This is to certify that the

thesis entitled

DISSOLUTION SHELF LIFE OF PREDNISONE
THERAPEUTIC DOSAGE FORM TABLET

presented by

Matthew S. Thomas

has been accepted towards fulfillment
of the requirements for

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Hugh E. Lockhart

Major professor

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DISSOLUTION SHELF LIFE OF PREDNISONE

THERAPEUTIC DOSAGE FORM TABLET

by

Matthew S. Thomas

A Thesis

Submitted to
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Abstract

DISSOLUTION SHELF LIFE OF PREDNISONE
THERAPEUTIC DOSAGE FORM TABLET
by
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Uncoated 5 mg Prednisone tablets were stored (open dish) in humidity buckets, which included nominal relative humidities (RH) of 12%, 33%, 50%, 65%, 75%, 80% and 90% at three ICH temperatures (25C, 30C and 40C). Moisture sorption isotherms, initial and critical moisture contents were determined for the product and used in a dissolution shelf life model.

Critical moisture content data was generated using a dissolution procedure according to United States Pharmacopoeia (USP) section <711>. Prednisone tablets were stored at conditions mentioned above and dissolution testing was performed in triplicate at each storage condition every three days for approximately two months. Dissolution failures were identified at storage conditions corresponding to RH of 75% and higher for each temperature.

The dissolution shelf life model was used to suggest packaging materials, which minimize material costs while providing sufficient protection over a desired shelf life. This study shows that PVC blister materials (low moisture barrier) may not provide enough protection from moisture. So, a higher moisture barrier material, such as 0.6 mil Aclar (more expensive than PVC), may be required.

Acknowledgments

First of all, my love and appreciation goes out to my family for all of their support throughout the years. Thanks to Mom and Dad for always being there, no matter what the issue. Thanks to my brothers and sisters for being such a big part of my life. Thanks to my wife for being so supportive and patient through the years. I could not have done any of this without you.

I would also like to thank my colleagues and the faculty at the School of Packaging for making my second college adventure so memorable. It is this group of people who truly makes the School of Packaging a special place. Special thanks to my committee members; Dr. Hugh Lockhart, Dr. Susan Selke and Dr. Dennis Gilliland.

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Introduction

Stability testing is required by federal Food and Drug Administration (FDA) regulations. It is taken as a laboratory verification that the drug in its package will continue to meet USP monograph requirements during its expiration dating period (shelf life).

The pharmaceutical industry relies on efficient and timely drug development plans, which are often described as "speed to market". The objective is to get the drug product to market as quickly as possible. The primary responsibility of each participating group in a drug development plan is not to delay the drug development timeline. Every day wasted in the timeline can mean the loss of millions of dollars.

Package development groups rely on experience to dictate which packaging materials will be used for product stability testing. Stability testing can be very expensive, so the number of package alternatives should be limited and chosen very carefully. For example, three blister materials may be used to package a product for initial stability testing. Usually these three blisters will incorporate high, medium and low barriers to moisture. If the high barrier material does not protect the product adequately, the stability process must start over. This is the worst case scenario, and should be avoided at all costs. A low barrier material offers the opportunity to save money if the product passes

stability requirements. Therefore, such a barrier should be included in stability testing.

Prior to putting a package scenario together for a product entering initial stability, any package/product information a packaging engineer can find will be useful. Upon final product formulation, characterization testing of the drug product is performed to provide sensitivity information about that product. These tests take the form of open dish studies at designated ICH (International Conference on Harmonisation) temperatures and relative humidities (RH). If a product formulation is extremely sensitive to moisture or light, for example, the package selections for stability will take this into account.

Dissolution shelf life (DSL) can be used for moisture sensitive products to provide additional information before package materials are chosen for stability testing. Since moisture is often the major concern for product sensitivity, the DSL model can prove to be very powerful. The study objectives listed below highlight key areas of this project.

1. Standardize the dissolution testing procedure for recording dissolution data. USP standards were used to develop a calibration curve, which determined the percent dissolution values from absorbance units (AU). These AU were the direct readings from an ultra violet/visible spectrophotometer (UV-Vis). USP dissolution calibrator tablets were used to calibrate the performance of the dissolution apparatus.

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2. Determine the initial moisture content of the Prednisone tablets using a Karl Fisher autotitration method.

3. Develop moisture sorption isotherms using a gravimetric method for product stored in open dish at various ICH RH and temperatures.

4. Perform dissolution testing of the product being stored at various ICH temperatures and RH. Determine the critical moisture content of the product from respective dissolution failures, which were used in the shelf life model. The critical moisture content is defined as the moisture content at which the product fails dissolution, or at which there is a significant change in dissolution behavior.

5. Use the critical moisture content in the shelf life model to determine package selection options for stability testing of the drug product.

Pharmaceutical companies will conduct many analytical tests during the product characterization phase. These tests can be expensive and time consuming, but they provide essential testing data. Since chemical testing resources were limited at the School of Packaging, one test method (dissolution) was chosen to indicate critical conditions. Dissolution is a physical test based on physical properties. The following quotes verify that dissolution testing is an excellent choice, especially for a moisture sensitive pharmaceutical product.

"Dissolution analysis of pharmaceutical solid dosage forms has emerged as the single most important test that, when carried out appropriately, will ensure the quality of the product" (Banaker, 1992).

"The importance of dissolution rate on clinical performance of drugs and drug delivery systems has long been recognized. It is the overwhelmingly important property of dosage forms that contributes to the rate and extent of drug availability to the body and, as such, is deserving of the effort that has been put forth to develop dissolution systems that provide fundamental information on the dissolution process of many drugs and chemicals as well as meaningful in vitro dissolution system models that can be correlated with some index of in vivo performance" (Banaker, 1992).

"Dissolution testing, of course, is a regular quality control procedure in good manufacturing practice. Whether or not its numbers have been correlated with biological effectiveness, the standard dissolution test is a simple and inexpensive indicator of a product's physical consistency" (Hanson,1991).

This thesis is the sixth in a series of theses reporting the development at the School of Packaging of a method for calculating the moisture barrier requirements for drug products. The two previous theses (Adams, Yoon) are listed in the bibliography. The work done involved method development and application of the method to hard gelatin capsules, coated tablets and two variations of uncoated tablets.

Literature Review

Many sources have indicated that dissolution is one of the most important tests to verify the efficacy of pharmaceutical products. In fact, over 100 years ago, scientists recognized dissolution as an important prerequisite for drug absorption. Other theses (Adams, Yoon) published at the School of Packaging, based on shelf life modeling, have detailed literature reviews, which highlight the history and importance of dissolution in measuring drug product efficacy.

Many studies have correlated drug bioavailability (in-vivo) and drug dissolution (in-vitro). The following schematic illustrates the dissolution process of solid dosage forms (Banakar, 1992).

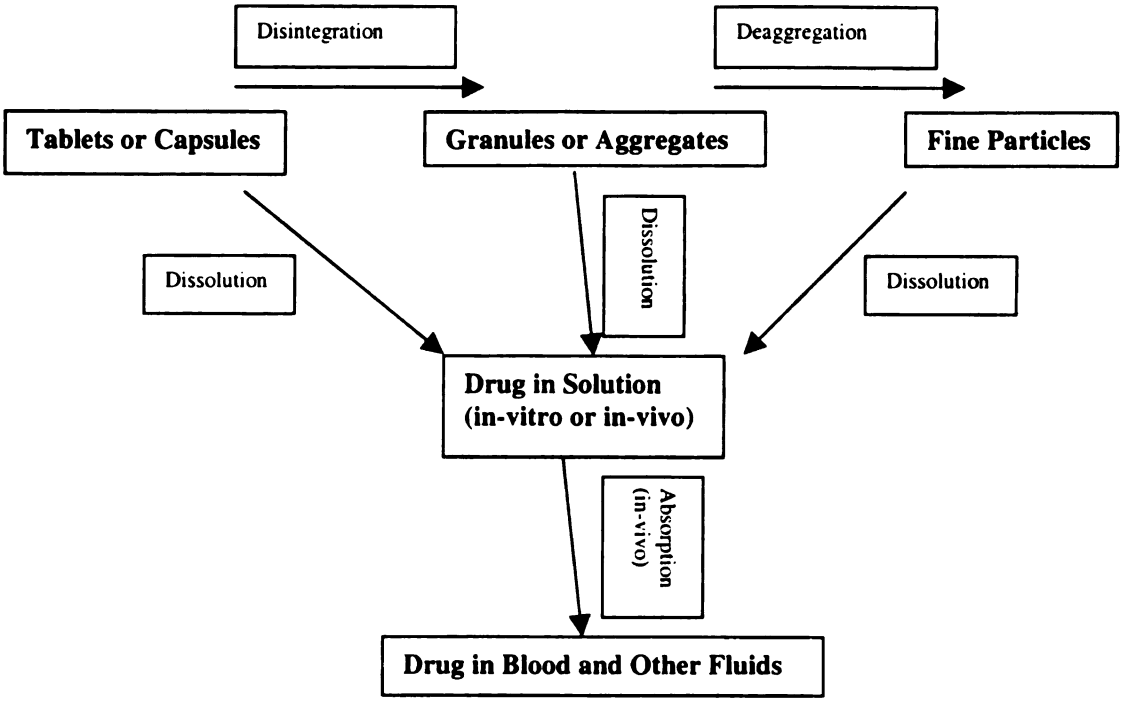

Figure 1. Dissolution process of solid dosage forms

In Figure 1, the rate of drug dissolution can be the rate-limiting step before the drug appears in the blood. This establishes the important link between dissolution and bioavailability. Various dosage forms can have different dissolution rates, which correspond to different bioavailabilities. Figure 2 shows the order of dissolution rates and thus absorption rates for various dosage forms (Banakar, 1992).

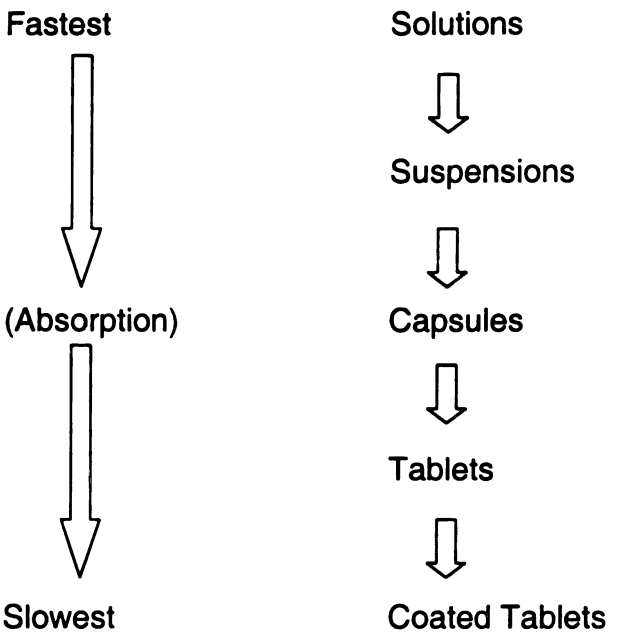

Figure 2. Dissolution rates for various dosage forms

Looking back on the long history of dissolution, an important milestone was the development of the USP paddle method in 1978. This is the method used in this study for dissolution testing. This method contains specific

requirements for the positioning of the paddles, shaft rotation, medium temperature, etc. Figure 3 illustrates the forced-convection nonsink dissolution testing method of the USP paddle apparatus (Banakar, 1992).

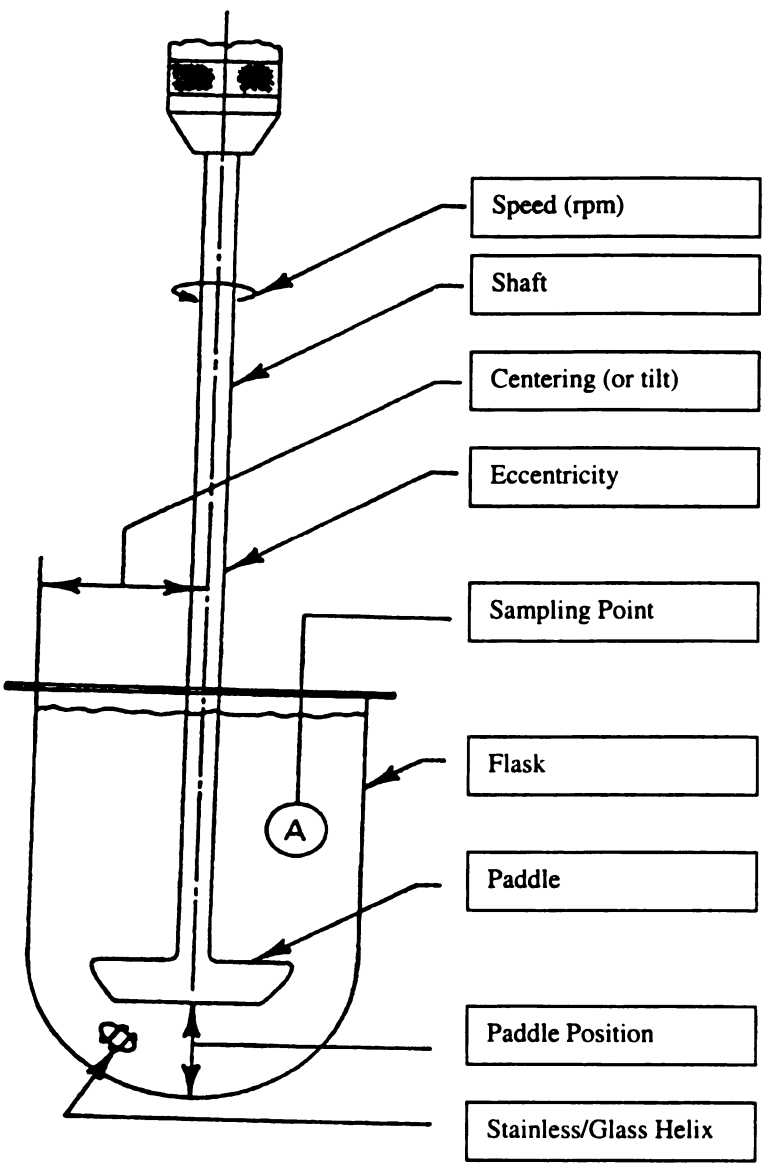

Figure 3. USP dissolution method (paddle)

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When a dissolution test is initiated, especially when a new dissolution test is being developed, it is important to recognize all the variables. In the case of this study, specific protocols are followed, such as the procedure developed by the UpJohn Company for Prednisone 5 mg therapeutic tablets. Following a specific procedure will keep dissolution variables to a minimum.

