The dissolution was not measured.
***Testing stopped because the mold growth is a physical failure that would end a stability test at day 15.

Table 13. Moisture content at dissolution testing interval of USP 10mg Prednisone calibrator tablets.

Temp.	Time (days)	Nominal RH (%)				
		50%	65%	75%	80%	90%
25 °C	15	3.41%	4.03%	4.89%	5.41%	*6.60%
	30	3.41%	4.03%	4.89%	5.41%	*6.62%
	45	**	4.03%	4.89%	5.41%	***
	60	3.41%	4.03%	4.89%	5.41%	***
	90	3.41%	4.03%	4.89%	5.41%	***
30 °C	15	3.70%	4.34%	5.38%	5.76%	*7.77%
	30	3.70%	4.34%	5.39%	5.76%	*7.77%
	45	**	4.34%	5.39%	5.76%	*7.77%
	60	3.70%	4.34%	5.39%	5.76%	***
	90	3.70%	4.34%	5.38%	5.76%	***
40 °C	15	3.91%	4.57%	5.47%	6.04%	8.58%
	30	3.89%	4.56%	5.47%	6.04%	8.58%
	45	3.87%	4.56%	5.47%	6.04%	8.57%
	60	3.85%	4.56%	**	6.04%	8.56%
	90	3.82%	4.55%	**	6.04%	8.53%

*Tablets became moldy. The mold was not identified.
**The moisture content was not measured.
***Testing stopped because the mold growth is a physical failure that would end a stability test at day 15.

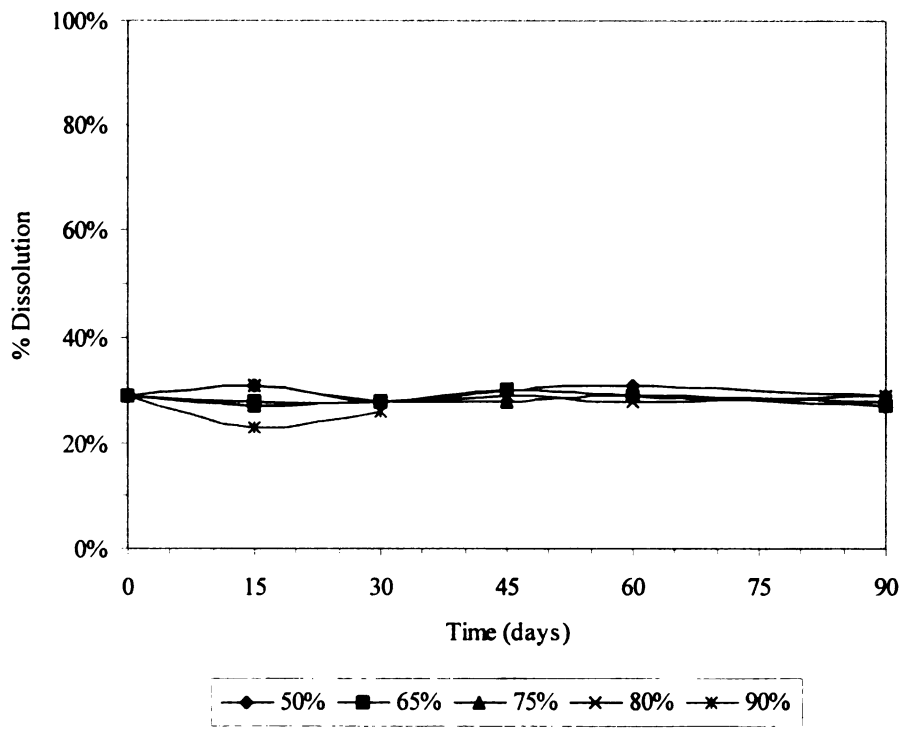


Figure 11. 30 minute dissolution isotherm of USP 10mg Prednisone calibrator tablets stored at 25 °C for 90 days.

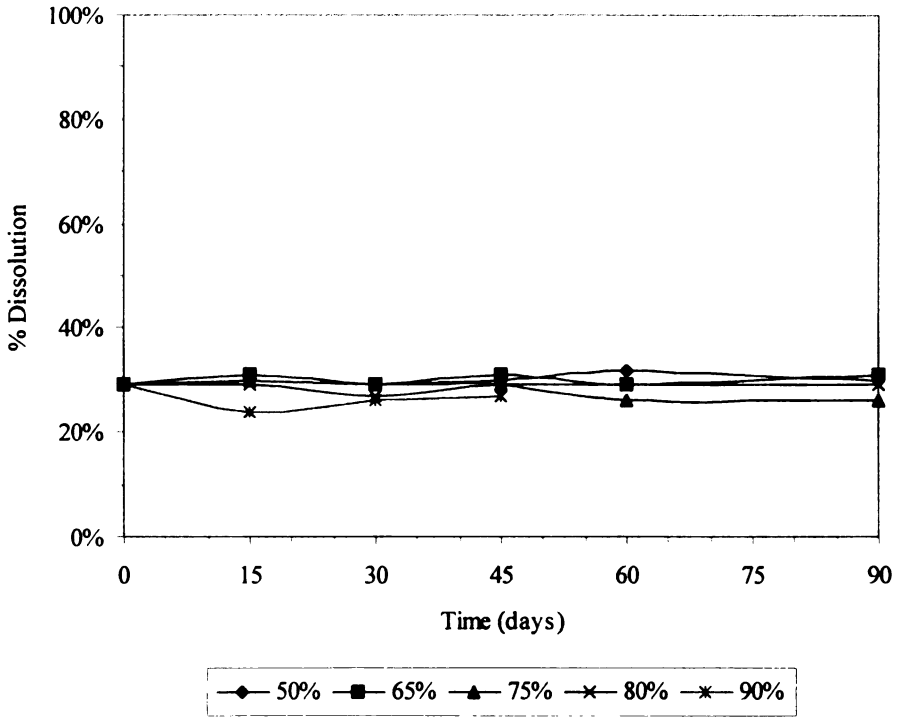


Figure 12. 30 minute dissolution isotherm of USP 10mg Prednisone calibrator tablets stored at 30 °C for 90 days.

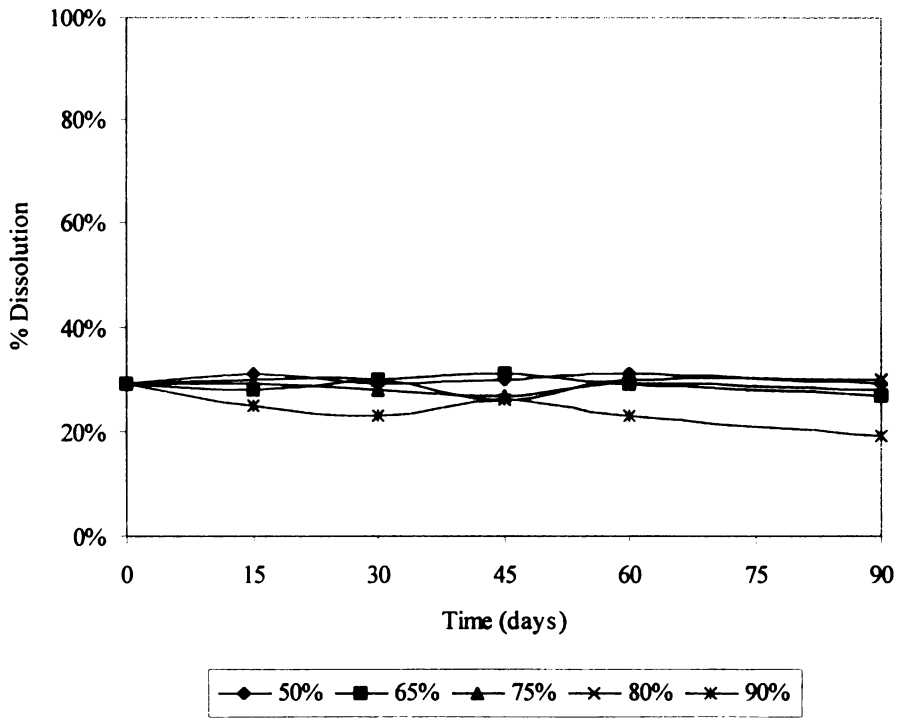
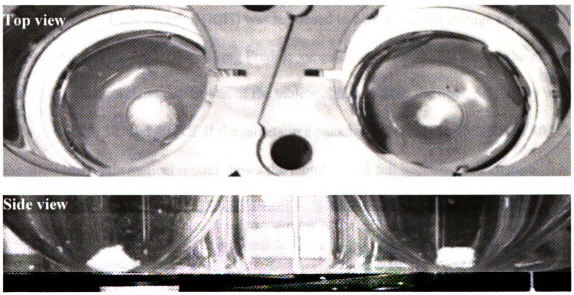


Figure 13. 30 minute dissolution isotherm of USP 10mg Prednisone calibrator tablets stored at 40 °C for 90 days.

