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Prediction of Shelf-Life of a Moisture-Sensitive Drug at High Relative Humidity and Temperature Using Dissolution as a Function of Moisture Content

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PREDICTION OF SHELF LIFE OF A MOISTURE SENSITIVE DRUG AT HIGH RELATIVE HUMIDITY AND TEMPERATURE USING DISSOLUTION AS A FUNCTION OF MOISTURE CONTENT

By

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ABSTRACT

PREDICTION OF SHELF LIFE OF A MOISTURE SENSITIVE DRUG AT HIGH RELATIVE HUMIDITY AND TEMPERATURE USING DISSOLUTION AS A FUNCTION OF MOISTURE CONTENT.

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This study was designed to determine if a prediction model developed by the School of Packaging could be used with dissolution as a function of moisture content to predict shelf life. The equilibrium moisture isotherm, the dissolution profiles, the package permeability and the storage conditions were used in the model to predict change in moisture content as a function of time, and the time required to reach a critical moisture content. If the present simulation model is sufficiently accurate, it will give us means to select packages which have a high probability of success for stability testing.

In this study, dissolution profiles at 18°C, 28°C, and 38°C were developed. The critical moisture content for dissolution failure was found. We used open dish storage without any packaging, thus measuring the performance of unpackaged product. The goal was to establish the unpackaged-product behavior as this information is not available in literature. A predictive equation was used to relate shelf life to dissolution failure for a product in two blister materials: PVC and PVC/0.6 mil Aclar. The results indicate that dissolution can be used to select appropriate packaging based on shelf-life requirements.

DEDICATION

This thesis is dedicated to my husband and soul-mate Dr. Prashant B. Kokitkar who has been very understanding and supportive. Special thanks to my parents, Mr. and Mrs. Dattatray S. Chavan, my sisters, my brother-in-law, and my brother in appreciation of their love, support and commitment to education.

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Chapter 1

INTRODUCTION

The moisture content of a product depends on its storage environment. The shelf life of a moisture sensitive product depends mainly on its moisture content. Product moisture content is related to external and internal package environment. The storage environment can be described by temperature and relative humidity.

Broadly, there are two methods of shelf life evaluation. The first method involves the actual long term storage testing, whereas the second method includes estimation techniques like shelf life simulation and accelerated studies. Actual storage testing by a long term stability study involves storing a packaged dry product under typical storage conditions of temperature and relative humidity. Samples are examined at regular time intervals and the degradation factor is recorded. Although these studies are expensive and require long time periods, they are required by the Federal Food and Drug Administration (FDA) as part of a New Drug Application (NDA)[1].

A computer simulation model can be used for calculating the shelf life of a moisture sensitive product. This estimation technique is less costly, and more rapid than the actual storage testing but FDA does not allow simulation as a substitute for actual testing. However, it can be used to select product formulation, and packaging materials for product storage stability tests. Such a computer simulation model has been developed by the School of Packaging at Michigan State University. This project was designed to predict shelf-life with this simulation model using dissolution as a function of moisture content. Axid™ 150 mg pulvules, manufactured by Eli Lilly and Company, were used in these experiments.

Nowadays, a wide variety of packaging materials is available. It is very costly to test every material physically, so computer simulation is useful. Because of the inherent errors involved in accelerated storage test procedures, recently more emphasis has been placed on utilizing a computer simulation approach to select packages for stability testing.

Moisture content is not a property of much interest to the pharmaceutical industry; they do not use it for other than product manufacture. On the other hand, dissolution is a property of much interest to the pharmaceutical industry. For drug tablets and capsules, dissolution is listed as a stability indicating property in the United States Pharmacopoeia (USP) monographs. Failure to meet USP limits can result in recall of a product. From literature and our studies, we have learned that dissolution can be negatively affected by high temperature and high humidity. Failure to meet USP dissolution specifications, can result from these negative effects and subsequently that results in product recall. Dissolution can be negatively affected by other factors as well. FDA specifies the USP dissolution test as the bioavailability indicating test. However, sometimes dissolution has not been necessarily related to bioavailability. Sometimes a drug dosage fails the dissolution test, but passes other tests such as presence in blood or urine sample. In such a case, for regulatory purpose, it is nevertheless considered as failed. This complicates the issue of using dissolution for shelf life prediction.