"The dissolution-rate data can be meaningful only if the results of successive tests on the same dosage form are consistent within reason. The dissolution test should yield reproducible results even when it is performed in different laboratories or with different personnel" (Banakar, 1992).

Looking at the specific parameters involved in dissolution testing, it is very important to minimize the variables within the testing protocol. For example, the preparation of the dissolution medium is a critical step. The USP dissolution section <711> specifically notes, "Dissolved gases can cause bubbles to form, which may change the results of the test. In such cases, dissolved gases should be removed prior to testing." (USP 23, 1995)

When analytical development creates a dissolution procedure for a new drug, many variables are taken into account. Banaker (1992) wrote "The various factors affecting the dissolution rate of a drug from a dosage form fall in six main classes:

1. Factors related to the physicochemical properties of the drug

2. Factors related to drug product formulation
3. Factors related to dosage form
4. Factors related to dissolution testing device
5. Factors related to dissolution test parameters
6. Miscellaneous factors

It must be stated at the outset that this classification is oversimplified for the purpose of understanding their influence on the dissolution process".

The factors listed above, when related to dosage form, can significantly influence dissolution. Depending on the form of the product (coated tablet, uncoated tablet, gelatin capsule), several intermediate steps will be involved, which influence the dissolution process.

"The process of dissolution of an active ingredient from solid pharmaceutical dosage forms involves several intermediate physicochemical steps such as wetting, swelling, capillarity, solubility, and diffusion" (Banakar, 1992). For example, wetting is one of the first steps in the dissolution process, in which the outside surface of the product is initially penetrated by the liquid dissolution medium. Development chemists must understand complex variables such as this when new formulations are developed. Minor changes within the formulation can create significant changes in dissolution, which indicates potential problems with bioavailability.

The dissolution procedures used in this research were developed with reference to the Dissolution general chapter <711> (USP 23, 1995). As stated earlier, the USP paddle method (Figure 3, Page 7) is the preferred dissolution setup for this product. The assembly is similar to the USP basket method except for a blade, which replaces a basket. To verify that the system is working correctly, a suitability test can be performed using USP Dissolution Calibrator Tablets. These tablets will deliver a specific amount of active ingredient (Prednisone) if the apparatus is functioning correctly. This dissolution chapter (USP<711>) continues to discuss parameters within the test, such as dissolution medium and time. The official monograph for Prednisone tablets can be referenced within the USP for specific dissolution information. A pharmaceutical testing laboratory would implement an in-house procedure, which includes these testing parameters and references the USP's official monograph.

Taborsky used dissolution testing to show that Prednisone is a moisture sensitive product. "This study demonstrates a direct correlation between an important performance feature of the pharmaceutical product and the moisture barrier of its packaging" (Taborsky-Urdinola, 1981). Taking this study one step further, the dissolution tests can determine a critical storage condition, while moisture isotherms and initial moisture content data can be used to generate shelf life information. Shelf life programs can be utilized to take a product's moisture sensitivity into account, and determine the proper amount of protection needed to package a pharmaceutical product for a defined shelf life.

The shelf life program used in this study was developed at the School of Packaging by Seung-Yil Yoon (Yoon, 2000). The program uses product moisture contents and isotherms and package permeability and dimensional information to determine a shelf life for a specific package selection. The program can also be used to determine the type of package needed for a desired shelf life. For example, the desired shelf life can be entered into the program along with the product information. The program will then calculate the required package permeance to create a given shelf life for a specific product. At this point, the desired package can be selected based on the permeance alone.

The program calculates shelf life by either a linear method or the G.A.B. method. Both methods use mathematical expressions to represent a product's moisture isotherm. The linear method simply uses a linear model, while the G.A.B. model uses a complex non-linear regression. For example, Figure 4 shows a typical moisture isotherm for a dry pharmaceutical product (Adams, 1998).

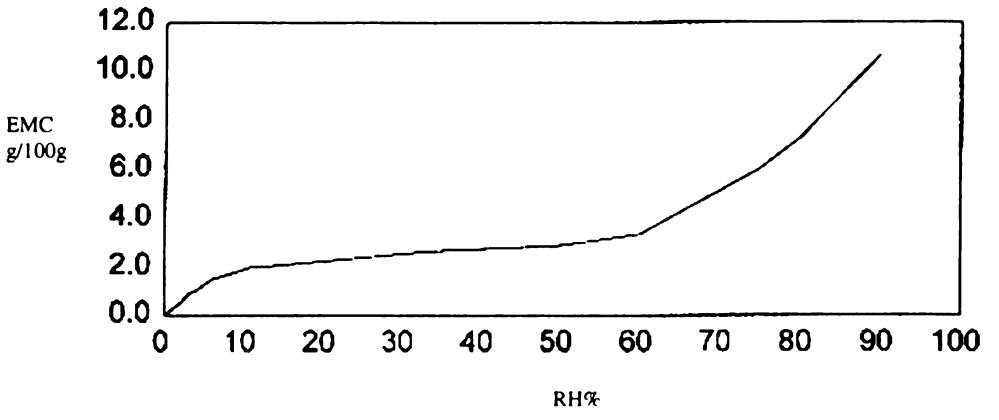

Figure 4. Moisture sorption isotherm (example)

A linear model does not represent the entire curve. However, if the portion of the isotherm, which represents all of the testing conditions, is linear, then that linear equation can be used in the shelf life calculations.

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Chapter 3: Materials and Methods

3.1 Standardizing the Dissolution Procedure

Purpose

The dissolution procedure must be calibrated to validate the generated dissolution data. Dissolution samples were analyzed by a UV-visible spectrophotometer, which generates absorbance units (AU). These AU are relative numbers, which correspond to specific dissolution values. USP Prednisone standards were used to correlate AU to specific dissolution values (percent dissolution).

Materials

- VanKel VK6010 Dissolution Apparatus (paddle)
- USP Prednisone Reference Standard
- UV-Vis Spectrophotometer (Perkin-Elmer, Lambda 20)
- USP Calibrator Tablets

Methods

A specific amount of reference standard was added to the dissolution medium to represent dissolution percentages of 100%, 75%, 50% and 25% for Prednisone tablets. The corresponding absorbance values were plotted versus the dissolution percentages. The resulting linear regression of these points was used as the calibration curve. USP calibrator tablets were then tested in the dissolution apparatus. The dissolution percentage for these tablets was determined by using the calibration curve. Standardization of the dissolution

apparatus was verified by comparing the calibrator tablet's experimental dissolution percentage to the actual dissolution percentage, which was listed on the calibrator tablet's label.

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3.2 Moisture Sorption Isotherms

Purpose

Determine moisture sorption isotherms of the 5 mg Prednisone tablets at three ICH temperatures (25C, 30C, and 40C) by gravimetric methods.

Materials

- Temperature Chambers for 25C, 30C and 40C
- Five-Gallon Plastic Buckets (RH Buckets)
- Product Racks and Recrystallization Dishes
- "Hygrodynamics" RH Monitoring Equipment
- Saturated Salt Solutions (Table 3, Page 26)
- 5 mg Prednisone Tablets
- Mettler Analytical Balance (+/- 0.05 mg)

Methods

Each temperature chamber contained seven RH buckets corresponding to nominal RH of 12%, 33%, 50%, 65%, 75%, 80% and 90%. The RH of each bucket was achieved by preparing the appropriate salt solution (Table 3, Page 26) in a Pyrex recrystallization dish. After this dish was placed in the corresponding bucket, the bucket was sealed and allowed to equilibrate before the RH was monitored and product was placed inside.

Each bucket contained a product rack, which was placed over the top of the recrystallization dish. This rack allowed an open dish of product to safely rest inside the bucket while being exposed to the RH within the bucket. Each bucket

contained 15 Prednisone tablets, which were carefully placed in an aluminum weighing dish (open dish).

As the RH buckets equilibrated over a period of at least 24 hours, the RH inside each bucket was measured and recorded (Table 4, Page 27) at various intervals during the test procedure. Once the desired RH was measured for each bucket, fifteen Prednisone tablets were placed in aluminum weighing dishes for each bucket. The weight of the weighing dishes was initially recorded along with the weight of the dish containing fifteen tablets. After approximately two days, all of these dishes (with tablets) were weighed. To verify that the tablets reached an equilibrium moisture content (EMC), periodic weighings continued (Tables 5, 6 and 7; Pages 28, 28 and 29).

To construct an isotherm for the Prednisone tablets, the tablet EMC (g*Water/100g Dry Product) for each temperature was plotted versus the corresponding RH (Figure 11, Page 31).

Calculations

*Equilibrium Moisture Content (EMC) = [(Pf(1+IMC)/Pi)-1]*100* ***(1)***

Pf = Weight of dry product

Pi = Initial weight of product

IMC = Initial Moisture Content (g*Water/100g Dry Product)

Water Activity (Aw) = %RH / 100 ***(2)***

%RH = Percent Relative Humidity

3.3 Initial Moisture Content

Purpose

The initial moisture content (IMC) data represents the average amount of moisture contained in a five mg Prednisone tablet, when the tablet's original container was first opened. The IMC was used in the computer shelf life model.

Materials

- Brinkmann Karl Fisher Autotitrator
- Hydranal Composite 5 Titrant
- Deionized Water
- HPLC Grade Methanol
- Mettler Analytical Balance (+/- 0.05 mg)
- Prednisone 5 mg Tablets

Methods

Prednisone 5 mg tablets were received from the Pharmacia and UpJohn Company in high density polyethylene bottles (approximately 170mLs) containing 1000 tablets. Five tablets were taken out of a new bottle and tested individually on the Brinkmann autotitrator. The autotitrator was set up to calculate MC on a wet weight basis. This MC was converted to a MC on a dry weight basis (Table 9, Page 33).

A standardization check was performed to ensure the autotitrator was properly calibrated. Injecting a specific amount of water into the titrator should theoretically yield a value of 100%. Results in triplicate between 98% and 102% were required to confirm the unit was calibrated properly.

Calculations

*Initial Moisture Content (IMC) = [(Wi – Wf) / Wf]*100 "dry basis"* ***(3)***

IMC = Initial Moisture Content

Wi = Weight of product containing initial moisture

Wf = Weight of dry product

*Initial Moisture Content (IMC) = [(Wi – Wf) / Wi]*100 "wet basis"* ***(4)***

IMC = Initial Moisture Content

Wi = Weight of product containing initial moisture

Wf = Weight of dry product

3.4 Dissolution Testing

Purpose

Dissolution testing data was used to identify critical conditions (temperature and RH) and corresponding critical moisture contents, which represented the Prednisone tablets failing, or beginning to fail, USP dissolution limits.

Materials

- Temperature Chambers for 25C, 30C and 40C
- Five-Gallon Plastic Buckets (RH Buckets)
- Product Racks and Recrystallization Dishes
- "Hygrodynamics" RH Monitoring Equipment
- Saturated Salt Solutions (Table 3, Page 26)
- 5 mg Prednisone Tablets
- VanKel VK6010 Dissolution Apparatus (paddle)
- UV/Vis Spectrophotometer (Perkin Elmer, Lambda 20)

Methods

Five-gallon buckets containing equilibrated saturated-salt solutions, corresponding to specific RH (12%, 33%, 50%, 65%, 75%, 80%, 90%), were placed in three separate chambers set to ICH temperatures (25C, 30C, 40C). Prednisone tablets were placed in these buckets corresponding to the specific RH and temperatures mentioned above. These tablets were tested for dissolution every three days for nearly two months. In addition, tablets were tested at time zero to establish a dissolution profile. For the dissolution profile,

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dissolution data was generated at 10, 20, 30, 40, 50 and 60 minutes. To determine critical conditions for the Prednisone tablets at the various temperatures and RH, dissolution data was generated at 30 minutes according to the USP dissolution monograph. Per the monograph, less than 80% dissolution was determined to be a failure.

Calculations

*Absorbance (AU) = 0.4576 * (% Dissolution) – 0.0025 (Figure 7)* ***(5)***

Absorbance (AU) = absorbance units (UV/Vis) from dissolution samples

% Dissolution = percentage of active ingredient in dissolution medium

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3.5 Shelf Life Determination

Purpose

The shelf life computer model recommends the use of specific packaging materials for the Prednisone tablets being studied. The goal is to minimize material costs by choosing the least expensive packaging materials, which provide sufficient protection from moisture over a desired shelf life.

Materials

- School of Packaging Shelf Life Computer Model (Windows based program for IBM Compatible Computers)

Methods

The shelf life computer model performs shelf life calculations using data generated for a specific moisture sensitive product. For this study, the initial moisture content, moisture sorption isotherm data, critical moisture contents, and a desired shelf life value, are entered into the shelf life computer model. From this data, a permeance value is generated. This permeance value is used to suggest a packaging material, which minimizes costs and provides sufficient moisture protection for a desired shelf life. For example, looking at permeance values for various blister materials, a specific material's permeance value must be lower than the permeance value specified by the shelf life computer model. Since higher moisture barrier materials tend to be more expensive, choosing a material which has a permeance value closest to the permeance value generated by the shelf life computer program will minimize material costs.