3.6 Dissolution Behavior in the Dissolution Medium

Based on the general idea of dissolution, the dissolution behavior of USP 10mg Prednisone calibrator tablets can be explained. Figure 14-(a) shows a fresh Prednisone tablet that is almost disintegrated within one minute of stirring in the dissolution apparatus. Particles of the tablet floated freely in the medium during stirring. Then they settled into a conical heap at the bottom of the vessel. Figure 14-(b) shows a failed Prednisone tablet that did not separate or disintegrate at all, even at 30 minutes. The tablet retained its general shape, and no particles were seen floating in the medium.

The fresh tablet doesn't have much moisture in the tablet. Therefore, it is not swollen and there is weak intermolecular hydrogen bonding among the excipients. However, the failed tablet might be swelled and the excipients might be bonded by strong intermolecular hydrogen bonding.



(a) Fresh tablet disintegrated by one minute stirring

(b) Failed tablet not disintegrated at 30 minutes stirring

Figure 14. The conceptual illustration of the tablet behavior between fresh and failed tablet.

3.7 Shelf Life

For the purpose of this study, the 26% dissolution limit was used as the critical dissolution point. The dissolution values of tablets stored in 90% RH at 25, 30, and 40 °C were significantly changed. Therefore, those conditions were used as critical environment conditions to estimate the shelf life. A barrier package can be designed to protect from moisture in this high humidity environmental condition, but not from temperature.

Five blister packages were chosen to estimate the shelf life of USP 10mg Prednisone calibrator tablets. One tablet was regarded as packed in one blister and the cavity unit was used as a unit of thickness and area because the water vapor transmission rate was measured per cavity of blister package.

The accelerated testing condition (40 °C, 75% RH) specified by the International Conference on Harmonization (ICH) was supposed to be used as the storage condition to estimate shelf lives of the USP 10mg Prednisone calibrator tablets. However, the critical dissolution environment conditions of the tablets obtained from the open dish study were 90% RH at 25, 30, and 40 °C. If the tablets in a package are stored in 75% RH at 40 °C, the shelf life mathematical model shows the tablets never fail because the moisture content of the tablets stored in 75% RH at 40 °C will not reach the moisture content of tablets obtained in 90% RH at 40 °C. Therefore, a higher relative humidity than the critical dissolution value was used to estimate the shelf life.

The shelf lives were estimated for tablets stored in 92% RH at 20, 25, 30, 35, and 40 °C and the permeability required to meet an expiration date was determined. These

results (Table 14, 15, and 16) were estimated by the Windows based shelf life program (see Appendix C).

Table 14 shows the RH at the initial moisture content (IMC) and critical moisture content (CMC) at 90% RH critical environmental conditions that are used in the shelf life estimation model. Table 15 shows the permeability required to achieve a given shelf life and Table 16 shows the results of the shelf life.

Table 14. Moisture contents and relative humidities that are used to estimate shelf life.

Temperature	IMC ↔ RH	CMC ↔ RH
20 °C	3.24% ↔ 36%	8.2% ↔ 90%[1)]
25 °C	3.24% ↔ 41.04%	8.05% ↔ 91%
30 °C	3.24% ↔ 43.25%	7.7% ↔ 91.2%
35 °C	3.24% ↔ 46%	7.32% ↔ 90%[1)]
40 °C	3.24 % ↔ 49.14%	6.54% ↔ 87.45%

1) The critical environment condition was assumed to 90%.

Table 15. Maximum permeabilities required to achieve given shelf lives using the 90% RH dissolution failure point.

Given Shelf Life (years)	Storage Condition	Permeability (g/day.cavity.mmHg)
1	40 °C 92% RH	2.6×10^{-4}
2		1.3×10^{-4}
3		8.66×10^{-5}
4		6.5×10^{-5}
1	30 °C 92% RH	1.08×10^{-3}
2		5.41×10^{-4}
3		3.61×10^{-4}
4		2.71×10^{-4}
1	25 °C 92% RH	1.47×10^{-4}
2		7.34×10^{-4}
3		4.89×10^{-4}
4		3.67×10^{-4}

Table 16. Shelf life for packaged USP 10mg Prednisone calibrator tablets using the 90% dissolution failure point and the permeability calculated from the permeability constant.

Materials	Permeability (g/day.cavity.mmHg)	Storage Condition	Shelf Life (years)
PVC/PVDC 250/40(1)	3.0879×10^{-5}	40 °C 92% RH	8.7
PVC/PVDC 250/40(2)	2.4517×10^{-5}		10.9
250/25/90	1.2524×10^{-5}		21.3
PVC/PE/0.0006 Aclar	1.0548×10^{-5}		25.3
PVC/PE Aclar 22A	8.1498×10^{-6}		32.8
PVC/PVDC 250/40(1)	2.48×10^{-5}	35 °C 92% RH	16.8
PVC/PVDC 250/40(2)	1.9628×10^{-5}		21.2
250/25/90	9.3161×10^{-6}		44.7
PVC/PE/0.0006 Aclar	8.9644×10^{-6}		46.4
PVC/PE Aclar 22A	6.7861×10^{-6}		61.3
PVC/PVDC 250/40(1)	1.9615×10^{-5}	30 °C 92% RH	56.8
PVC/PVDC 250/40(2)	1.6735×10^{-5}		66.6
250/25/90	7.4550×10^{-6}		149.6
PVC/PE/0.0006 Aclar	7.9250×10^{-6}		140.7
PVC/PE Aclar 22A	6.3600×10^{-6}		175.3
PVC/PVDC 250/40(1)	1.5605×10^{-5}	25 °C 92% RH	94.0
PVC/PVDC 250/40(2)	1.2593×10^{-5}		116.5
250/25/90	5.1420×10^{-6}		285.3
PVC/PE/0.0006 Aclar	6.4649×10^{-6}		226.9
PVC/PE Aclar 22A	4.8132×10^{-6}		304.8
PVC/PVDC 250/40(1)	1.2233×10^{-5}	20 °C 92% RH	85.9
PVC/PVDC 250/40(2)	9.9730×10^{-6}		91.7
250/25/90	3.7625×10^{-6}		279.4
PVC/PE/0.0006 Aclar	5.4444×10^{-6}		193.1
PVC/PE Aclar 22A	4.0181×10^{-6}		261.7

Also, another approach was used to estimate the shelf life of tablets. Manufacturers don't allow the product to fail at the storage condition (40 °C, 92% RH). It is universal practice to use a safety factor. That is, the maximum moisture content allowed will be some value well below the critical value. Therefore, the shelf lives using a lower dissolution failure point were estimated for packaged tablets stored at 92% RH. The lower failure point was chosen to be the moisture content at 75% RH. Table 17 shows the moisture content at 75% for five storage temperatures. Table 18 shows the permeability required to achieve a given shelf life and Table 19 shows the shelf life resulting from the permeability calculated for each blister material. The moisture content is limited to one which is below the critical moisture content. It is also the equilibrium moisture content for 75% RH. Thus, we are choosing a package which keeps the internal RH $\leq$ 75% when the external RH is 92%.

In addition, other combinations of parameters (storage conditions, failure points) that can be used to estimate shelf life are shown in Appendix D.

Table 17. Moisture contents at 75% RH that are used to estimate shelf life.