Since other factors than dissolution can affect shelf life, dissolution is not the sole predictor. The evidence is strong however, that it will be a useful indicator of the best water vapor barrier package to choose for stability studies. A relationship between the moisture content of the Axid™ Pulvule and its dissolution rate will be important in determining the shelf life and that way dissolution can be used as an endpoint in the shelf life estimation.

In this project, open dish storage was used for dissolution studies. As no packages were used for the dissolution studies, we have measured the performance of the unpackaged product. The goal of these dissolution studies were to establish the product behavior. As the information was not available anywhere, we included this study in the project.

Chapter 2

LITERATURE REVIEW

Dissolution stability is a critical parameter from the standpoint of quality control, regulatory compliance, and impact on the bioavailability of the product. Factors that affect the dissolution stability of a product during aging include formulation components, processing factors, storage conditions, and packaging. The role of each of these factors is discussed by Murthy, et al.[2] An automated dissolution rate apparatus meeting requirements of the USP-NF dissolution test and applicable to various other agitation systems in common usage is described by Johnson et al.[3] Dissolution changes in capsule products under accelerated storage conditions depend on the storage conditions, the colorants present in the capsule shell, and the aqueous solubility of the drug substance involved.[4]

A mathematical model for the prediction of shelf life of solid dosage forms in moisture semi-permeable packages, including multi-layer overwrapped packaging systems is available.[5] Solid dosage forms such as tablets and capsules more often deteriorate as a result of two factors, the moisture content and the ambient temperature, than the moisture content alone. The iteration procedure using the mathematical model derived by Nakabayashi, et al.[6] helps to predict the shelf life of packaged solid dosage forms.

A differential analysis procedure was found useful for kinetic studies of the deterioration of solid dosage forms under the influence of the moisture content and ambient temperature.[7] Nakabayashi, et al. studied the degradation reaction of Aspirin

Aluminum tablets under heat and moisture. They found that the reaction follows zero order kinetics and the degradation rate constants are affected by both moisture and heat. Carstensen formulae are used to describe the extent of the effect.[8] In another study, Nakabayashi et al. show that the effect of aging on the disintegration of packaged tablets is influenced by moisture and heat. Their measurements followed prediction reasonably.[9] In a follow up study, the authors used iterative calculations to predict dissolution rate.[10] Dey, et al. studied the stability of Etodolac capsule at high relative humidity and high temperature and found it to be unaffected. [11] The in-vivo bioavailability of Etodolac capsules stored at 40°C/75% RH was not adversely affected.

Mizrahi and Karel[12] have developed a method for accelerated stability tests that is applicable to isothermal storage of moisture sensitive dehydrated products packaged in water-vapor-permeable containers. They have also expanded the method to include storage at different temperatures which can be applied to dehydrated products when moisture content changes continuously during storage and when the rate of deterioration depends only on moisture content and temperature.[13] The application of annual atmospheric temperature distribution to the shelf-life prediction of pharmaceutical preparations in distribution channels has been proposed by Terao, et al.[14] Deterioration of solid dosage forms due to the change of moisture content in moisture-semipermeable packages has been investigated by Nakabayashi, et al.[15] The authors used a mathematical model based on the physico-chemical properties of the drug and the moisture permeabilities of the packaging materials to predict the shelf-life in a drug-package combination. Quast and Karel have applied numerical techniques to predict the storage life of a dry food product undergoing spoilage by two mechanisms simultaneously, with interactions between the mechanisms.[16] The authors claim that the technique can be applied to any package size and configuration, as well as to package design and optimization. Clifford, et al. have estimated the shelf life of moisture sensitive packaged products by 1) accelerated tests and 2) calculations based on properties of the product and package[17]. The report demonstrates a procedure that may be used for some products. After reporting on the results of actual storage tests and comparing these results with calculated results, the authors claim that the calculated method not only requires much less time and resources but is also more accurate when moisture change is the only shelf life criteria.

A comparative performance of Carbamazepine 200 mg tablet products available in the Kenyan market was done[18]. Drug dissolution was found to vary between batches for one product. At each sampling time, most generics had wide variations in amount of dissolved drug.