Calculations

The calculation for the linear model is:

$$t = (l * W * B / A * P * p_s) * \ln [(RH_e - RH_i) / (RH_e - RH_c)] \quad (6)$$

t = Desired Product Shelf Life

l = Material Thickness

W = Product Weight

B = Slope of "EMC (g*Water/100g Dry Product) versus Aw" Graph (Unitless)

A = Area of Material

P = Permeance (Unknown)

p_s = Partial Pressure

RH_e = Relative Humidity of Storage Condition (External)

RH_i = Relative Humidity Corresponding to Initial Moisture Content of Product

RH_c = Relative Humidity Corresponding to Critical Moisture Content of Product

Chapter 4: Data and Results

4.1 Standardizing the Dissolution Procedure

Looking at the three calibration curves (Figures 5, 6, and 7; Page 24, Page 24 and Page 25), the average of the three slopes will be used to determine dissolution percentages (ex: Table 11, Page 35) throughout this paper. The specification for calibrator tablet lot "L" shows the dissolution percentages to be between 38% and 44%. Table 2 (Page 25) obviously shows values within this range, so the dissolution apparatus can be considered calibrated and standardized.

Table 1. Dissolution Calibration Data

Conc (mg/mL)	Dilution	Absorbance		
		1/5/99	1/6/99	1/10/99
0.100	100%	0.457	0.460	0.458
0.075	75%	0.346	0.342	0.336
0.050	50%	0.227	0.228	0.224
0.025	25%	0.116	0.115	0.115

*100% Dilution represents 100% Dissolution of 5 mg Prednisone tablets

Figure 5. Dissolution Calibration Curve (1/5/99)

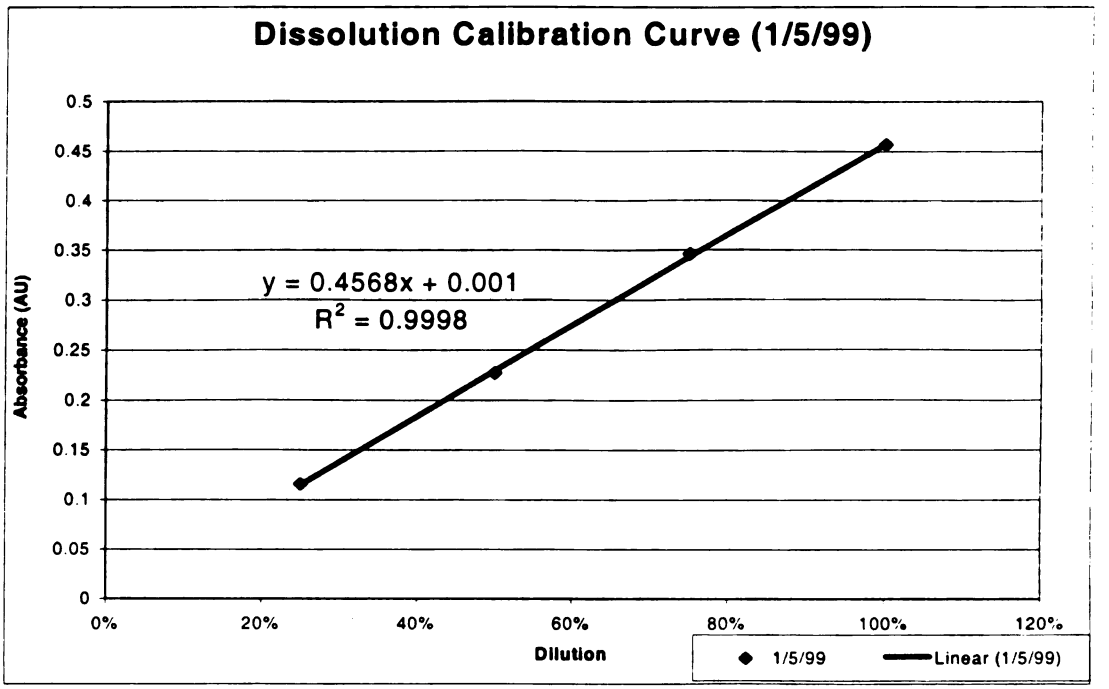


Figure 6. Dissolution Calibration Curve (1/6/99)

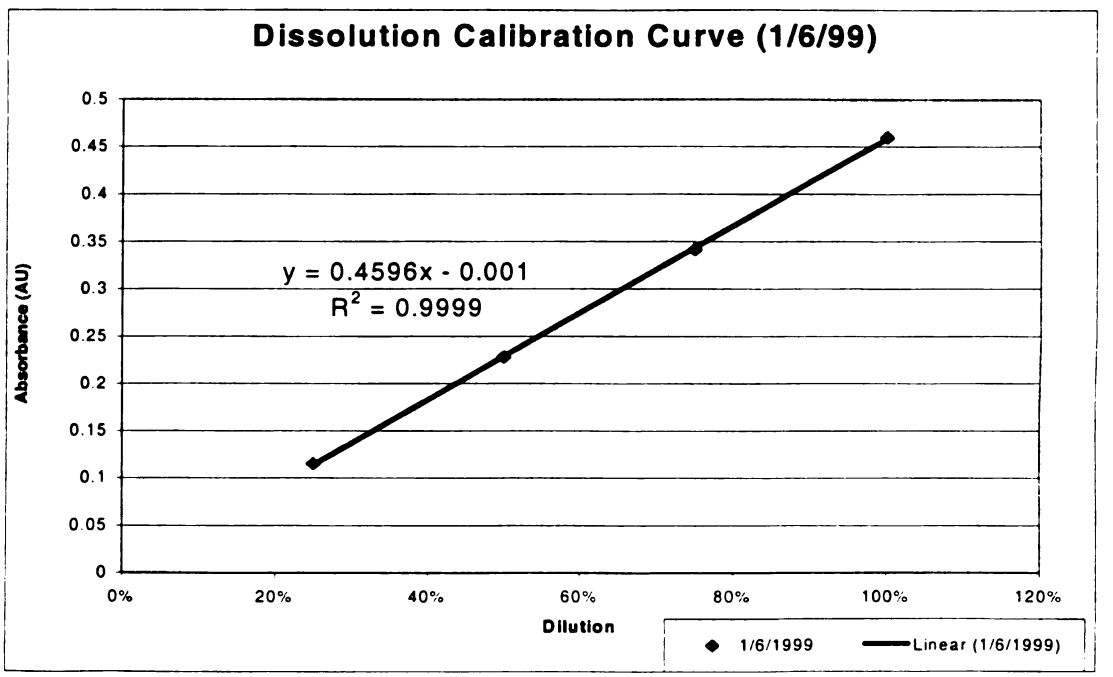


Figure 7. Dissolution Calibration Curve (1/10/99)

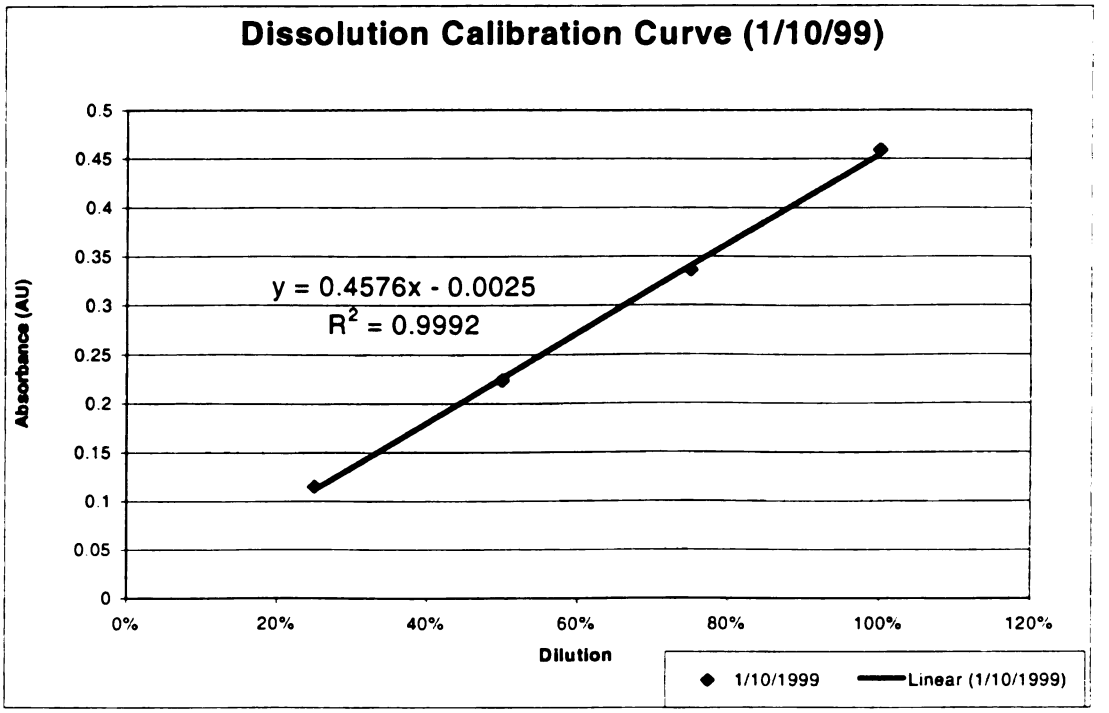


Table 2. USP Calibrator Tablet Dissolution Results

Tablet #	Absorbance (AU)	% Dissolution
1	0.177	39.2
2	0.181	40.1
3	0.192	42.5
4	0.182	40.3
5	0.185	41.0
6	0.174	38.6

*Figure 7 calibration curve was used to determine % dissolution
**USP lot "L" calibrator tablets should be between 38% and 44% dissolution

4.2 Moisture Sorption Isotherms

Looking at Figure 11 (Page 31), we can see that the isotherm data for all three temperatures follow similar patterns. The data points between 30% RH and 80% RH are well represented by a linear regression (Figure 12, Page 32). Therefore, a linear equation will be used in the shelf life computer model to represent specific moisture sorption isotherms. The isotherms in Figure 11 could not be represented using the GAB model.

Since the product will not be exposed to a RH above 80% in our shelf life model, this linear region will be sufficient to represent the product's sorption isotherms. For example, the product fails dissolution at a storage condition which corresponds to 75% RH. Therefore, concerning the shelf life calculation, the highest RH is 75%.

The isotherms were obtained using tablets stored in five-gallon buckets over salt solutions as shown in Table 3. The humidities achieved at 25C, 30C and 40C are shown in Table 4 (Page 27).

Table 3. Salt Solution RH at Three Temperatures

Salt Solution	Formula	%RH at Stated Temperature		
		20C	25C	30C
Lithium Chloride	$LiCl \cdot H_2O$	12.4	12	11.8
Magnesium Chloride	$MgCl_2 \cdot 6H_2O$	33.6	33.2	32.8
Magnesium Nitrate	$Mg(NO_3)_2 \cdot 6H_2O$	54.9	53.4	52
Sodium Nitrite	$NaNO_2$	65.3	64.3	63.3
Sodium Chloride	NaCl	75.5	75.8	75.6
Ammonium Sulfate	$(NH_4)_2SO_4$	80.6	80.3	80
Potassium Nitrate	KNO_4	93.2	92	90.7

Table 4. Bucket RH Readings for Isotherms

Chamber #4: 25 degrees Celsius (3/16/99 11:35a)		
Mercury Thermometer	Chart Recorder	Digital Chamber Recorder
25C	25C	24.7
	Hygrometer	
RH "nominal" Bucket	Dial Reading	%RH
12%	94	22.2*
33%	46	32.75
50%	75	51
65%	85	69.25
75%	54	77.25
80%	75	80.5
90%	63	90.75
Chamber #3: 30 degrees Celsius (3/16/99 8:00p)		
Mercury Thermometer	Chart Recorder	Digital Chamber Recorder
32C	33C	31.0C
	Hygrometer	
RH "nominal" Bucket	Dial Reading	%RH
12%	20	11.8
33%	59	32.75
50%	77	49.75
65%	78	65.5
75%	67	77.75
80%	83	81.25
90%	67	90.25
Chamber #1: 40 degrees Celsius (3/16/99 11:55p)		
Mercury Thermometer	Chart Recorder	Digital Chamber Recorder
40C	41C	40.1C
	Hygrometer	
RH "nominal" Bucket	Dial Reading	%RH
12%	53	13
33%	72	32.25
50%	80	47.5
65%	82	63
75%	77	77.25
80%	88	80
90%	64	88.25

*The reading for this bucket was abnormally high because the seal was faulty.