Temperature	MC at 75% RH
20 °C	5.7%
25 °C	5.47%
30 °C	5.27%
35 °C	5.1%
40 °C	4.93 %

Table 18. Permeabilities required to achieve given shelf lives using the 75% RH dissolution failure point.

Given Shelf Life (years)	Storage Condition	Permeability (g/day.cavity.mmHg)
1	40 °C 92% RH	7.12×10^{-5}
2		3.56×10^{-5}
3		2.37×10^{-5}
4		1.78×10^{-5}
1	30 °C 92% RH	1.37×10^{-4}
2		6.83×10^{-5}
3		4.55×10^{-5}
4		3.42×10^{-5}
1	25 °C 92% RH	2.07×10^{-4}
2		1.04×10^{-4}
3		6.91×10^{-5}
4		5.18×10^{-5}

Table 19. Shelf life for packaged USP 10mg Prednisone calibrator tablets using the 75% dissolution failure point and the permeability calculated from the permeability constant

Materials	Permeability (g/day.cavity.mmHg)	Storage Condition	Shelf Life (years)
PVC/PVDC 250/40(1)	3.0879×10^{-5}	40 °C 92% RH	2.3
PVC/PVDC 250/40(2)	2.4517×10^{-5}		2.9
250/25/90	1.2524×10^{-5}		5.7
PVC/PE/0.0006 Aclar	1.0548×10^{-5}		6.7
PVC/PE Aclar 22A	8.1498×10^{-6}		8.7
PVC/PVDC 250/40(1)	2.48×10^{-5}	35 °C 92% RH	3.7
PVC/PVDC 250/40(2)	1.9628×10^{-5}		4.7
250/25/90	9.3161×10^{-6}		9.8
PVC/PE/0.0006 Aclar	8.9644×10^{-6}		10.2
PVC/PE Aclar 22A	6.7861×10^{-6}		13.5
PVC/PVDC 250/40(1)	1.9615×10^{-5}	30 °C 92% RH	7.0
PVC/PVDC 250/40(2)	1.6735×10^{-5}		10.8
250/25/90	7.4550×10^{-6}		18.3
PVC/PE/0.0006 Aclar	7.9250×10^{-6}		17.2
PVC/PE Aclar 22A	6.3600×10^{-6}		21.5
PVC/PVDC 250/40(1)	1.5605×10^{-5}	25 °C 92% RH	13.3
PVC/PVDC 250/40(2)	1.2593×10^{-5}		16.5
250/25/90	5.1420×10^{-6}		40.3
PVC/PE/0.0006 Aclar	6.4649×10^{-6}		32.1
PVC/PE Aclar 22A	4.8132×10^{-6}		43.1
PVC/PVDC 250/40(1)	1.2233×10^{-5}	20 °C 92% RH	21.1
PVC/PVDC 250/40(2)	9.9730×10^{-6}		25.9
250/25/90	3.7625×10^{-6}		68.7
PVC/PE/0.0006 Aclar	5.4444×10^{-6}		47.4
PVC/PE Aclar 22A	4.0181×10^{-6}		64.3

CHAPTER 4

CONCLUSIONS AND FUTURE WORK

With the open dish study, the failure points of USP 10mg Prednisone calibrator tablets can be found more quickly than during stability testing. It was found that dissolution depends on the moisture content and temperature. High relative humidity (90%) and high temperature (40 °C) caused decrease in the dissolution. Based on the open dish data, the shelf life can be estimated or package barrier requirements to achieve a desired shelf life can be calculated by using Windows based shelf life computer program (see Results and Appendix D).

As shown in Figure 11, 12, and 13, the dissolution of tablets was very stable for 90 days except for 40 °C, 90% RH. Therefore, the tablets will be stable for a long time when stored at room condition of 25 °C, 65% RH even if the tablets are packaged with a low barrier material. In Table 15, the permeability required to achieve 3 years shelf life at 40 °C, 92% RH storage condition is 8.66×10^{-5} g/day.cavity.mmHg. This permeability value is almost the same as the permeability of the PVC blister package at 40 °C. Therefore, if 3 years shelf life at 40 °C, 92% RH storage condition is desired, even the PVC blister package that is a low barrier blister material can be used.

Based on estimated shelf life and calculated barrier requirements, a package suitable for stability testing can be chosen early on before performing time-consuming stability testing. The shelf life estimation model based on the open dish study can be used to reduce the time required for a stability testing program for a product/package system. This is so because the estimation method will select the correct package and

avoid choosing a wrong package. This avoids the multiple trial and error approach and it avoids the need to prepare, test and assay product in a large number of package designs in order to find one that works.

This example of using a computer simulation model for the shelf life of moisture sensitive product is not a substitute for stability testing. In the future, shelf life results between open dish study and stability testing should be compared to verify the open dish results. Furthermore, the relationship between dissolution, moisture content, and storage time should be explained experimentally and mathematically. After that, the dissolution of tablets in the package should be accurately estimated based on open dish study.

Appendix A

Dissolution Raw Data

Table 20. USP 10mg Prednisone Calibrator Tablets Dissolution Value Raw Data at 15 days.

Dissolution Condition	Temperature	RH (%)	Number of trial						Average (6)	SD (6)	**Average (4)	**SD (4)
			1	2	3	4	5	6				
Paddle at 50 rpm	40 °C	90	25%	20%	29%	26%	28%	22%	25%	3%	25%	2%
		80	28%	32%	36%	32%	27%	31%	31%	3%	30%	2%
		75	23%	28%	30%	31%	33%	27%	29%	3%	29%	2%
		65	27%	34%	29%	25%	27%	27%	28%	3%	28%	1%
		50	33%	31%	32%	27%	36%	25%	31%	4%	31%	3%
	30 °C	*90	22%	26%	28%	19%	21%	26%	24%	4%	24%	3%
		80	25%	31%	33%	27%	37%	26%	30%	5%	29%	3%
		75	30%	31%	29%	36%	30%	30%	31%	2%	30%	1%
		65	31%	29%	26%	39%	36%	29%	32%	5%	31%	3%
		50	28%	31%	30%	27%	33%	32%	30%	2%	30%	2%
	25 °C	*90	27%	23%	22%	22%	24%	22%	23%	2%	23%	1%
		80	28%	31%	32%	27%	32%	37%	31%	3%	31%	2%
		75	23%	24%	30%	28%	28%	25%	27%	3%	27%	2%
		65	27%	35%	27%	26%	28%	29%	29%	3%	28%	1%
		50	30%	32%	33%	30%	34%	31%	32%	2%	31%	2%

*Tablets got mold.

**The largest and the smallest dissolution are not included to calculate.

Table 21. USP 10mg Prednisone Calibrator Tablets Dissolution Value Raw Data at 30 days.

Dissolution Condition	Temperature	RH (%)	Number of trial						Average (6)	SD (6)	**Average (4)	**SD (4)
			1	2	3	4	5	6				
Paddle at 50 rpm	40 °C	90	22%	22%	25%	27%	24%	22%	24%	2%	23%	1%
		80	28%	28%	28%	34%	33%	31%	30%	3%	30%	3%
		75	28%	29%	29%	28%	25%	26%	28%	2%	28%	1%
		65	28%	29%	33%	29%	34%	31%	30%	3%	30%	2%
		50	26%	32%	30%	28%	30%	29%	29%	2%	29%	1%
	30 °C	*90	24%	27%	24%	20%	30%	30%	26%	4%	26%	3%
		80	26%	31%	28%	27%	25%	26%	27%	2%	27%	1%
		75	28%	29%	27%	30%	29%	33%	29%	2%	29%	1%
		65	28%	28%	30%	29%	26%	31%	29%	2%	29%	1%
		50	27%	30%	28%	25%	33%	30%	29%	3%	29%	2%
	25 °C	*90	17%	24%	28%	31%	22%	39%	27%	8%	26%	4%
		80	26%	28%	26%	29%	29%	34%	29%	3%	28%	1%
		75	25%	27%	29%	29%	26%	30%	28%	2%	28%	2%
		65	27%	28%	35%	25%	28%	27%	28%	3%	28%	1%
		50	28%	32%	27%	29%	29%	28%	29%	2%	28%	0%

*Tablets got mold.