The effect of storage at accelerated conditions is a very important issue in packaging. Studies of storage of controlled release isosorbide dinitrate pellets indicate that both temperature and humidity accelerate the degradation of the formulation[19]. The dissolution and bioavailability of ectodolac from capsules exposed to high relative humidity and temperature (40°C and 75% RH) were compared to those from capsules stored at 25°C[20]. The authors found that the capsules exposed to stressed conditions failed the dissolution. In another study on bioavailability, the moisture-exposed CBZ tablets were of expected weight but were swollen and enlarged[21]. Analysis was done and it was proposed that poor dissolution of moisture-exposed CBZ tablets results in reduced bioavailability.

Dissolution is a central tool available for practical application of innovations resulting from studies of biopharmaceutics and pharmacokinetics. New test criteria should include factors such as, repeatability, bioavailability prediction, rigorous protocol, degradates, and constant validation.[22] The dissolution test method given in the U.S. Pharmacopoeia XXII will be followed in this study.[23,24]

Aging of a drug is affected by various types of formulation factors. Other factors affecting disintegration of a dosage form and dissolution of a drug at the time of manufacture also influence aging.[25] Taborsky et al.[26] concluded that packaging and storage conditions markedly affect tablet dissolution characteristics. Product protection and dissolution of a package is related to barrier properties of a package. Tablets stored in containers that have the highest moisture permeability experience the greatest loss in rate of dissolution. Dissolution decreases with time after reaching the moisture equilibrium. This was the first such type of package study in the open literature.

From the literature review, we can see that no one has done work to correlate moisture content, dissolution, and shelf life together. Except for Taborsky[26], the packaging mechanism has not been studied in the past. A new approach is needed to study the packages in detail and it is necessary to understand the mechanism of how packages work. That is why we designed this study. The requirements for dissolution do not apply to soft gelatin capsules unless specified in the individual monograph. The guidelines for conducting a dissolution study are available.[27,28]

Chapter 3

OBJECTIVES

Researchers at the School of Packaging at Michigan State University have developed a computer program to predict within ten percent the shelf life (or the moisture content) of pharmaceutical tablets stored under cycling conditions. The research presented here was undertaken to verify the accuracy of prediction of shelf life by this computer program when dissolution failure is the endpoint. The specific objectives of the research were:

1. To determine the initial moisture content of Axid™ powder, shell, and product.
2. To determine the equilibrium sorption isotherms at 18°C, 28°C, and 38°C for nine different humidities.
3. To determine the dissolution profiles at 18°C, 28°C, and 38°C for nine different humidities.
4. To measure the water vapor permeability of three different blister materials.
5. To predict the shelf-life using the computer simulation model with dissolution as a function of moisture content.

Chapter 4

MATERIALS; EQUIPMENT, AND METHODS

MATERIALS AND EQUIPMENT

1. Axid™ pulvules, 150 mg
   a) Axid™ pulvules (Manufactured by Eli Lilly and Company, Indianapolis, IN) were used for this study. This drug is used as an anti-ulcer drug. In order to eliminate variability between different lots of the drug, pulvules from the same lot were used for the entire study. The active ingredient in each pulvule is Nizatidine USP 150 mg, the other ingredients in this capsule are gelatin, pregelatanized starch, silicone, starch, titanium dioxide, yellow iron oxide, Magnesium Stearate and other inactive ingredients.
2. Molecular sieve desiccants provided by Eli Lilly and Company.
3. Mettler balance Model no. AE 160 manufactured by Mettler-Toledo Inc.
4. Vacuum oven Model no. 524 manufactured by Precision Scientific.
5. Humidity buckets (Plastic 5-gallon buckets)
6. Nine humidity/temperature sensors ("Hygrodynamics" Newport Scientific, Inc. 8246-E. Sandy Court, Jessup,. MD 20794-0189)
7. Nine Saturated Salt Solutions (nine different humidities) (see Table 1)
8. Storage Chambers (at 18°C, 28° C, and 38°C) manufactured by Nor Lake Scientific and Lab-line instruments Inc.