Table 5. Moisture Gain for Prednisone Tablets at 25C

Chamber #4: 25 degrees Celsius							
Bucket/Dish	Dish Wt (g)	3/16/99 1:18p Dish +Smp (g)	3/18/99 2:15p Dish +Smp (g)	3/20/99 12:55p Dish +Smp (g)	3/22/99 2:40p Dish +Smp (g)	3/29/99 3:15p Dish +Smp (g)	4/5/99 10:25p Dish +Smp (g)
12%/1	1.2783	2.7764	2.7771	2.777	2.7774	2.7767	2.7769
33%/2	1.2854	2.7882	2.7905	2.7905	2.7912	2.7901	2.7901
50%/3	1.2763	2.7785	2.7847	2.7839	2.7845	2.784	2.7835
60%/4	1.2801	2.7755	2.785	2.7846	2.7843	2.7842	2.784
75%/5	1.2716	2.772	2.7849	2.784	2.7834	2.7834	2.7827
80%/6	1.2778	2.782	2.7965	2.7956	2.7951	2.795	2.7945
90%/7	1.2813	2.7798	2.8089	2.8093	2.8092	2.8092	2.8116

Table 6. Moisture Gain for Prednisone Tablets at 30C

Chamber #3: 30 degrees Celsius							
Bucket/Dish	Dish Wt (g)	3/16/99 8:00p Dish +Smp (g)	3/18/99 9:15p Dish +Smp (g)	3/20/99 11:00p Dish +Smp (g)	3/23/99 12:10a Dish +Smp (g)	3/29/99 10:50p Dish +Smp (g)	4/6/99 8:05p Dish +Smp (g)
12%/1	1.2811	2.7806	2.779	2.7788	2.7783	2.7789	2.7785
33%/2	1.2701	2.7629	2.7633	2.7631	2.7631	2.7633	2.7636
50%/3	1.2653	2.7657	2.7712	2.7697	2.7694	2.7695	2.7695
60%/4	1.2687	2.7742	2.7819	2.7809	2.7805	2.7805	2.7804
75%/5	1.277	2.7743	2.7853	2.7845	2.7839	2.7838	2.7833
80%/6	1.2694	2.7625	2.7744	2.7741	2.7731	2.7731	2.7726
90%/7	1.2738	2.7728	2.7963	2.796	2.7953	2.7964	2.7966

Table 7. Moisture Gain for Prednisone Tablets at 40C

Chamber #1: 40 degrees Celsius							
Bucket/Dish	Dish Wt (g)	3/16/99 11:55p Dish +Smp (g)	3/19/99 12:35a Dish +Smp (g)	3/21/99 12:00a Dish +Smp (g)	3/23/99 1:30a Dish +Smp (g)	3/30/99 1:00a Dish +Smp (g)	4/7/99 9:00p Dish +Smp (g)
12%/1	1.2779	2.7762	2.773	2.7741	2.7736	2.7738	2.7736
33%/2	1.2781	2.7818	2.7823	2.7827	2.7824	2.7824	2.7822
50%/3	1.2768	2.7753	2.778	2.7773	2.7773	2.7774	2.7768
60%/4	1.2829	2.7828	2.7876	2.7879	2.7873	2.7874	2.7873
75%/5	1.2857	2.7922	2.8016	2.8009	2.8	2.8	2.7998
80%/6	1.2736	2.781	2.791	2.7906	2.7897	2.7898	2.7891
90%/7	1.2694	2.7696	2.7888	2.788	2.788	2.7877	2.7883

Figure 8. Moisture Gain for Prednisone Tablets at 25C

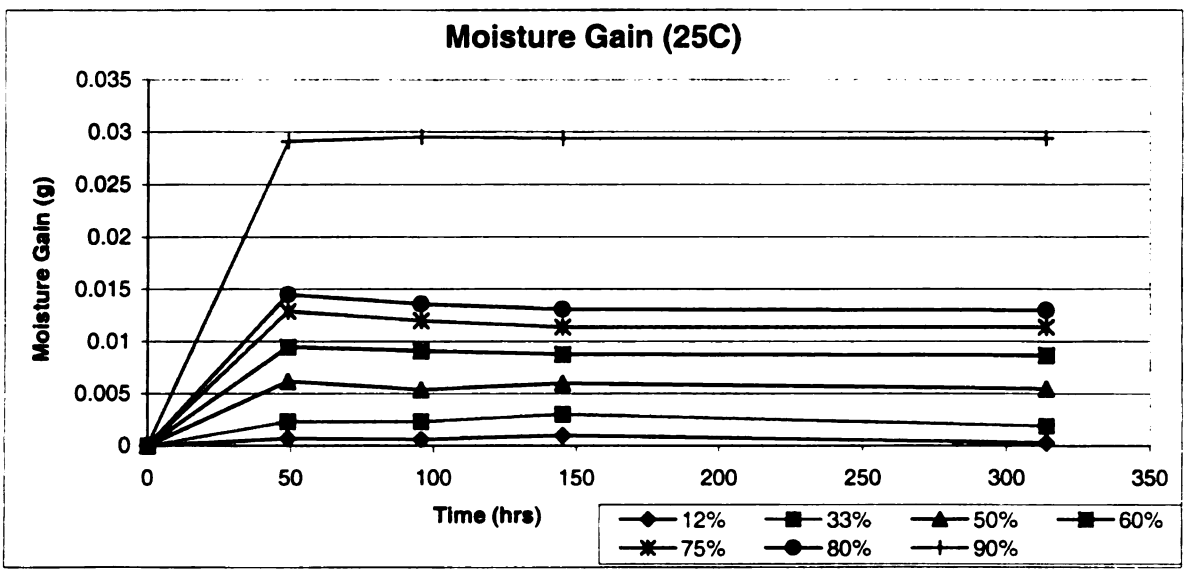


Figure 9. Moisture Gain for Prednisone Tablets at 30C

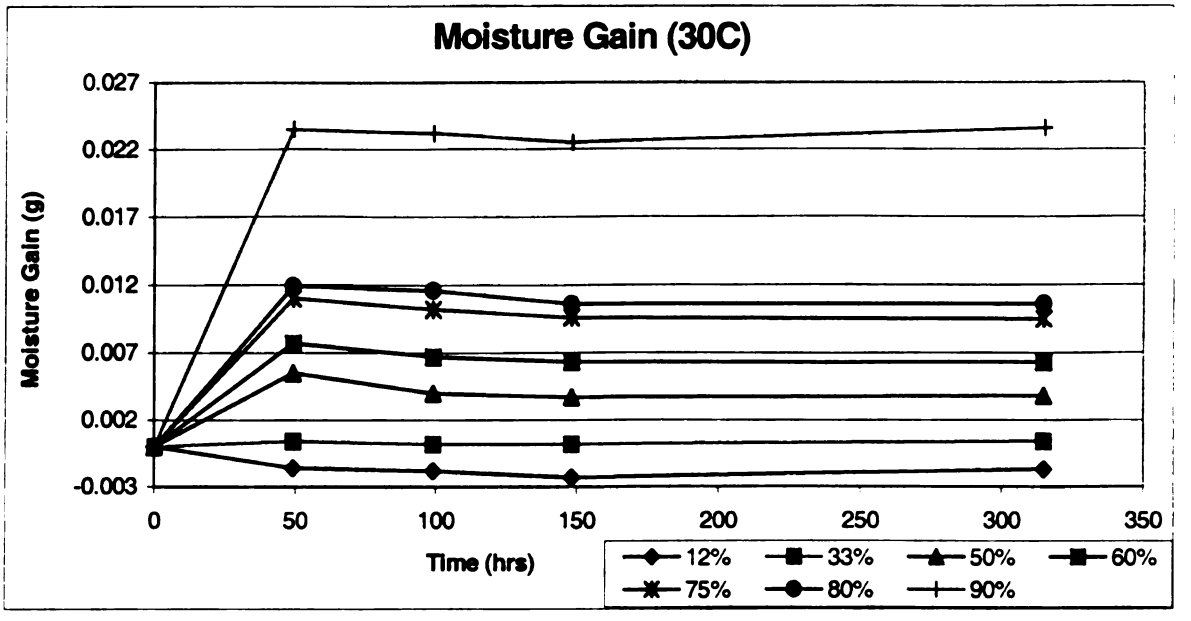


Figure 10. Moisture Gain for Prednisone Tablets at 40C

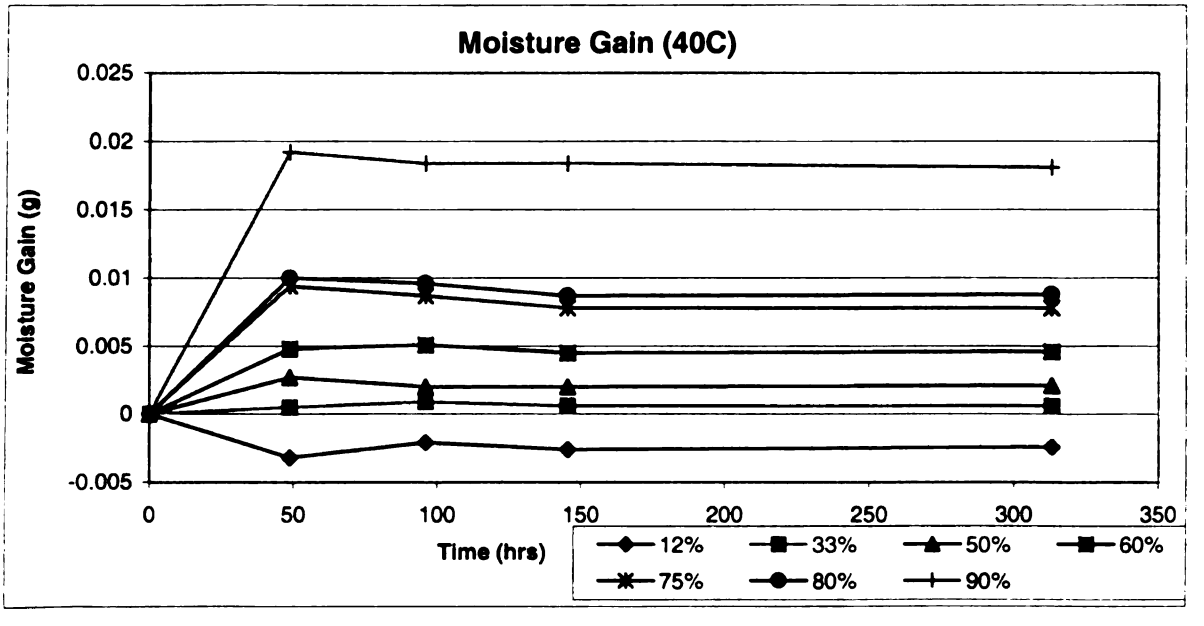


Table 8. Moisture Sorption Isotherm Data

MSU Isotherm (25C) EMC (gWater/100g Dry Product)	Aw	MSU Isotherm (30C) EMC (gWater/100g Dry Product)	Aw	MSU Isotherm (40C) EMC (gWater/100g Dry Product)	Aw
0	0	0	0	0	0
4.9613	.2220	4.8858	.1180	4.8593	.1300
5.0215	.3275	4.9652	.3275	4.9726	.3225
5.1577	.5100	5.0942	.4975	5.0294	.4750
5.2790	.6925	5.1883	.6550	5.1235	.6300
5.3816	.7725	5.3094	.7775	5.2432	.7725
5.4404	.8050	5.3527	.8125	5.2821	.8000
6.0600	.9075	5.8433	.9025	5.6359	.8825

Figure 11. Moisture Sorption Isotherms

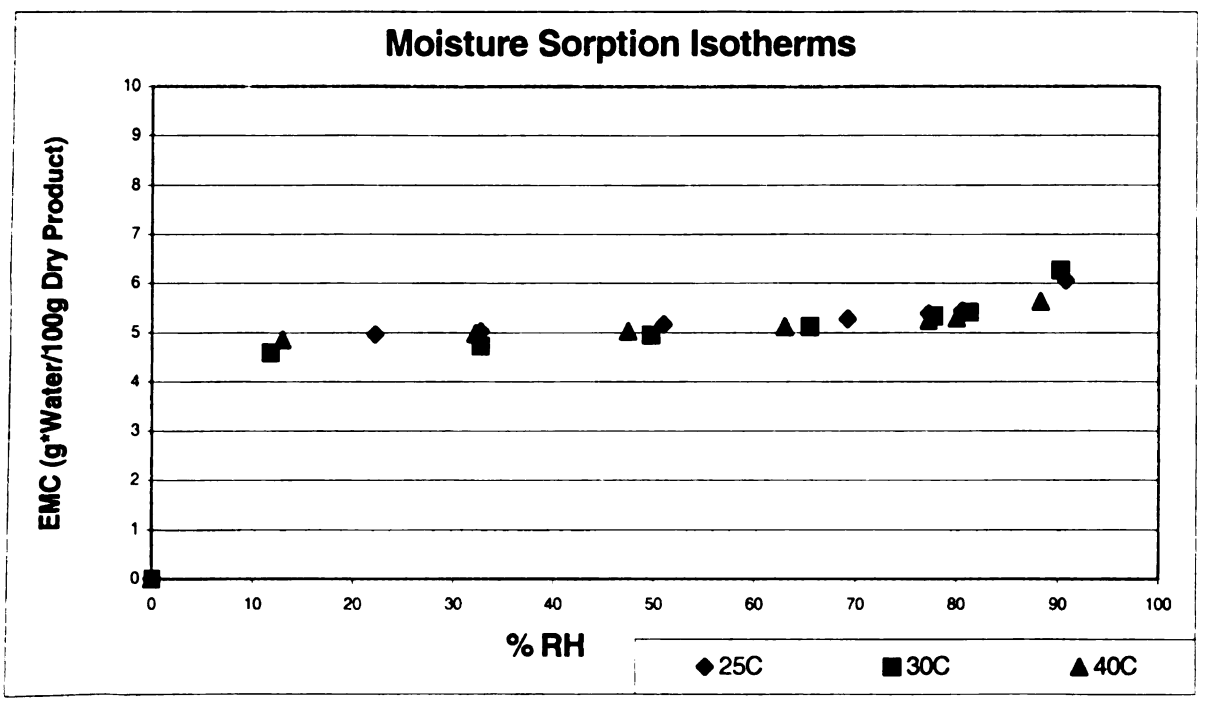
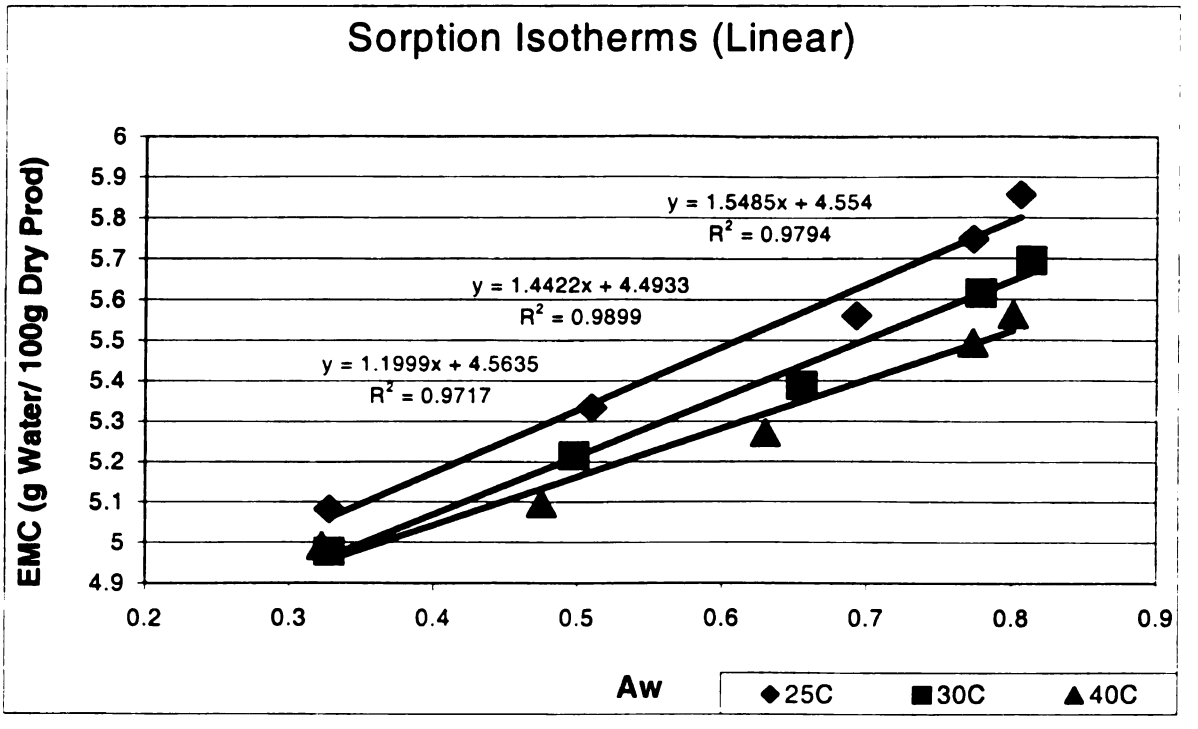