**The largest and the smallest dissolution are not included to calculate.

Table 22. USP 10mg Prednisone Calibrator Tablets Dissolution Value Raw Data at 45 days.

Dissolution Condition	Temperature	RH (%)	Number of trial						Average (6)	SD (6)	**Average (4)	**SD (4)
			1	2	3	4	5	6				
Paddle at 50 rpm	40 °C	90	28%	25%	30%	24%	24%	25%	26%	3%	26%	2%
		80	26%	26%					26%	0%	26%	0%
		75	29%	28%	26%	26%	30%	24%	27%	2%	27%	2%
		65	29%	32%	30%	31%	34%	29%	31%	2%	31%	1%
		50	31%	35%	29%	29%	28%	31%	31%	3%	30%	1%
	30 °C	*90	24%	17%	38%	28%	21%	35%	27%	8%	27%	6%
		80	25%	27%	28%	31%	29%	33%	29%	3%	29%	2%
		75	31%	29%	31%	30%	28%	27%	29%	2%	29%	2%
		65	30%	31%	30%	32%	27%	32%	30%	2%	31%	1%
		***50										
	25 °C	*90										
		80	27%	29%	36%	26%	40%	26%	31%	6%	29%	5%
		75	25%	30%	27%	30%	31%	24%	28%	3%	28%	2%
		65	25%	28%	31%	31%	31%	31%	30%	3%	30%	2%
		***50										

*Tablets got mold.

**The largest and the smallest dissolution are not included to calculate.

***Dissolution was not measured.

Table 23. USP 10mg Prednisone Calibrator Tablets Dissolution Value Raw Data at 60 days.

Dissolution Condition	Temperature	RH (%)	Number of trial						Average (6)	SD (6)	**Average (4)	**SD (4)
			1	2	3	4	5	6				
Paddle at 50 rpm	40 °C	90	24%	24%	24%	23%	22%	21%	23%	1%	23%	1%
		80	31%	29%	30%	29%	32%	26%	30%	2%	30%	1%
		75	28%	32%	31%	29%	23%	31%	29%	3%	30%	2%
		65	24%	34%	33%	33%	27%	25%	29%	4%	30%	4%
		50	28%	28%	36%	29%	29%	35%	31%	4%	30%	3%
	30 °C	*90										
		80	32%	34%	25%	26%	29%	30%	29%	4%	29%	3%
		75	27%	22%	28%	27%	30%	25%	26%	3%	27%	1%
		65	27%	26%	32%	33%	28%	31%	29%	3%	29%	2%
		50	32%	27%	32%	32%	33%	33%	32%	2%	32%	1%
	25 °C	*90										
		80	27%	45%	29%	27%	26%	28%	30%	7%	28%	1%
		75	25%	24%	32%	32%	32%	25%	28%	4%	29%	4%
		65	28%	28%	29%	27%	29%	30%	29%	1%	29%	1%
		50	27%	30%	33%	33%	32%	30%	31%	2%	31%	1%

*Tablets got mold.

**The largest and the smallest dissolution are not included to calculate.

Table 24. USP 10mg Prednisone Calibrator Tablets Dissolution Value Raw Data at 90 days.

Dissolution Condition	Temperature	RH (%)	Number of trial						Average (6)	SD (6)	**Average (4)	**SD (4)
			1	2	3	4	5	6				
Paddle at 50 rpm	40 °C	90	17%	22%	15%	22%	22%	15%	19%	3%	19%	3%
		80	28%	29%	33%	29%	26%	35%	30%	3%	30%	2%
		75	24%	28%	28%	33%	29%	29%	28%	3%	28%	1%
		65	31%	34%	26%	25%	26%	29%	28%	4%	28%	3%
		50	26%	26%	34%	27%	25%	27%	27%	3%	27%	1%
	30 °C	*90										
		80	31%	33%	29%	28%	29%	26%	29%	2%	29%	1%
		75	31%	33%	23%	24%	25%	25%	27%	4%	26%	3%
		65	26%	32%	31%	29%	33%	33%	31%	3%	31%	2%
		50	30%	29%	30%	30%	29%	29%	30%	1%	30%	1%
	25 °C	*90										
		80	29%	31%	28%	30%	29%	30%	30%	1%	29%	1%
		75	25%	28%	28%	28%	26%	29%	27%	1%	28%	1%
		65	29%	26%	26%	26%	32%	27%	28%	3%	27%	2%
		50	25%	26%	29%	28%	32%	31%	29%	3%	29%	2%

*Tablets got mold.

**The largest and the smallest dissolution are not included to calculate.

Appendix B

G.A.B. Quadratic Regressions

Table 25. Experimental sorption isotherm data at 40 °C.

a_w	M	a_w/M
0	0	0
0.128	0.01754	7.297605
0.328	0.02679	12.23881
0.495	0.03409	14.52039
0.6455	0.04027	16.0293
0.7605	0.04889	15.55533
0.79	0.05407	14.61069
0.8745	0.06599	13.25201

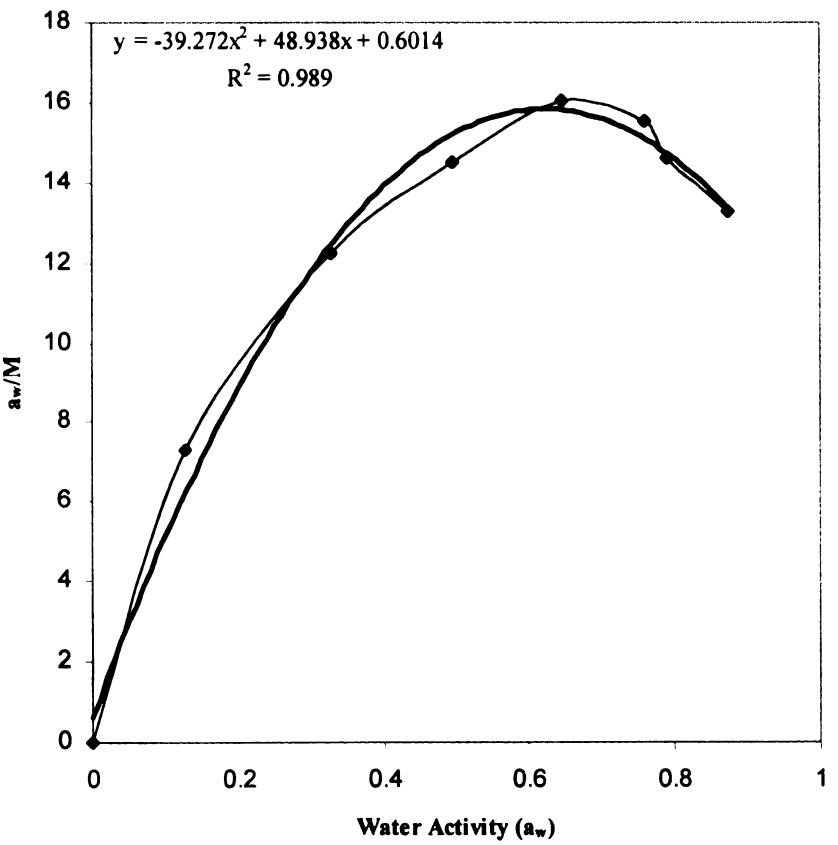


Figure 15. G.A.B. quadratic regression conducted on experimental values at 40 °C.