9. Computer Program on Shelf life, developed by the School of Packaging at Michigan State University
10. Dissolution Apparatus VK 7000 from VanKel, 36 Meridian Road, Edison, New Jersey
11. Spectrophotometer from Perkin Elmer Lambda 3 B, UV/VIS Spectrophotometer.
12. Plastic syringes 5 cc, B-D manufactured by Becton-Dickinson.
13. Polyethylene Tygon tubes from Michigan State University Store.
14. Glass Petri dishes
15. Glass test tubes manufactured by Corning 13 X 100 mm; Borosilicate Pyrex glass tubes.
16. Cotton balls
17. Pipetman by Rainin Model no. P1000, P5000.
18. Disposable pipette tips by Dot Scientific Inc. for 101-1000 µl Pipetman.
19. Rainin Certified disposable microliter Pipette tips 5 ml
20. Calibrated Thermometer, Fisher Scientific Catalog # 15041 A.
21. Paper Clips by Acco International Inc. # 1 premium.
22. Parafilm- 4 in X 125 ft roll; Laboratory film manufactured by American National Can.
23. Fisherbrand Latex Examination gloves (Powdered Non-sterile Ambidextrous single-use large gloves by Fisher Scientific.
24. Plasti Dip (industrial grade USDA accepted) manufactured by PDI Inc.
25. Fisher brand Pasteur Pipettes, Flint glass; size 5 3/4 in.

26. Three blister package types containing a molecular sieve desiccant were evaluated. The composition of these packages were as follows:
    a) a blister package fabricated from 0.010 in Polyvinyl Chloride (PVC) film,
    b) a blister package made with a laminate of 0.0020 in Aclar 33C / 0.0020 in Polyethylene (PE) laminate adhesive / 0.0075 in American Hoechst "Mirrex" MCFD-1025 clear PVC, and,
    c) a blister package made with a laminate of 0.0006 in Aclar RX-160 / 0.00200 in PE laminate adhesive / 0.00750 in American Hoechst "Mirrex" / MCFD-1025 clear PVC.

STORAGE CONDITIONS

Initially, the moisture isotherms were determined at three different temperatures at seven different humidities. Later on during the research, two more relative humidities were added in order to get precise information about the critical moisture content. The nine humidity levels are listed in Table 1.

The three temperatures used were 18°C, 28°C, and 38°C in order to cover the entire temperature range the product is likely to encounter all over the world. At each temperature, the humidity was varied from the lowest value to the highest value.

Nine humidity buckets were prepared by placing nine different saturated salt solutions into tightly closed 5 gal plastic containers. Calibrated hygrometer sensors were installed in each bucket to monitor the humidity values. The equilibrium moisture isotherms were developed separately for Axid™ powder, empty shells, and unopened pulvules. During the entire experiment, precaution was taken to maintain constant conditions (temperature and relative humidity) of the humidity chambers and humidity buckets. Before weighing any particular sample at each time point, the temperature and humidity of the bucket were measured to ensure that these were within the range (± 2 % for Relative Humidity and ± 2°C for temperature) for that particular bucket.

The water vapor permeability study was carried out for blisters at 89% relative humidity at the same three temperatures of 18°C, 28°C, and 38°C.

EXPERIMENTAL PROCEDURES

A. Determination of Moisture Isotherm

1. Preparation of nine humidity buckets

A list of saturated salt solutions[29] used to provide the required range of relative humidities is given in Table 1.

Table 1. Salt solutions used to prepare the humidity chambers (buckets) and their respective relative humidities (% RH)

Bucket No.	Saturated Salt Solution	Relative Humidity (%RH)		
		18°C	28°C	38°C
1	Lithium Chloride	16.10	12.10	14.20
2	Potassium Acetate	22.50	22.00	23.60
3	Magnesium Chloride	36.75	32.50	35.25
4	Potassium Carbonate	45.75	43.75	44.50
5	Magnesium Nitrate	55.00	51.50	53.75
6	Sodium Nitrite	67.00	64.00	63.25
7	Sodium Chloride	74.70	75.20	75.70
8	Ammonium Sulfate	79.20	80.00	80.20
9	Potassium Nitrate	92.80	91.00	89.80

Nine humidity buckets were prepared by placing nine different saturated salt solutions into tightly closed 5 gal plastic containers. Calibrated hygrometer sensors were installed in each bucket to monitor the humidity values.