Figure 12. Linear Regression of Moisture Sorption Isotherms



4.3 Initial Moisture Content

The average of the "dry weight" IMC values, based on 100 grams of dry product, was used in the shelf life calculations.

Table 9. Initial Moisture Content of Prednisone 5 mg Tablets

IMC		
Standardization Check: 99.31%, 98.91%, 100.09%		
Sample Wt (g) "wet"	IMC (g*Water/100g Product) "wet weight"	IMC (g*Water/100g Product) "dry weight"
0.099	4.740	4.976
0.0999	4.700	4.932
0.1005	4.670	4.899
0.0993	4.730	4.965
0.1001	4.730	4.965
		Average = 4.947

4.4 Dissolution Testing

Dissolution data was gathered for Prednisone tablets at various RH to determine critical conditions at each ICH temperature (25C, 30C, 40C). Looking at Table 12 (Page 36), dissolution failures only occurred at RH of 75% or higher for each temperature. So, the critical RH used in shelf life calculations for each ICH temperature was 65%.

65% RH was used as the critical RH, instead of 75%, because the tablets were failing dissolution at a condition somewhere between 65% and 75%. This is one example of conservatism, which is built into the system.

Table 12 (Page 36) is a summary table, which reports the average dissolution values. The average dissolution values displayed in the table represent triplicate dissolution testing. So, if one of the average dissolution values in Table 12 (Page 36) is identified as a failure, this means that at least one of the three tablets failed dissolution according to the USP Prednisone monograph, which specifies that dissolution values below 80% are considered failures. These failures within Table 12 (Page 36) are indicated by a dark outline.

Table 10. Absorbances of Dissolution Profile

Absorbances (AU)

Amp #	0 min	10 min	20 min	30 min	40 min	50 min	60 min
1	0	0.279	0.422	0.456	0.464	0.467	0.469
2	0	0.263	0.415	0.455	0.463	0.467	0.469
3	0	0.326	0.438	0.457	0.462	0.465	0.466
4	0	0.31	0.441	0.459	0.463	0.465	0.468
5	0	0.277	0.426	0.454	0.46	0.467	0.466
6	0	0.261	0.424	0.456	0.465	0.468	0.469

Table 11. % Dissolution of Dissolution Profile

% Dissolution

Samp #	0 min	10 min	20 min	30 min	40 min	50 min	60 min
1	0	61.5	92.7	100.1	101.9	102.5	102.9
2	0	58.0	91.2	99.9	101.6	102.5	102.9
3	0	71.7	96.2	100.3	101.4	102.1	102.3
4	0	68.2	96.8	100.8	101.6	102.1	102.7
5	0	61.0	93.6	99.7	101.0	102.5	102.3
6	0	57.5	93.1	100.1	102.1	102.7	102.9

Figure 13. Prednisone Tablet Dissolution Profile

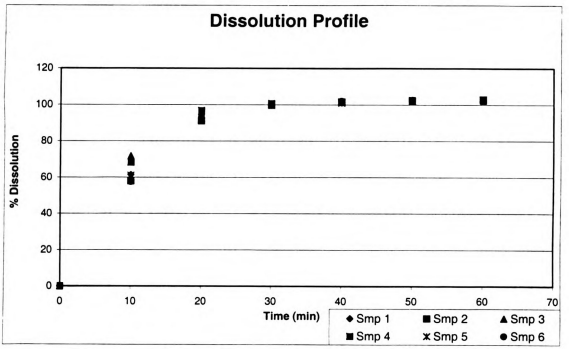


Table 12. Summary of Dissolution Data (Averages)

25C Average %Dissolution Values

		Day											
%RH	0	3	6	9	12	15	18	21	24	37	44	51	58
50	100	96.98	97.2	97.49	95.82	99.82	97.93	97.13	97.64	96.03	97.49	94.72	96.83
65	100	98.58	90.14	95.52	97.34	96.69	96.54	95.89	95.02	97.2	96.03	96.69	95.52
75	100	94.8	91.96	88.03	94	91.89	94.29	86.28	89.92	92.98	86.14	85.77	86.86
80	100	92.69	83.59	88.9	88.03	83.37	87.52	81.91	81.26	81.55	70.12	81.84	84.39
90	100	22.74									6.95		

30C Average %Dissolution Values

		Day											
%RH	0	3	6	9	12	15	18	21	27	33	40	47	54
33	100	93.27	95.52	93.78	95.52	X	X	98	X	95.82	96.98	X	98.58
50	100	97.64	96.69	101.3	97.64	94.51	98.95	95.31	96.76	94.94	94.36	96.03	96.47
65	100	95.74	96.11	101.3	94.65	94.65	96.25	94.43	94.29	93.27	95.09	90.58	96.47
75	100	95.74	95.6	89.56	88.32	94.36	91.96	91.16	89.19	92.39	86.28	93.41	88.83
80	100	87.59	80.68	84.39	87.23	82.93	84.03	79.66	86.06	73.62	76.24	82.72	83.37
90	100	28.28											

40C Average %Dissolution Values

		Day											
%RH	0	3	6	9	12	15	18	21	27	33	40	47	54
12	100	97.93	92.03	97.05	96.11	X	96.76	X	X	96.83	X	X	X
33	100	96.33	97.56	96.83	96.03	X	97.78	X	X	96.18	X	X	X
50	100	93.92	96.11	96.11	94.72	95.74	97.56	95.74	93.71	95.89	93.63	92.1	95.09
65	100	96.03	97.93	98	96.91	96.33	95.23	96.03	94.51	96.4	91.08	91.45	94.14
75	100	96.03	84.03	89.19	90.14	86.06	84.61	88.83	84.68	83.88	82.72	80.82	85.26
80	100	91.89	78.2	80.17	81.11	74.2	62.05	65.1	75.22	71.87	73.69	52.95	72.82
90	100	41.52											

= Failure (at least 1 of 3) X = not tested

*Appendix A contains all of the raw dissolution data.

**Each value in this table is an average of three dissolution tests. A failure is defined by the USP official monograph for Prednisone tablets as not less than 80% dissolved in 30 minutes.

4.5 Statistical Analysis

Each sampling point was tested in triplicate nearly every three days for approximately two months. Appendix A contains raw dissolution data and statistical analysis for every testing point.

First of all, as the raw dissolution data is reviewed for each storage temperature, dissolution failures (< 80% dissolution) only occur at RH of 75% or higher. This means that we are reaching our critical condition somewhere between 65% and 75% RH. The conservative approach is to conclude 65% to be the critical RH. The critical moisture content is then determined by using the corresponding isotherm (Figure 12, Page 32).

To reinforce this conclusion, the variability of the individual dissolution testing points can be analyzed. Table 14 (Page 46) lists the standard deviations for the dissolution testing at each test interval. Looking at the average of the standard deviations for each RH, a significant increase in variation occurs at 75%. This corresponds to the dissolution failures previously mentioned.

As the testing conditions become more severe (higher RH and temperatures), the Prednisone tablets are less likely to readily disintegrate in the dissolution medium. In fact, for most of the dissolution failures (Appendix A, Page 48), especially for samples stored at 90% RH, large chunks of tablet were found in the bottom of the dissolution vessel when samples were taken at 30 minutes. These dissolution failures were accompanied by high variability between dissolution values taken at the same testing intervals.

Table 13. Summary of Dissolution Data (Standard Deviations)

25C Dissolution Testing: Standard Deviations from Triplicate Testing													
	Day												
%RH	3	6	9	12	15	18	21	24	37	44	51	58	Ave
50	1.957	0.504	0.655	2.531	1.668	1.135	0.550	1.032	2.605	6.839	4.314	3.033	**2.235**
65	4.008	7.745	0.218	0.504	3.859	1.857	1.120	1.077	1.580	3.106	1.316	0.756	**2.262**
75	1.334	2.241	11.722	2.461	3.720	1.668	6.150	2.395	1.120	10.122	8.211	6.602	**4.812**
80	1.364	5.282	2.559	5.456	6.685	6.850	5.057	11.630	11.446	3.938	4.869	3.431	**5.714**

30C Dissolution Testing: Standard Deviations from Triplicate Testing													
	Day												
%RH	3	6	9	12	15	18	21	27	33	40	47	54	Ave
50	0.549	1.486	5.412	0.630	3.241	0.882	1.941	1.778	1.639	3.385	2.435	0.882	**2.022**
65	1.155	2.405	0.334	3.725	5.575	2.314	2.150	0.909	4.476	0.952	5.460	1.765	**2.602**
75	1.513	2.531	10.374	8.132	2.605	0.767	3.712	5.677	0.882	3.314	0.882	2.355	**3.562**
80	2.605	11.347	3.297	4.560	6.537	5.929	8.816	4.685	9.009	3.363	1.696	2.782	**5.386**

40C Dissolution Testing: Standard Deviations from Triplicate Testing													
	Day												
%RH	3	6	9	12	15	18	21	27	33	40	47	54	Ave
50	4.745	2.335	2.899	2.355	1.216	1.099	5.689	1.077	0.985	1.120	2.531	1.891	**2.329**
65	3.636	1.513	2.605	1.279	1.404	1.981	2.559	4.087	1.216	1.421	1.203	0.549	**1.954**
75	3.285	9.911	5.571	3.278	8.147	9.919	3.550	7.269	4.369	8.953	4.269	5.614	**6.178**
80	1.316	4.582	1.580	8.893	15.362	8.083	10.420	9.965	7.029	6.626	6.078	3.172	**6.926**

Chapter 5: Conclusions

The calculations below were accomplished using the shelf life equation (Eq 6) described on page 22. Using the data within the sections of Chapter 4, permeance values (P) were calculated given a desired shelf life (t). The permeance values were then used to determine package options. Blister calculations are listed first.