Table 26. Experimental sorption isotherm data at 30 °C.

a_w	M	a_w/M
0	0	0
0.152	0.02114	7.190161
0.353	0.03014	11.71201
0.5125	0.03704	13.83639
0.648	0.04336	14.94465
0.7625	0.05376	14.18341
0.798	0.05755	13.8662
0.912	0.07773	11.73292

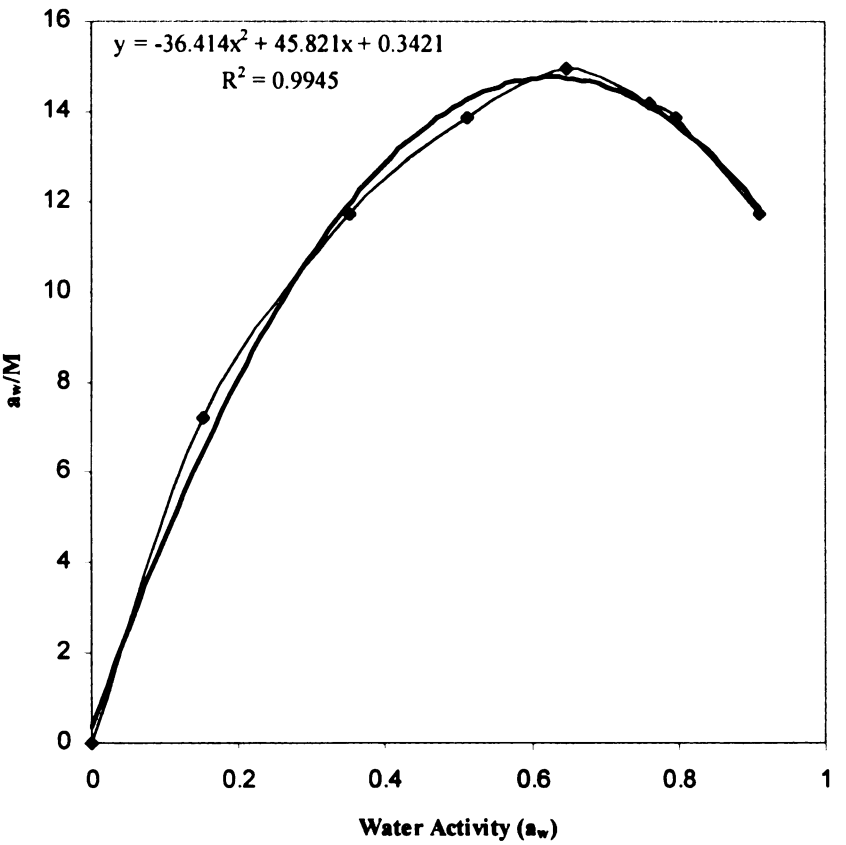


Figure 16. G.A.B. quadratic regression conducted on experimental values at 30 °C.

Table 27. Experimental sorption isotherm data at 25 °C.

a_w	M	a_w/M
0	0	0
0.16	0.02127	7.522332
0.3405	0.03197	10.65061
0.5325	0.03913	13.60848
0.663	0.04574	14.49497
0.7675	0.05466	14.04135
0.8005	0.06037	13.2599
0.9195	0.08577	10.72053

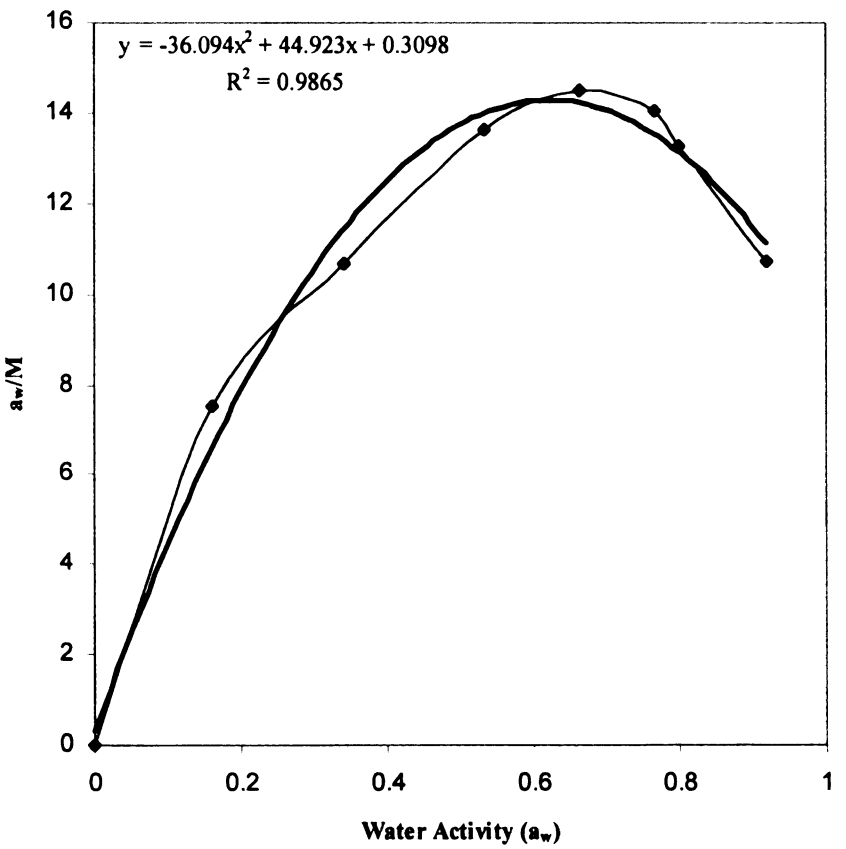


Figure 17. G.A.B. quadratic regression conducted on experimental values at 25 °C.

Table 28. G.A.B. quadratic forms describing moisture sorption isotherm of USP 10mg Prednisone calibrator tablets

Temperature, °C	G.A.B. quadratic equation	% RMS
25 °C	$\left(\frac{a_w}{M}\right) = -36.094a_w^2 + 44.923a_w + 0.3098$	6.04%
30 °C	$\left(\frac{a_w}{M}\right) = -36.414a_w^2 + 45.821a_w + 0.3421$	4.24%
40 °C	$\left(\frac{a_w}{M}\right) = -39.272a_w^2 + 48.938a_w + 0.6014$	6.45%

The relationship between M and a_w was represented by G.A.B. quadratic equation. Therefore, the sorption isotherms using G.A.B model can be constructed as shown in Figure 7 (Data & Results).

$$M = \frac{a_w}{-36.094a_w^2 + 44.923a_w + 0.3098} \quad (25°C)$$

$$M = \frac{a_w}{-36.414a_w^2 + 45.821a_w + 0.3421} \quad (30°C)$$

$$M = \frac{a_w}{-39.272a_w^2 + 48.938a_w + 0.6014} \quad (40°C)$$

G.A.B. quadratic equation is modified:

$$(-36.094 \cdot M) \cdot a_w^2 + (44.923 \cdot M - 1) \cdot a_w + 0.3098 \cdot M = 0 \quad (25\,°C)$$
$$(-36.414 \cdot M) \cdot a_w^2 + (45.821 \cdot M - 1) \cdot a_w + 0.3421 \cdot M = 0 \quad (30\,°C)$$
$$(-39.272 \cdot M) \cdot a_w^2 + (48.938 \cdot M - 1) \cdot a_w + 0.6014 \cdot M = 0 \quad (40\,°C)$$

Calculation

Initial Moisture Content (IMC): 3.24% (M: 0.0324)

By quadratic formula

$$RH = 41.04\%\,(25\,°C),\quad RH = 43.25\%\,(30\,°C),\quad RH = 49.14\%\,(40\,°C)$$

Appendix C

Windows Based Shelf Life Computer Program

Introduction

In 1989, a DOS based computer simulation program for shelf life was developed at the School of Packaging at Michigan State University. However, it was difficult to use and time consuming. The new Windows based shelf life program is much more user friendly than the DOS version. Calculations for many alternative packages can be made rapidly.

In this new program, the most powerful advantage is that the data are changeable and movable and can minimize error because all data can be seen on one screen. Also, the linear and non-linear shelf life models can be compared at the same time. This program also can convert between permeabilities that use different units, and it can use the Arrhenius equation. Therefore, shelf life can be estimated more effectively. Parameters necessary to estimate shelf life can be easily changed. As a result, rapid comparison can be made for a variety of situations. The parameters can all be changed as needed: package permeability, storage conditions, and product moisture isotherm. Therefore, the program can be used to calculate the permeability required to achieve a desired shelf life for a specific product.

To explain the program, data obtained from an open dish study were used. All shelf life calculations can be solved in the program without opening other spreadsheet programs or using a calculator. Even the sorption isotherm curve can be constructed with the program.

First, when the program is opened, there are "Raw Data", "Graph", and "Shelf Life Calculation" windows in the main window as shown in Figure 18. In this shelf life program, there are 5 different sorption isotherms, using 5-9 data points. In this study, 7 data points were used for the moisture sorption isotherm. The "Graph" window is to construct the moisture sorption isotherm curve. The "Conversion" program is to convert units for permeabilities that are using different units.

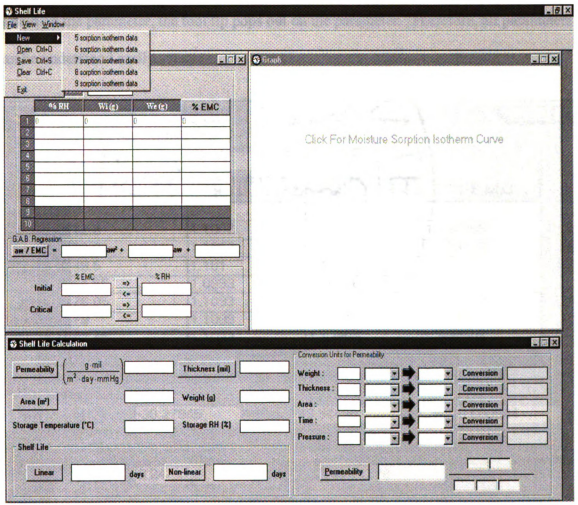


Figure 18. The front page of the shelf life program.

The initial moisture content (IMC), relative humidity (RH), initial weight of product (W_i), and equilibrium weight of product (W_e) are inserted and then clicked to calculate the equilibrium moisture content (EMC). If the G.A.B. regression button is clicked, the G.A.B. quadratic equation is calculated. This equation is programmed with the polynomial regression method.

This program has "Save" and "Open" functions. Therefore, the data can be transferred and don't need to be put in again. As shown in Figure 19, if the mouse point is held on the parameter, the tool tip pops out on the parameter. Therefore, all parameters can be understood easily.

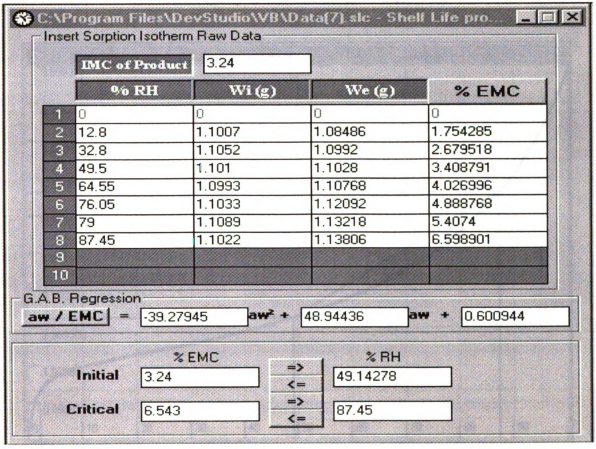


Figure 19. The G.A.B. Model of the shelf life program

By clicking the "Sorption Isotherm" window, the moisture sorption isotherm curve is constructed automatically by the G.A.B. quadratic equation, and initial and critical moisture points can be shown on the graph. The quality of fit between the experimental moisture sorption isotherm data and the G.A.B. model is judged by %RMS. As shown in Figure 20, the shelf life model can be determined by the line between the initial and the critical point. In this case, the non-linear shelf life model should be used to estimate the shelf life more accurately. The relative humidity (RH) at the initial moisture content or critical moisture content (CMC) at the critical environment condition on the graph can be calculated automatically without reading the numbers on the graph. Also, these numbers are used automatically to estimate the shelf life.

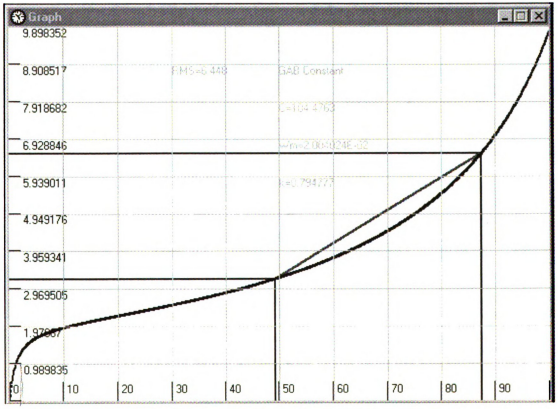


Figure 20. The moisture sorption isotherm graph of the shelf life program

Finally, to estimate the shelf life, a blister package is used and the product is represented as stored at 40 °C, 92% RH. By clicking the "Linear" or "Non-linear" button, the shelf life can be estimated. As shown in Figure 21, these shelf lives differ a little because of the different slope values between initial and critical point. Also, the package can be designed at given shelf life by clicking the "Permeability", "Thickness", or "Area". This function is very valuable for calculating shelf life and choosing a package for stability testing because a lot of situations can be simulated easily, based on open dish data.

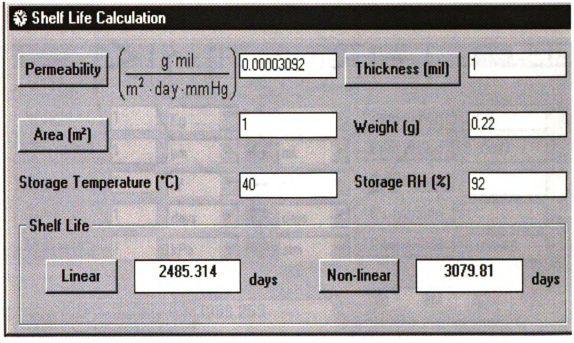


Figure 21. The shelf life calculation of the shelf life program

As shown in Figure 22, the "Conversion" program is used as a utility in the shelf life program. Although there is a standard unit for permeability, many other units are used. For example, consider the following two permeabilities that use different units. To compare those two permeabilities, units must be identical. In this program, after the intended units are selected, the permeability can be converted easily.

For example, to convert the permeability 1) to the same units as permeability 2), the program provides the choices in Figure 22.

$$1)\ \frac{kg \cdot \mu m}{m^2 \cdot day \cdot kPa}$$

$$2)\ 3.989 \times 10^3\ \frac{g \cdot mil}{m^2 \cdot day \cdot atm}$$

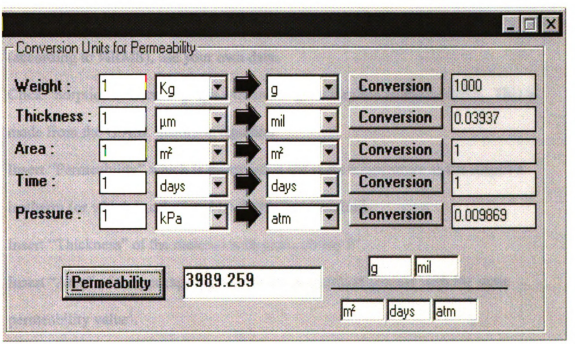


Figure 22. The conversion program for the permeability

Program procedures to estimate the shelf life of a product in the package.

1. Open the shelf life program on the "file" menu.
2. Insert the initial moisture content (IMC) based on dry weight basis, g of water/100g of solids when the product is fresh.
3. Insert the relative humidity (%RH).
4. Insert average initial product weight (W_i), and average final product weight (W_e) at each RH.
5. Click "%EMC" button to calculate the %EMC (gram/100g dry product).
6. Click "aw/EMC" button to get the G.A.B. quadratic equation.
7. Click "→" to get an intended relative humidity or click "←" to get an intended moisture content. If your data does not fit well the G.A.B. quadratic regression well (according to %RMS), use your own data.
8. Click "Sorption Isotherm" graph window to get a sorption isotherm curve. This is made from the G.A.B. quadratic equation.
9. Insert "Permeability" which is measured at the same temperature as the sorption isotherm (or which is calculated by Arrhenius equation).
10. Insert "Thickness" of the material with permeability P[1].
11. Insert "Area" of the package exposed to the permeation process with the same permeability value[1].
12. Insert "Weight" of the product in the package.