25C / 75% RH Testing (Blisters)

t = 730 days (2 years) [desired shelf life]

l = 1 mil (Use a value of 1 for blisters)

W = 0.1 g per tablet

B = 1.5485 (unitless) (Reference Figure 11, Page 31)

A = 1 m^2 (Use a value of 1 for blisters)

P = Permeance (Unknown)

p_s = 23.756 mm Hg

RH_e = 75% (RH of storage conditions)

RH_i = 25.4% (RH generated by shelf life computer model using the IMC)

RH_c = 65% (Same RH for all three temperatures)

730 days = (1mil*0.1g*1.5485/1m^2*P*23.756mmHg)*ln[(.75–.254)/(.75–.65)]

P = 1.43 * 10^{-5} g/day*cavity*mmHg

30C / 75% RH Testing (Blisters)

t = 365 days (1 year) [desired shelf life]

l = 1 mil (Use a value of 1 for blisters)

W = 0.1 g per tablet

B = 1.4422 (unitless) (Reference Figure 11, Page 31)

A = 1 m^2 (Use a value of 1 for blisters)

P = Permeance (Unknown)

p_s = 31.824 mm Hg

RH_e = 75% (RH of storage conditions)

RH_i = 31.5% (RH generated by shelf life computer model using the IMC)

RH_c = 65% (Same RH for all three temperatures)

365 days = (1mil*0.1g*1.4422/1m^2*P*31.824mmHg)*ln[(.75–.315)/(.75–.65)]

P = 1.83 * 10^{-5} g/day*cavity*mmHg

40C / 75% RH Testing (Blisters)

t = 180 days (6 months) [desired shelf life]

l = 1 mil (Use a value of 1 for blisters)

W = 0.1 g per tablet

B = 1.2000 (unitless) (Reference Figure 11, Page 31)

A = 1 m^2 (Use a value of 1 for blisters)

P = Permeance (Unknown)

p_s = 55.324 mm Hg

RH_e = 75% (RH of storage conditions)

RH_i = 32.2% (RH generated by shelf life computer model using the IMC)

RH_c = 65% (Same RH for all three temperatures)

180 days = (1mil*0.1g*1.2000/1m^2*P*55.324mmHg)*ln[(.75–.322)/(.75–.65)]

P = 1.75 * 10^{-5} g/day*cavity*mmHg

Looking at the 25C (room temperature) shelf life calculation for blisters, 730 days (two years) was used as the desired shelf life. For marketed products, this is a typical shelf life to use during the initial stages of development for room temperature or real-time stability. For the 30C (accelerated) blister calculation, 365 days (one year) was used as the desired shelf life. As a rule of thumb, if packaged product passes analytical testing after one year at 30C, the packaged product can be assumed to pass two years at 25C. For similar reasons, the 40C (accelerated) calculations use 180 days (six months) as the desired shelf life. If

the packaged product passes analytical testing after six months at 40C, the packaged product can be assumed to pass two years at 25C.

Using the 40C permeation result as an example, blister materials which have a permeance value below 1.75 * 10-5 g/day*cavity*mmHg (tested at 40C / 75%RH) will be packaging options for this Prednisone product. The calculated permeance value identifies a specific level of moisture, which will initiate product failure within a package. For example, PVC is a relatively inexpensive material, which has a high permeance to moisture. Using PVC blisters for a developmental product is an excellent way to reduce material costs once the product is packaged at high volumes for market. A typical permeance value for PVC blisters at 40C / 75% RH is $4.57 * 10^{-5}$ g/day*cavity*mmHg (Eli Lilly and Company, 2000). Since this value is higher than the calculated permeance value for blisters at 40C, PVC may not be an option, and a more expensive, higher barrier material will be recommended. Aclar is a popular high barrier blister used in the pharmaceutical industry. A typical permeance value for 0.6mil Aclar blisters at 40C / 75% RH is $3.88 * 10^{-6}$ g/day*cavity*mmHg (Eli Lilly and Company, 2000). Reviewing the calculated permeance value for blisters at 40C, the level of moisture protection received from 0.6mil Aclar is sufficient.

Pharmaceutical companies typically use high density polyethylene (HDPE) containers when a solid oral product requires a bottle for packaging. The Prednisone tablets being used for this study were supplied in HDPE bottles. These bottles contained 1000 tablets and were approximately 170cc in volume.

The permeance calculations at three conditions for the bottles described above are as follows.

25C / 75% RH Testing (Bottles)

t = 730 days (2 years) [desired shelf life]

l = 34 mil

W = 100 g (0.1 g per tablet, 1000 tablets per bottle)

B = 1.5485 (unitless) (Reference Figure 11, Page 31)

A = 0.03m^2 (Area of bottle walls)

P = Permeance (Unknown)

p_s = 23.756 mm Hg

RH_e = 75% (RH of storage conditions)

RH_i = 25.4% (RH generated by shelf life computer model using the IMC)

RH_c = 65% (Same RH for all three temperatures)

730 days = (34mil*100g*1.5485/0.03m^2*P*23.756mmHg)*ln[(.75–.254)/(.75–.65)]

P = 16.2 g/day*bottle*mmHg

30C / 75% RH Testing (Bottles)

t = 365 days (1 year) [desired shelf life]

l = 34 mil

W = 100 g (0.1 g per tablet, 1000 tablets per bottle)

B = 1.4422 (unitless) (Reference Figure 11, Page 31)

A = 0.03 m^2 (Area of bottle walls)

P = Permeance (Unknown)

p_s = 31.824 mm Hg

RH_e = 75% (RH of storage conditions)

RH_i = 31.5% (RH generated by shelf life computer model using the IMC)

RH_c = 65% (Same RH for all three temperatures)

365 days = (34mil*100g*1.4422/0.03m^2*P*31.824mmHg)*ln[(.75–.315)/(.75–.65)]

P = 20.7 g/day*bottle*mmHg

40C / 75% RH Testing (Bottles)

t = 180 days (6 months) [desired shelf life]

l = 34 mil

W = 100 g (0.1 g per tablet, 1000 tablets per bottle)

B = 1.2000 (unitless) (Reference Figure 11, Page 31)

A = 0.03 m^2 (Area of bottle walls)

P = Permeance (Unknown)

p_s = 55.324 mm Hg

RH_e = 75% (RH of storage conditions)

RH_i = 32.2% (RH generated by shelf life computer model using the IMC)

RH_c = 65% (Same RH for all three temperatures)

180 days = (34mil*100g*1.2000/0.03m^2*P*55.324mmHg)*ln[(.75–.322)/(.75–.65)]

P = 19.9 g/day*bottle*mmHg

A typical HDPE bottle (34mil thickness and area equal to 0.03m^2) at 170cc will have a permeance value of approximately 0.04 g/day*bottle*mmHg at 40C / 75% RH (Eli Lilly and Company, 2000). Comparing this value to the bottle permeation results for 40C, 0.04 is much lower than 19.9. The level of protection for this product in a 1000 count HDPE bottle with minimal head space is very high. However, as the bottle count decreases, the permeation value in the shelf life calculation will decrease. So, a lower count in the same bottle will ultimately be less protected because there are fewer tablets to share the moisture permeating into the bottle.

The shelf life calculations have provided packaging options for this Prednisone product for blisters and bottles. Concerning blisters, this product may not meet stability requirements in PVC blisters, but should be protected sufficiently in 0.6 mil Aclar. For bottles, higher count bottle presentations (bulk) in typical HDPE bottles should provide sufficient protection. However, as the product count significantly decreases for a specific bottle presentation, permeation values should be reviewed closely.

Table 14. Summary of Calculated Permeance Values

Condition	Package	Permeance (g/day*package*mmHg)	Desired Shelf Life
25C/75%RH	Blister	$1.43 * 10^{-5}$	2 years
30C/75%RH	Blister	$1.83 * 10^{-5}$	1 year
40C/75%RH	Blister	$1.75 * 10^{-5}$	6 months
25C/75%RH	Bottle	16.2	2 years
30C/75%RH	Bottle	20.7	1 year
40C/75%RH	Bottle	19.9	6 months

These packaging calculations are not meant to replace any type of product/package stability test. However, the information gathered and calculations made in such a study, especially for early development products, can identify packaging options for early phase stability studies. For example, instead of using four or five blister materials in initial product/package stability testing, shelf life modeling can narrow the choices down to two or three options, which can significantly reduce development costs.

Chapter 6: Recommendations for Future Work

My recommendation for future work is to expand the existing shelf life model at the School of Packaging to include other packaging components. For example, isotherms can be developed for desiccant packages and bottle fillers (ex: cotton), which compete with the product to absorb moisture. The moisture contents of these components can be accounted for within the model, similar to the product moisture content. Packaging components such as fillers and desiccant are popular materials in the pharmaceutical industry. Modeling a complex system such as a bottle containing product, cotton and desiccant, is a realistic packaging option used in industry.

Appendix A

25C Dissolution Values (Raw Data and Statistics)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.437	0.452	0.436		95.96	99.24	95.74	
	Mean =	0.442	STD =	0.00896	Mean =	96.980	STD =	1.95696
65	0.428	0.457	0.462		94.00	100.33	101.42	
	Mean =	0.449	STD =	0.0184	Mean =	98.581	STD =	4.00820
75	0.437	0.433	0.425		95.96	95.09	93.34	
	Mean =	0.432	STD =	0.0061	Mean =	94.796	STD =	1.33408
80	0.415	0.427	0.424		91.16	93.78	93.12	
	Mean =	0.422	STD =	0.0062	Mean =	92.686	STD =	1.36354
90	0.113	0.097	0.095		25.22	21.72	21.29	
	Mean =	0.102	STD =	0.0099	Mean =	22.744	STD =	2.15410

Time(days)= 3 Calibration Curve: "y=0.458 x - 0.0025"

Table 15. 25C Raw Dissolution Data and Statistics (Day3)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.44	0.444	0.444		96.62	97.49	97.49	
	Mean =	0.443	STD =	0.00231	Mean =	97.198	STD =	0.50424
65	0.442	0.417	0.372		97.05	91.59	81.77	
	Mean =	0.410	STD =	0.0355	Mean =	90.138	STD =	7.74520
75	0.416	0.43	0.41		91.38	94.43	90.07	
	Mean =	0.419	STD =	0.0103	Mean =	91.958	STD =	2.24087
80	0.389	0.353	0.399		85.48	77.62	87.66	
	Mean =	0.380	STD =	0.0242	Mean =	83.588	STD =	5.28246

Time(days)= 6 Calibration Curve: "y=0.458 x - 0.0025"

Table 16. 25C Raw Dissolution Data and Statistics (Day6)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.444	0.447	0.441		97.49	98.14	96.83	
	Mean =	0.444	STD =	0.00300	Mean =	97.489	STD =	0.65502
65	0.436	0.434	0.435		95.74	95.31	95.52	
	Mean =	0.435	STD =	0.0010	Mean =	95.524	STD =	0.21834
75	0.426	0.437	0.339		93.56	95.96	74.56	
	Mean =	0.401	STD =	0.0537	Mean =	88.028	STD =	11.72213
80	0.396	0.4	0.418		87.01	87.88	91.81	
	Mean =	0.405	STD =	0.0117	Mean =	88.901	STD =	2.55872

Time(days)= 9 Calibration Curve: "y=0.458 x - 0.0025"

Table 17. 25C Raw Dissolution Data and Statistics (Day9)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.424	0.447	0.438		93.12	98.14	96.18	
	Mean =	0.436	STD =	0.01159	Mean =	95.815	STD =	2.53062
65	0.442	0.442	0.446		97.05	97.05	97.93	
	Mean =	0.443	STD =	0.0023	Mean =	97.344	STD =	0.50424
75	0.415	0.435	0.434		91.16	95.52	95.31	
	Mean =	0.428	STD =	0.0113	Mean =	93.996	STD =	2.46057
80	0.379	0.428	0.395		83.30	94.00	86.79	
	Mean =	0.401	STD =	0.0250	Mean =	88.028	STD =	5.45560

Time(days)= 12 Calibration Curve: "y=0.458 x - 0.0025"

Table 18. 25C Raw Dissolution Data and Statistics (Day12)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.463	0.453	0.448		101.64	99.45	98.36	
	Mean =	0.455	STD =	0.00764	Mean =	99.818	STD =	1.66760
65	0.449	0.452	0.42		98.58	99.24	92.25	
	Mean =	0.440	STD =	0.0177	Mean =	96.689	STD =	3.85872
75	0.402	0.417	0.436		88.32	91.59	95.74	
	Mean =	0.418	STD =	0.0170	Mean =	91.885	STD =	3.72034
80	0.344	0.396	0.398		75.66	87.01	87.45	
	Mean =	0.379	STD =	0.0306	Mean =	83.370	STD =	6.68469

Time(days)= 15 Calibration Curve: "y=0.458 x - 0.0025"

Table 19. 25C Raw Dissolution Data and Statistics (Day15)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.452	0.443	0.443		99.24	97.27	97.27	
	Mean =	0.446	STD =	0.00520	Mean =	97.926	STD =	1.13453
65	0.431	0.448	0.44		94.65	98.36	96.62	
	Mean =	0.440	STD =	0.0085	Mean =	96.543	STD =	1.85697
75	0.421	0.431	0.436		92.47	94.65	95.74	
	Mean =	0.429	STD =	0.0076	Mean =	94.287	STD =	1.66760
80	0.375	0.434	0.386		82.42	95.31	84.83	
	Mean =	0.398	STD =	0.0314	Mean =	87.518	STD =	6.85024

Time(days)= 18 Calibration Curve: "y=0.458 x - 0.0025"

Table 20. 25C Raw Dissolution Data and Statistics (Day18)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.442	0.44	0.445		97.05	96.62	97.71	
	Mean =	0.442	STD =	0.00252	Mean =	97.125	STD =	0.54948
65	0.431	0.441	0.438		94.65	96.83	96.18	
	Mean =	0.437	STD =	0.0051	Mean =	95.888	STD =	1.12044
70	0.363	0.419	0.396		79.80	92.03	87.01	
	Mean =	0.393	STD =	0.0281	Mean =	86.281	STD =	6.14594
80	0.392	0.379	0.347		86.14	83.30	76.31	
	Mean =	0.373	STD =	0.0232	Mean =	81.914	STD =	5.05652

Time(days)= 21 Calibration Curve: "y=0.458 x - 0.0025"

Table 21. 25C Raw Dissolution Data and Statistics (Day21)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.441	0.45	0.443		96.83	98.80	97.27	
	Mean =	0.445	STD =	0.00473	Mean =	97.635	STD =	1.03184
65	0.435	0.436	0.427		95.52	95.74	93.78	
	Mean =	0.433	STD =	0.0049	Mean =	95.015	STD =	1.07705
70	0.397	0.413	0.418		87.23	90.72	91.81	
	Mean =	0.409	STD =	0.0110	Mean =	89.920	STD =	2.39512
80	0.383	0.415	0.311		84.17	91.16	68.45	
	Mean =	0.370	STD =	0.0533	Mean =	81.259	STD =	11.63027

Time(days)= 24 Calibration Curve: "y=0.458 x - 0.0025"

Table 22. 25C Raw Dissolution Data and Statistics (Day24)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.432	0.429	0.451		94.87	94.21	99.02	
	Mean =	0.437	STD =	0.01193	Mean =	96.033	STD =	2.60488
65	0.439	0.451	0.438		96.40	99.02	96.18	
	Mean =	0.443	STD =	0.0072	Mean =	97.198	STD =	1.57951
75	0.429	0.419	0.422		94.21	92.03	92.69	
	Mean =	0.423	STD =	0.0051	Mean =	92.977	STD =	1.12044
80	0.313	0.415	0.385		68.89	91.16	84.61	
	Mean =	0.371	STD =	0.0524	Mean =	81.550	STD =	11.44571

Time(days)= 37 Calibration Curve: "y=0.458 x - 0.0025"

Table 23. 25C Raw Dissolution Data and Statistics (Day37)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.408	0.465	0.459		89.63	102.07	100.76	
	Mean =	0.444	STD =	0.03132	Mean =	97.489	STD =	6.83863
65	0.444	0.421	0.447		97.49	92.47	98.14	
	Mean =	0.437	STD =	0.0142	Mean =	96.033	STD =	3.10576
75	0.339	0.412	0.425		74.56	90.50	93.34	
	Mean =	0.392	STD =	0.0464	Mean =	86.135	STD =	10.12168
80	0.336	0.32	0.3		73.91	70.41	66.05	
	Mean =	0.319	STD =	0.0180	Mean =	70.124	STD =	3.93821
90	0.028	0.028	0.032		6.66	6.66	7.53	
	Mean =	0.029	STD =	0.0023	Mean =	6.951	STD =	0.50424

Time(days)= 44 Calibration Curve: "y=0.458 x - 0.0025"

Table 24. 25C Raw Dissolution Data and Statistics (Day44)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.435	0.41	0.449		95.52	90.07	98.58	
	Mean =	0.431	STD =	0.01976	Mean =	94.723	STD =	4.31372
65	0.446	0.441	0.434		97.93	96.83	95.31	
	Mean =	0.440	STD =	0.0060	Mean =	96.689	STD =	1.31609
75	0.376	0.362	0.433		82.64	79.59	95.09	
	Mean =	0.390	STD =	0.0376	Mean =	85.771	STD =	8.21127
80	0.347	0.389	0.381		76.31	85.48	83.73	
	Mean =	0.372	STD =	0.0223	Mean =	81.841	STD =	4.86921

Time(days)= 51 Calibration Curve: "y=0.458 x - 0.0025"

Table 25. 25C Raw Dissolution Data and Statistics (Day51)

%Dissolution Determination (25C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.437	0.448	0.448		95.96	98.36	98.36	
	Mean =	0.444	STD =	0.00635	Mean =	97.562	STD =	1.38665
33	0.446	0.452	0.448		97.93	99.24	98.36	
	Mean =	0.449	STD =	0.0031	Mean =	98.508	STD =	0.66704
50	0.425	0.448	0.45		93.34	98.36	98.80	
	Mean =	0.441	STD =	0.0139	Mean =	96.834	STD =	3.03328
65	0.433	0.433	0.439		95.09	95.09	96.40	
	Mean =	0.435	STD =	0.0035	Mean =	95.524	STD =	0.75635
75	0.407	0.361	0.418		89.41	79.37	91.81	
	Mean =	0.395	STD =	0.0302	Mean =	86.863	STD =	6.60217
80	0.401	0.381	0.37		88.10	83.73	81.33	
	Mean =	0.384	STD =	0.0157	Mean =	84.389	STD =	3.43149

Time(days)= 58 Calibration Curve: "y=0.458 x - 0.0025"

Table 26. 25C Raw Dissolution Data and Statistics (Day58)

30C Dissolution Values (Raw Data and Statistics)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
33	0.443	0.402	0.429		97.27	88.32	94.21	
	Mean =	0.425	STD =	0.02084	Mean =	93.268	STD =	4.55036
50	0.442	0.445	0.447		97.05	97.71	98.14	
	Mean =	0.445	STD =	0.0025	Mean =	97.635	STD =	0.54948
65	0.432	0.442	0.434		94.87	97.05	95.31	
	Mean =	0.436	STD =	0.0053	Mean =	95.742	STD =	1.15535
75	0.432	0.444	0.432		94.87	97.49	94.87	
	Mean =	0.436	STD =	0.0069	Mean =	95.742	STD =	1.51271
80	0.407	0.404	0.385		89.41	88.76	84.61	
	Mean =	0.399	STD =	0.0119	Mean =	87.591	STD =	2.60488
90	0.146	0.087	0.148		32.42	19.54	32.86	
	Mean =	0.127	STD =	0.0347	Mean =	28.275	STD =	7.56669

Time(days)= 3 Calibration Curve: "y=0.458 x - 0.0025"

Table 27. 30C Raw Dissolution Data and Statistics (Day3)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.442	0.408	0.454		97.05	89.63	99.67	
	Mean =	0.435	STD =	0.02386	Mean =	95.451	STD =	5.20976
33	0.417	0.456	0.432		91.59	100.11	94.87	
	Mean =	0.435	STD =	0.0197	Mean =	95.524	STD =	4.29527
50	0.438	0.448	0.435		96.18	98.36	95.52	
	Mean =	0.440	STD =	0.0068	Mean =	96.689	STD =	1.48621
65	0.437	0.449	0.427		95.96	98.58	93.78	
	Mean =	0.438	STD =	0.0110	Mean =	96.106	STD =	2.40505
75	0.423	0.437	0.446		92.90	95.96	97.93	
	Mean =	0.435	STD =	0.0116	Mean =	95.597	STD =	2.53062
80	0.406	0.308	0.387		89.19	67.79	85.04	
	Mean =	0.367	STD =	0.0520	Mean =	80.677	STD =	11.34741

Time(days)= 6 Calibration Curve: "y=0.458 x - 0.0025"

Table 28. 30C Raw Dissolution Data and Statistics (Day6)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.45	0.441	0.437		98.80	96.83	95.96	
	Mean =	0.443	STD =	0.00666	Mean =	97.198	STD =	1.45378
33	0.423	0.429	0.429		92.90	94.21	94.21	
	Mean =	0.427	STD =	0.0035	Mean =	93.777	STD =	0.75635
50	0.433	0.479	0.472		95.09	105.13	103.60	
	Mean =	0.461	STD =	0.0248	Mean =	101.274	STD =	5.41174
65	0.461	0.463	0.46		101.20	101.64	100.98	
	Mean =	0.461	STD =	0.0015	Mean =	101.274	STD =	0.33352
75	0.353	0.439	0.431		77.62	96.40	94.65	
	Mean =	0.408	STD =	0.0475	Mean =	89.556	STD =	10.37367
80	0.382	0.4	0.37		83.95	87.88	81.33	
	Mean =	0.384	STD =	0.0151	Mean =	84.389	STD =	3.29687

Time(days)= 9 Calibration Curve: "y=0.458 x - 0.0025"

Table 29. 30C Raw Dissolution Data and Statistics (Day9)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.439	0.45	0.431		96.40	98.80	94.65	
	Mean =	0.440	STD =	0.00954	Mean =	96.616	STD =	2.08284
33	0.436	0.43	0.439		95.74	94.43	96.40	
	Mean =	0.435	STD =	0.0046	Mean =	95.524	STD =	1.00056
50	0.443	0.448	0.443		97.27	98.36	97.27	
	Mean =	0.445	STD =	0.0029	Mean =	97.635	STD =	0.63030
65	0.417	0.426	0.45		91.59	93.56	98.80	
	Mean =	0.431	STD =	0.0171	Mean =	94.651	STD =	3.72461
75	0.359	0.423	0.424		78.93	92.90	93.12	
	Mean =	0.402	STD =	0.0372	Mean =	88.319	STD =	8.13154
80	0.387	0.421	0.383		85.04	92.47	84.17	
	Mean =	0.397	STD =	0.0209	Mean =	87.227	STD =	4.55909

Time(days)= 12 Calibration Curve: "y=0.458 x - 0.0025"

Table 30. 30C Raw Dissolution Data and Statistics (Day12)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.434	0.414	0.443		95.31	90.94	97.27	
	Mean =	0.430	STD =	0.01484	Mean =	94.505	STD =	3.24097
65	0.437	0.453	0.403		95.96	99.45	88.54	
	Mean =	0.431	STD =	0.0255	Mean =	94.651	STD =	5.57517
75	0.426	0.42	0.443		93.56	92.25	97.27	
	Mean =	0.430	STD =	0.0119	Mean =	94.360	STD =	2.60488
80	0.398	0.343	0.391		87.45	75.44	85.92	
	Mean =	0.377	STD =	0.0299	Mean =	82.933	STD =	6.53686

Time(days)= 15 Calibration Curve: "y=0.458 x - 0.0025"

Table 31. 30C Raw Dissolution Data and Statistics (Day15)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.447	0.45	0.455		98.14	98.80	99.89	
	Mean =	0.451	STD =	0.00404	Mean =	98.945	STD =	0.88241
65	0.427	0.448	0.44		93.78	98.36	96.62	
	Mean =	0.438	STD =	0.0106	Mean =	96.252	STD =	2.31414
75	0.419	0.422	0.415		92.03	92.69	91.16	
	Mean =	0.419	STD =	0.0035	Mean =	91.958	STD =	0.76679
80	0.351	0.397	0.399		77.18	87.23	87.66	
	Mean =	0.382	STD =	0.0272	Mean =	84.025	STD =	5.92880

Time(days)= 18 Calibration Curve: "y=0.458 x - 0.0025"

Table 32. 30C Raw Dissolution Data and Statistics (Day18)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.45	0.455	0.437		98.80	99.89	95.96	
	Mean =	0.447	STD =	0.00929	Mean =	98.217	STD =	2.02873
33	0.437	0.453	0.449		95.96	99.45	98.58	
	Mean =	0.446	STD =	0.0083	Mean =	97.999	STD =	1.81805
50	0.437	0.441	0.424		95.96	96.83	93.12	
	Mean =	0.434	STD =	0.0089	Mean =	95.306	STD =	1.94065
65	0.427	0.441	0.422		93.78	96.83	92.69	
	Mean =	0.430	STD =	0.0098	Mean =	94.432	STD =	2.15041
75	0.415	0.398	0.432		91.16	87.45	94.87	
	Mean =	0.415	STD =	0.0170	Mean =	91.157	STD =	3.71179
80	0.39	0.381	0.316		85.70	83.73	69.54	
	Mean =	0.362	STD =	0.0404	Mean =	79.658	STD =	8.81602

Time(days)= 21 Calibration Curve: "y=0.458 x - 0.0025"

Table 33. 30C Raw Dissolution Data and Statistics (Day21)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.435	0.437	0.45		95.52	95.96	98.80	
	Mean =	0.441	STD =	0.00814	Mean =	96.761	STD =	1.77828
65	0.426	0.434	0.428		93.56	95.31	94.00	
	Mean =	0.429	STD =	0.0042	Mean =	94.287	STD =	0.90902
75	0.406	0.38	0.432		89.19	83.52	94.87	
	Mean =	0.406	STD =	0.0260	Mean =	89.192	STD =	5.67686
80	0.367	0.406	0.402		80.68	89.19	88.32	
	Mean =	0.392	STD =	0.0215	Mean =	86.063	STD =	4.68458

Time(days)= 27 Calibration Curve: "y=0.458 x - 0.0025"

Table 34. 30C Raw Dissolution Data and Statistics (Day27)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.401	0.435	0.432		88.10	95.52	94.87	
	Mean =	0.423	STD =	0.01882	Mean =	92.831	STD =	4.10999
33	0.446	0.459	0.404		97.93	100.76	88.76	
	Mean =	0.436	STD =	0.0287	Mean =	95.815	STD =	6.27642
50	0.432	0.425	0.44		94.87	93.34	96.62	
	Mean =	0.432	STD =	0.0075	Mean =	94.942	STD =	1.63877
65	0.436	0.437	0.401		95.74	95.96	88.10	
	Mean =	0.425	STD =	0.0205	Mean =	93.268	STD =	4.47643
75	0.417	0.42	0.425		91.59	92.25	93.34	
	Mean =	0.421	STD =	0.0040	Mean =	92.394	STD =	0.88241
80	0.373	0.34	0.291		81.99	74.78	64.08	
	Mean =	0.335	STD =	0.0413	Mean =	73.617	STD =	9.00859

Time(days)= 33 Calibration Curve: "y=0.458 x - 0.0025"

Table 35. 30C Raw Dissolution Data and Statistics (Day33)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.45	0.439	0.448		98.80	96.40	98.36	
	Mean =	0.446	STD =	0.00586	Mean =	97.853	STD =	1.27936
33	0.439	0.443	0.443		96.40	97.27	97.27	
	Mean =	0.442	STD =	0.0023	Mean =	96.980	STD =	0.50424
50	0.412	0.436	0.441		90.50	95.74	96.83	
	Mean =	0.430	STD =	0.0155	Mean =	94.360	STD =	3.38487
65	0.428	0.436	0.435		94.00	95.74	95.52	
	Mean =	0.433	STD =	0.0044	Mean =	95.087	STD =	0.95172
75	0.39	0.409	0.379		85.70	89.85	83.30	
	Mean =	0.393	STD =	0.0152	Mean =	86.281	STD =	3.31370
80	0.316	0.35	0.374		69.54	76.97	82.21	
	Mean =	0.347	STD =	0.0291	Mean =	76.237	STD =	6.36317