[1] Use 1 for the thickness and 1 for the area when Permeability is for the package.

13. Insert "Temperature" at which you want to store. This should be the same temperature at which the sorption isotherm curve was determined.
14. Insert the "Relative Humidity" at which the product will be stored.
15. Click "Linear" to get shelf life[2].
16. Click "Non-linear" to get shelf life[2].

[2] See the "Sorption Isotherm Curve", to decide which model is more accurate.

Appendix D

Shelf Life Estimation

Table 29. Moisture contents and relative humidities that are used to estimate the shelf life at various combination situations

Temperature	Moisture Contents			
	90%	80%	75%	65%
20 °C	8.2%	6.3%	5.7%	4.6%
25 °C	8.05% (91% RH)	6.08%	5.47%	4.55%
30 °C	7.7% (91.2% RH)	5.84%	5.27%	4.41%
35 °C	7.32%	5.5%	5.1%	4.2%
40 °C	6.54% (87.45% RH)	5.47%	4.93%	4.11%

Table 30. Shelf life of USP 10mg Prednisone calibrator tablets in the PVC/PVDC 250/40 (1)

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
90%	20 °C	1.2233×10^{-5}	20 °C, 92% RH	85.9
	25 °C	1.5605×10^{-5}	25 °C, 92% RH	94.0
	30 °C	1.9615×10^{-5}	30 °C, 92% RH	56.8
	35 °C	2.48×10^{-5}	35 °C, 92% RH	16.8
	40 °C	3.0879×10^{-5}	40 °C, 92% RH	8.7
80%	20 °C	1.2233×10^{-5}	20 °C, 92% RH	30.1
			20 °C, 85% RH	44.6
	25 °C	1.5605×10^{-5}	25 °C, 92% RH	17.2
			25 °C, 85% RH	25.8
	30 °C	1.9615×10^{-5}	30 °C, 92% RH	9.6
			30 °C, 85% RH	14.5
	35 °C	2.48×10^{-5}	35 °C, 92% RH	4.6
			35 °C, 85% RH	6.8
	40 °C	3.0879×10^{-5}	40 °C, 92% RH	3.2
			40 °C, 85% RH	5.0

Table 30. Continued

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
75%	20 °C	1.2233×10^{-5}	20 °C, 92% RH	21.1
			20 °C, 85% RH	28.1
			20 °C, 80% RH	38.5
	25 °C	1.5605×10^{-5}	25 °C, 92% RH	13.3
			25 °C, 85% RH	15.8
			25 °C, 80% RH	22.0
	30 °C	1.9615×10^{-5}	30 °C, 92% RH	7.0
			30 °C, 85% RH	8.8
			30 °C, 80% RH	12.4
	35 °C	2.48×10^{-5}	35 °C, 92% RH	3.7
			35 °C, 85% RH	31.8
			35 °C, 80% RH	6.0
	40 °C	3.0879×10^{-5}	40 °C, 92% RH	2.3
			40 °C, 85% RH	2.9
			40 °C, 80% RH	4.2
65%	20 °C	1.2233×10^{-5}	20 °C, 92% RH	9.6
			20 °C, 85% RH	11.8
			20 °C, 80% RH	14.2
			20 °C, 75% RH	17.9
	25 °C	1.5605×10^{-5}	25 °C, 92% RH	5.7
			25 °C, 85% RH	7.0
			25 °C, 80% RH	8.5
			25 °C, 75% RH	10.9
	30 °C	1.9615×10^{-5}	30 °C, 92% RH	3.1
			30 °C, 85% RH	3.8
			30 °C, 80% RH	4.7
			30 °C, 75% RH	6.0
	35 °C	2.48×10^{-5}	35 °C, 92% RH	1.4
			35 °C, 85% RH	1.7
			35 °C, 80% RH	2.1
			35 °C, 75% RH	2.6
	40 °C	3.0879×10^{-5}	40 °C, 92% RH	0.9
			40 °C, 85% RH	1.1
			40 °C, 80% RH	1.4
			40 °C, 75% RH	1.8

Table 31. Shelf life of USP 10mg Prednisone calibrator tablets in the PVC/PVDC 250/40 (2)

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
90%	20 °C	9.9730×10^{-6}	20 °C, 92% RH	91.7
	25 °C	1.2593×10^{-5}	25 °C, 92% RH	116.5
	30 °C	1.6735×10^{-5}	30 °C, 92% RH	66.6
	35 °C	1.9628×10^{-5}	35 °C, 92% RH	21.2
	40 °C	2.4517×10^{-5}	40 °C, 92% RH	10.9
80%	20 °C	9.9730×10^{-6}	20 °C, 92% RH	36.9
			20 °C, 85% RH	54.7
	25 °C	1.2593×10^{-5}	25 °C, 92% RH	21.3
			25 °C, 85% RH	32.0
	30 °C	1.6735×10^{-5}	30 °C, 92% RH	11.3
			30 °C, 85% RH	17.0
	35 °C	1.9628×10^{-5}	35 °C, 92% RH	5.8
			35 °C, 85% RH	8.5
	40 °C	2.4517×10^{-5}	40 °C, 92% RH	4.1
			40 °C, 85% RH	6.3
75%	20 °C	9.9730×10^{-6}	20 °C, 92% RH	25.9
			20 °C, 85% RH	34.5
			20 °C, 80% RH	47.2
	25 °C	1.2593×10^{-5}	25 °C, 92% RH	16.5
			25 °C, 85% RH	19.6
			25 °C, 80% RH	27.2
	30 °C	1.6735×10^{-5}	30 °C, 92% RH	10.8
			30 °C, 85% RH	10.4
			30 °C, 80% RH	14.5
	35 °C	1.9628×10^{-5}	35 °C, 92% RH	4.7
			35 °C, 85% RH	5.5
			35 °C, 80% RH	7.6
	40 °C	2.4517×10^{-5}	40 °C, 92% RH	2.9
			40 °C, 85% RH	3.7
			40 °C, 80% RH	5.3

Table 31. Continued

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
65%	20 °C	9.9730×10^{-6}	20 °C, 92% RH	11.8
			20 °C, 85% RH	14.5
			20 °C, 80% RH	17.4
			20 °C, 75% RH	22.0
	25 °C	1.2593×10^{-5}	25 °C, 92% RH	7.0
			25 °C, 85% RH	8.7
			25 °C, 80% RH	10.6
			25 °C, 75% RH	13.5
	30 °C	1.6735×10^{-5}	30 °C, 92% RH	3.6
			30 °C, 85% RH	4.5
			30 °C, 80% RH	5.5
			30 °C, 75% RH	7.0
	35 °C	1.9628×10^{-5}	35 °C, 92% RH	1.8
			35 °C, 85% RH	2.2
			35 °C, 80% RH	2.6
			35 °C, 75% RH	3.3
	40 °C	2.4517×10^{-5}	40 °C, 92% RH	1.1
			40 °C, 85% RH	1.4
			40 °C, 80% RH	1.8
			40 °C, 75% RH	2.3

Table 32. Table xx. Shelf life of USP 10mg Prednisone calibrator tablets in the 250/25/90

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
90%	20 °C	3.7625×10^{-6}	20 °C, 92% RH	279.4
	25 °C	5.1420×10^{-6}	25 °C, 92% RH	285.3
	30 °C	7.4550×10^{-6}	30 °C, 92% RH	149.6
	35 °C	9.3161×10^{-6}	35 °C, 92% RH	44.7
	40 °C	1.2524×10^{-5}	40 °C, 92% RH	21.3
80%	20 °C	3.7625×10^{-6}	20 °C, 92% RH	97.8
			20 °C, 85% RH	144.7
	25 °C	5.1420×10^{-6}	25 °C, 92% RH	52.1
			25 °C, 85% RH	78.4
	30 °C	7.4550×10^{-6}	30 °C, 92% RH	25.3
			30 °C, 85% RH	38.2
	35 °C	9.3161×10^{-6}	35 °C, 92% RH	12.2
			35 °C, 85% RH	18.0
	40 °C	1.2524×10^{-5}	40 °C, 92% RH	8.0
			40 °C, 85% RH	12.4

Table 32. Continued

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
75%	20 °C	3.7625×10^{-6}	20 °C, 92% RH	68.7
			20 °C, 85% RH	91.5
			20 °C, 80% RH	125.2
	25 °C	5.1420×10^{-6}	25 °C, 92% RH	40.3
			25 °C, 85% RH	48.1
			25 °C, 80% RH	66.7
	30 °C	7.4550×10^{-6}	30 °C, 92% RH	18.3
			30 °C, 85% RH	23.3
			30 °C, 80% RH	32.5
	35 °C	9.3161×10^{-6}	35 °C, 92% RH	9.8
			35 °C, 85% RH	11.6
			35 °C, 80% RH	15.9
	40 °C	1.2524×10^{-5}	40 °C, 92% RH	5.7
			40 °C, 85% RH	7.3
			40 °C, 80% RH	10.3
65%	20 °C	3.7625×10^{-6}	20 °C, 92% RH	31.2
			20 °C, 85% RH	38.4
			20 °C, 80% RH	46.1
			20 °C, 75% RH	58.3
	25 °C	5.1420×10^{-6}	25 °C, 92% RH	17.2
			25 °C, 85% RH	21.3
			25 °C, 80% RH	25.9
			25 °C, 75% RH	33.2
	30 °C	7.4550×10^{-6}	30 °C, 92% RH	8.1
			30 °C, 85% RH	10.1
			30 °C, 80% RH	12.3
			30 °C, 75% RH	15.8
	35 °C	9.3161×10^{-6}	35 °C, 92% RH	3.7
			35 °C, 85% RH	4.6
			35 °C, 80% RH	5.5
			35 °C, 75% RH	6.9
	40 °C	1.2524×10^{-5}	40 °C, 92% RH	2.2
			40 °C, 85% RH	2.8
			40 °C, 80% RH	3.4
			40 °C, 75% RH	4.5

Table 33. Table xx. Shelf life of USP 10mg Prednisone calibrator tablets in the PVC/PE/0.0006 Aclar

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
90%	20 °C	5.444×10^{-6}	20 °C, 92% RH	193.1
	25 °C	6.4649×10^{-6}	25 °C, 92% RH	226.9
	30 °C	7.9250×10^{-6}	30 °C, 92% RH	140.7
	35 °C	8.9644×10^{-6}	35 °C, 92% RH	46.4
	40 °C	1.0548×10^{-5}	40 °C, 92% RH	25.3
80%	20 °C	5.444×10^{-6}	20 °C, 92% RH	67.6
			20 °C, 85% RH	100.2
	25 °C	6.4649×10^{-6}	25 °C, 92% RH	41.5
			25 °C, 85% RH	62.3
	30 °C	7.9250×10^{-6}	30 °C, 92% RH	23.8
			30 °C, 85% RH	36.0
	35 °C	8.9644×10^{-6}	35 °C, 92% RH	12.6
			35 °C, 85% RH	18.7
	40 °C	1.0548×10^{-5}	40 °C, 92% RH	9.5
			40 °C, 85% RH	14.7
75%	20 °C	5.444×10^{-6}	20 °C, 92% RH	47.4
			20 °C, 85% RH	63.3
			20 °C, 80% RH	86.6
	25 °C	6.4649×10^{-6}	25 °C, 92% RH	32.1
			25 °C, 85% RH	38.2
			25 °C, 80% RH	53.1
	30 °C	7.9250×10^{-6}	30 °C, 92% RH	17.2
			30 °C, 85% RH	21.9
			30 °C, 80% RH	30.6
	35 °C	8.9644×10^{-6}	35 °C, 92% RH	10.2
			35 °C, 85% RH	12.1
			35 °C, 80% RH	16.6
	40 °C	1.0548×10^{-5}	40 °C, 92% RH	6.7
			40 °C, 85% RH	8.6
			40 °C, 80% RH	12.3

Table 33. Continued

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
65%	20 °C	5.444×10^{-6}	20 °C, 92% RH	21.6
			20 °C, 85% RH	26.5
			20 °C, 80% RH	31.8
			20 °C, 75% RH	40.3
	25 °C	6.4649×10^{-6}	25 °C, 92% RH	13.7
			25 °C, 85% RH	17.0
			25 °C, 80% RH	20.6
			25 °C, 75% RH	26.4
	30 °C	7.9250×10^{-6}	30 °C, 92% RH	7.6
			30 °C, 85% RH	9.5
			30 °C, 80% RH	11.5
			30 °C, 75% RH	14.9
	35 °C	8.9644×10^{-6}	35 °C, 92% RH	3.9
			35 °C, 85% RH	4.7
			35 °C, 80% RH	5.7
			35 °C, 75% RH	7.2
	40 °C	1.0548×10^{-5}	40 °C, 92% RH	2.6
			40 °C, 85% RH	3.3
			40 °C, 80% RH	4.1
			40 °C, 75% RH	5.4

Table 34. Table xx. Shelf life of USP 10mg Prednisone calibrator tablets in the PVC/PE Aclar 22A

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
90%	20 °C	4.0181×10^{-6}	20 °C, 92% RH	261.7
	25 °C	4.8132×10^{-6}	25 °C, 92% RH	304.8
	30 °C	6.3600×10^{-6}	30 °C, 92% RH	175.3
	35 °C	6.7861×10^{-6}	35 °C, 92% RH	61.3
	40 °C	8.1498×10^{-6}	40 °C, 92% RH	32.8
80%	20 °C	4.0181×10^{-6}	20 °C, 92% RH	91.6
			20 °C, 85% RH	135.7
	25 °C	4.8132×10^{-6}	25 °C, 92% RH	55.7
			25 °C, 85% RH	83.7
	30 °C	6.3600×10^{-6}	30 °C, 92% RH	29.6
			30 °C, 85% RH	44.8
	35 °C	6.7861×10^{-6}	35 °C, 92% RH	16.7
			35 °C, 85% RH	24.7
	40 °C	8.1498×10^{-6}	40 °C, 92% RH	12.3
			40 °C, 85% RH	19.0

Table 34. Continued

Failure Points		Permeability	Storage Conditions	Shelf Life (yrs)
75%	20 °C	4.0181×10^{-6}	20 °C, 92% RH	64.3
			20 °C, 85% RH	85.7
			20 °C, 80% RH	117.3
	25 °C	4.8132×10^{-6}	25 °C, 92% RH	43.1
			25 °C, 85% RH	51.4
			25 °C, 80% RH	71.3
	30 °C	6.3600×10^{-6}	30 °C, 92% RH	21.5
			30 °C, 85% RH	27.3
			30 °C, 80% RH	38.1
	35 °C	6.7861×10^{-6}	35 °C, 92% RH	13.5
			35 °C, 85% RH	16.0
			35 °C, 80% RH	21.9
	40 °C	8.1498×10^{-6}	40 °C, 92% RH	8.7
			40 °C, 85% RH	11.1
			40 °C, 80% RH	15.9
65%	20 °C	4.0181×10^{-6}	20 °C, 92% RH	29.2
			20 °C, 85% RH	35.9
			20 °C, 80% RH	43.1
			20 °C, 75% RH	54.6
	25 °C	4.8132×10^{-6}	25 °C, 92% RH	18.4
			25 °C, 85% RH	22.8
			25 °C, 80% RH	27.6
			25 °C, 75% RH	35.4
	30 °C	6.3600×10^{-6}	30 °C, 92% RH	9.5
			30 °C, 85% RH	11.8
			30 °C, 80% RH	14.4
			30 °C, 75% RH	18.5
	35 °C	6.7861×10^{-6}	35 °C, 92% RH	5.1
			35 °C, 85% RH	6.3
			35 °C, 80% RH	7.5
			35 °C, 75% RH	9.5
	40 °C	8.1498×10^{-6}	40 °C, 92% RH	3.4
			40 °C, 85% RH	4.3
			40 °C, 80% RH	5.3
			40 °C, 75% RH	7.0

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