Time(days)= 40 Calibration Curve: "y=0.458 x - 0.0025"

Table 36. 30C Raw Dissolution Data and Statistics (Day40)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.429	0.45	0.433		94.21	98.80	95.09	
	Mean =	0.437	STD =	0.01115	Mean =	96.033	STD =	2.43460
65	0.395	0.441	0.401		86.79	96.83	88.10	
	Mean =	0.412	STD =	0.0250	Mean =	90.575	STD =	5.45997
75	0.421	0.429	0.426		92.47	94.21	93.56	
	Mean =	0.425	STD =	0.0040	Mean =	93.413	STD =	0.88241
80	0.37	0.374	0.385		81.33	82.21	84.61	
	Mean =	0.376	STD =	0.0078	Mean =	82.715	STD =	1.69595

Time(days)= 47 Calibration Curve: "y=0.458 x - 0.0025"

Table 37. 30C Raw Dissolution Data and Statistics (Day47)

%Dissolution Determination (30C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.437	0.432	0.448		95.96	94.87	98.36	
	Mean =	0.439	STD =	0.00819	Mean =	96.397	STD =	1.78719
33	0.452	0.447	0.448		99.24	98.14	98.36	
	Mean =	0.449	STD =	0.0026	Mean =	98.581	STD =	0.57767
50	0.443	0.435	0.44		97.27	95.52	96.62	
	Mean =	0.439	STD =	0.0040	Mean =	96.470	STD =	0.88241
65	0.43	0.444	0.444		94.43	97.49	97.49	
	Mean =	0.439	STD =	0.0081	Mean =	96.470	STD =	1.76483
75	0.392	0.412	0.409		86.14	90.50	89.85	
	Mean =	0.404	STD =	0.0108	Mean =	88.828	STD =	2.35498
80	0.371	0.373	0.394		81.55	81.99	86.57	
	Mean =	0.379	STD =	0.0127	Mean =	83.370	STD =	2.78188

Time(days)= 54 Calibration Curve: "y=0.458 x - 0.0025"

Table 38. 30C Raw Dissolution Data and Statistics (Day54)

40C Dissolution Values (Raw Data and Statistics)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.438	0.45	0.45		96.18	98.80	98.80	
	Mean =	0.446	STD =	0.00693	Mean =	97.926	STD =	1.51271
33	0.432	0.45	0.434		94.87	98.80	95.31	
	Mean =	0.439	STD =	0.0099	Mean =	96.325	STD =	2.15410
50	0.444	0.403	0.436		97.49	88.54	95.74	
	Mean =	0.428	STD =	0.0217	Mean =	93.923	STD =	4.74525
65	0.424	0.456	0.432		93.12	100.11	94.87	
	Mean =	0.437	STD =	0.0167	Mean =	96.033	STD =	3.63610
75	0.445	0.447	0.42		97.71	98.14	92.25	
	Mean =	0.437	STD =	0.0150	Mean =	96.033	STD =	3.28480
80	0.424	0.419	0.412		93.12	92.03	90.50	
	Mean =	0.418	STD =	0.0060	Mean =	91.885	STD =	1.31609
90	0.206	0.169	0.188		45.52	37.45	41.59	
	Mean =	0.188	STD =	0.0185	Mean =	41.521	STD =	4.03979

Time(days)= 3 Calibration Curve: "y=0.458 x - 0.0025"

Table 39. 40C Raw Dissolution Data and Statistics (Day3)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.388	0.429	0.44		85.26	94.21	96.62	
	Mean =	0.419	STD =	0.02740	Mean =	92.031	STD =	5.98349
33	0.437	0.461	0.435		95.96	101.20	95.52	
	Mean =	0.444	STD =	0.0145	Mean =	97.562	STD =	3.15903
50	0.426	0.44	0.447		93.56	96.62	98.14	
	Mean =	0.438	STD =	0.0107	Mean =	96.106	STD =	2.33465
65	0.438	0.45	0.45		96.18	98.80	98.80	
	Mean =	0.446	STD =	0.0069	Mean =	97.926	STD =	1.51271
75	0.33	0.406	0.411		72.60	89.19	90.28	
	Mean =	0.382	STD =	0.0454	Mean =	84.025	STD =	9.91068
80	0.332	0.372	0.363		73.03	81.77	79.80	
	Mean =	0.356	STD =	0.0210	Mean =	78.202	STD =	4.58169

Time(days)= 6 Calibration Curve: "y=0.458 x - 0.0025"

Table 40. 40C Raw Dissolution Data and Statistics (Day6)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.45	0.439	0.437		98.80	96.40	95.96	
	Mean =	0.442	STD =	0.00700	Mean =	97.052	STD =	1.52838
33	0.44	0.444	0.439		96.62	97.49	96.40	
	Mean =	0.441	STD =	0.0026	Mean =	96.834	STD =	0.57767
50	0.43	0.43	0.453		94.43	94.43	99.45	
	Mean =	0.438	STD =	0.0133	Mean =	96.106	STD =	2.89936
65	0.433	0.45	0.456		95.09	98.80	100.11	
	Mean =	0.446	STD =	0.0119	Mean =	97.999	STD =	2.60488
75	0.377	0.425	0.416		82.86	93.34	91.38	
	Mean =	0.406	STD =	0.0255	Mean =	89.192	STD =	5.57090
80	0.373	0.361	0.36		81.99	79.37	79.15	
	Mean =	0.365	STD =	0.0072	Mean =	80.167	STD =	1.57951

Time(days)= 9 Calibration Curve: "y=0.458 x - 0.0025"

Table 41. 40C Raw Dissolution Data and Statistics (Day9)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.435	0.431	0.447		95.52	94.65	98.14	
	Mean =	0.438	STD =	0.00833	Mean =	96.106	STD =	1.81805
33	0.441	0.444	0.427		96.83	97.49	93.78	
	Mean =	0.437	STD =	0.0091	Mean =	96.033	STD =	1.98117
50	0.436	0.439	0.419		95.74	96.40	92.03	
	Mean =	0.431	STD =	0.0108	Mean =	94.723	STD =	2.35498
65	0.439	0.448	0.437		96.40	98.36	95.96	
	Mean =	0.441	STD =	0.0059	Mean =	96.907	STD =	1.27936
75	0.395	0.411	0.425		86.79	90.28	93.34	
	Mean =	0.410	STD =	0.0150	Mean =	90.138	STD =	3.27753
80	0.322	0.394	0.391		70.85	86.57	85.92	
	Mean =	0.369	STD =	0.0407	Mean =	81.114	STD =	8.89319

Time(days)= 12 Calibration Curve: "y=0.458 x - 0.0025"

Table 42. 40C Raw Dissolution Data and Statistics (Day12)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.431	0.435	0.442		94.65	95.52	97.05	
	Mean =	0.436	STD =	0.00557	Mean =	95.742	STD =	1.21567
65	0.434	0.436	0.446		95.31	95.74	97.93	
	Mean =	0.439	STD =	0.0064	Mean =	96.325	STD =	1.40373
75	0.35	0.403	0.422		76.97	88.54	92.69	
	Mean =	0.392	STD =	0.0373	Mean =	86.063	STD =	8.14716
80	0.367	0.388	0.257		80.68	85.26	56.66	
	Mean =	0.337	STD =	0.0704	Mean =	74.199	STD =	15.36214

Time(days)= 15 Calibration Curve: "y=0.458 x - 0.0025"

Table 43. 40C Raw Dissolution Data and Statistics (Day15)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.445	0.445	0.432		97.71	97.71	94.87	
	Mean =	0.441	STD =	0.00751	Mean =	96.761	STD =	1.63877
33	0.444	0.442	0.45		97.49	97.05	98.80	
	Mean =	0.445	STD =	0.0042	Mean =	97.780	STD =	0.90902
50	0.439	0.445	0.449		96.40	97.71	98.58	
	Mean =	0.444	STD =	0.0050	Mean =	97.562	STD =	1.09896
65	0.435	0.442	0.424		95.52	97.05	93.12	
	Mean =	0.434	STD =	0.0091	Mean =	95.233	STD =	1.98117
75	0.333	0.417	0.405		73.25	91.59	88.97	
	Mean =	0.385	STD =	0.0454	Mean =	84.607	STD =	9.91949
80	0.244	0.318	0.283		53.82	69.98	62.34	
	Mean =	0.282	STD =	0.0370	Mean =	62.045	STD =	8.08254

Time(days)= 18 Calibration Curve: "y=0.458 x - 0.0025"

Table 44. 40C Raw Dissolution Data and Statistics (Day18)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.406	0.449	0.453		89.19	98.58	99.45	
	Mean =	0.436	STD =	0.02606	Mean =	95.742	STD =	5.68944
65	0.442	0.446	0.424		97.05	97.93	93.12	
	Mean =	0.437	STD =	0.0117	Mean =	96.033	STD =	2.55872
75	0.41	0.386	0.417		90.07	84.83	91.59	
	Mean =	0.404	STD =	0.0163	Mean =	88.828	STD =	3.54985
80	0.257	0.349	0.281		56.66	76.75	61.90	
	Mean =	0.296	STD =	0.0477	Mean =	65.102	STD =	10.41952

Time(days)= 21 Calibration Curve: "y=0.458 x - 0.0025"

Table 45. 40C Raw Dissolution Data and Statistics (Day21)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.43	0.429	0.421		94.43	94.21	92.47	
	Mean =	0.427	STD =	0.00493	Mean =	93.705	STD =	1.07705
65	0.438	0.444	0.409		96.18	97.49	89.85	
	Mean =	0.430	STD =	0.0187	Mean =	94.505	STD =	4.08672
75	0.402	0.407	0.347		88.32	89.41	76.31	
	Mean =	0.385	STD =	0.0333	Mean =	84.680	STD =	7.26892
80	0.356	0.379	0.291		78.28	83.30	64.08	
	Mean =	0.342	STD =	0.0456	Mean =	75.218	STD =	9.96504

Time(days)= 27 Calibration Curve: "y=0.458 x - 0.0025"

Table 46. 40C Raw Dissolution Data and Statistics (Day27)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
12	0.44	0.441	0.442		96.62	96.83	97.05	
	Mean =	0.441	STD =	0.00100	Mean =	96.834	STD =	0.21834
33	0.43	0.445	0.439		94.43	97.71	96.40	
	Mean =	0.438	STD =	0.0075	Mean =	96.179	STD =	1.64844
50	0.432	0.441	0.437		94.87	96.83	95.96	
	Mean =	0.437	STD =	0.0045	Mean =	95.888	STD =	0.98455
65	0.434	0.438	0.445		95.31	96.18	97.71	
	Mean =	0.439	STD =	0.0056	Mean =	96.397	STD =	1.21567
75	0.381	0.362	0.402		83.73	79.59	88.32	
	Mean =	0.382	STD =	0.0200	Mean =	83.879	STD =	4.36863
80	0.319	0.299	0.362		70.20	65.83	79.59	
	Mean =	0.327	STD =	0.0322	Mean =	71.870	STD =	7.02885

Time(days)= 33 Calibration Curve: "y=0.458 x - 0.0025"

Table 47. 40C Raw Dissolution Data and Statistics (Day33)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.425	0.432	0.422		93.34	94.87	92.69	
	Mean =	0.426	STD =	0.00513	Mean =	93.632	STD =	1.12044
65	0.408	0.415	0.421		89.63	91.16	92.47	
	Mean =	0.415	STD =	0.0065	Mean =	91.084	STD =	1.42061
75	0.329	0.401	0.399		72.38	88.10	87.66	
	Mean =	0.376	STD =	0.0410	Mean =	82.715	STD =	8.95285
80	0.3	0.351	0.354		66.05	77.18	77.84	
	Mean =	0.335	STD =	0.0303	Mean =	73.690	STD =	6.62620

Time(days)= 40 Calibration Curve: "y=0.458 x - 0.0025"

Table 48. 40C Raw Dissolution Data and Statistics (Day40)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.406	0.427	0.425		89.19	93.78	93.34	
	Mean =	0.419	STD =	0.01159	Mean =	92.103	STD =	2.53062
65	0.42	0.419	0.41		92.25	92.03	90.07	
	Mean =	0.416	STD =	0.0055	Mean =	91.448	STD =	1.20253
75	0.384	0.373	0.346		84.39	81.99	76.09	
	Mean =	0.368	STD =	0.0196	Mean =	80.822	STD =	4.26929
80	0.245	0.265	0.21		54.04	58.41	46.40	
	Mean =	0.240	STD =	0.0278	Mean =	52.948	STD =	6.07835

Time(days)= 47 Calibration Curve: "y=0.458 x - 0.0025"

Table 49. 40C Raw Dissolution Data and Statistics (Day47)

%Dissolution Determination (40C)

	ABS(AU)				%Dissolution			
%RH	#1	#2	#3		#1	#2	#3	
50	0.438	0.423	0.438		96.18	92.90	96.18	
	Mean =	0.433	STD =	0.00866	Mean =	95.087	STD =	1.89089
65	0.426	0.431	0.429		93.56	94.65	94.21	
	Mean =	0.429	STD =	0.0025	Mean =	94.141	STD =	0.54948
75	0.397	0.359	0.408		87.23	78.93	89.63	
	Mean =	0.388	STD =	0.0257	Mean =	85.262	STD =	5.61352
80	0.332	0.345	0.316		73.03	75.87	69.54	
	Mean =	0.331	STD =	0.0145	Mean =	72.817	STD =	3.17158

Time(days)= 54 Calibration Curve: "y=0.458 x - 0.0025"

Table 50. 40C Raw Dissolution Data and Statistics (Day54)

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