Different humidities were obtained by using saturated aqueous salt solutions in contact with an excess of the solids (salt) phase. Distilled, deionized pure water and chemically pure salt was used to obtain stable humidity. The solution was a slush consisting of a solution with excess undissolved crystals. A good solution could usually be made by adding distilled water slowly, with constant stirring, until about half of the salt crystals present were dissolved. Fresh solutions should be made up well in advance of actual use and sufficient time must be allowed for them to cool to room temperature. The prepared salt solutions were placed within the tightly closed buckets and allowed to equilibrate for at least four hours. The relative humidity within each of these buckets was monitored daily by temperature and humidity sensors.

A saturated salt solution has a definite water vapor pressure at a given solution temperature. The relative humidity created in the vapor space is determined by the water vapor pressure and the saturation water vapor pressure at the temperature of the vapor. “Hygrodynamics” hygrosensors were used to determine the actual humidity condition created and to monitor its stability. They were mounted directly in the lid of the buckets. Temperature and relative humidity were monitored periodically to insure stable conditions of the buckets.

2. Determination of Sorption Isotherm

To determine the isotherms, we had to develop the technique for determining moisture content. For the purpose of selecting the packaging material, we need moisture content of the whole product entity, i.e. capsule with powder in it. Pharmaceutical companies measure moisture content of the product powder removed from the capsule, but not for the entire capsule with powder in it. At first, tweezers were used to open the pulvules which resulted in some spilling of the contents, so surgical gloves were then used instead for opening the pulvules. This results in lower standard deviation, as seen from Table 7 in Chapter 5 on page 30.

The equilibrium moisture content (EMC) can be expressed as a percent moisture on a dry weight basis or wet weight basis of the product. In case of dry weight basis , it is calculated with respect to the total dry weight of the product i.e. with respect to weight without weight of water molecules present in the ingredients of the product. For wet weight basis , weight of the water molecules present in the ingredients is taken into account while calculating the total weight of the product. We have calculated the equilibrium moisture content as a percent moisture based on a dry weight of the product. Researchers at Lilly calculate it on a wet weight basis. The equilibrium moisture content calculated on a wet basis is less than the equilibrium moisture content calculated on a dry basis. In the case of Axid there is no significant difference between the EMC values calculated on wet and dry basis. The moisture sorption isotherms were developed by exposing the pulvules of known initial moisture content at nine different relative humidities at three different temperatures. Then a gravimetric method was used for determining the moisture sorption isotherm at nine humidities and three temperatures.

Different humidities were obtained by using saturated aqueous salt solutions in contact with excess of the solid (salt) phase. These were placed in the 5-gallon plastic buckets. The buckets were transferred to the storage chambers maintained at 18°C, 28°C, and 38°C. Once the buckets were kept at a particular temperature setting, equilibrium was attained after three days. Temperature and humidity readings were taken periodically to confirm the equilibrium.

The EMC was determined for unopened Axid™ pulvules, empty gelatin shells, and Axid™ powder. First, empty glass petri dishes and lids were dried in the convection oven for 1 hr at 100-105°C. Then they were cooled in a desiccator. After that these empty dishes were weighed. Then a known quantity of the product was added to each dish. In the case of powder, it was spread uniformly over the bottom of the petri dish. Then the bottom parts of the petri dishes were placed on their lids to prevent the salt solution from touching the petri dishes. Bottom parts of the glass petri dishes were marked for identification purpose. Then those bottom parts were weighed without lids and a known quantity of pulvules was accurately weighed into them and recorded. After that, these petri dishes were placed over the saturated salt solutions in the closed buckets. The petri dishes holding samples were weighed without lids after a predetermined time interval until no change in weight was observed. Each weight change was measured till a constant weight was achieved. Then the equilibrium moisture content of the product at each specific relative humidity at all the three temperatures was calculated.

3. Determination of Initial Moisture Content (IMC)

The IMC was determined for unopened Axid™ pulvules, empty gelatin shells, and Axid™ powder. First empty glass petri dishes and lids were dried in the convection oven for 1 hr at 100-105°C. Then they were cooled in a desiccator. After that these empty dishes were weighed. Then a known quantity of the product was added to each dish. In the case of powder, it was spread uniformly over the bottom of the petri dish. Then the bottom parts of the petri dishes were placed on their lids to prevent the salt solution from touching the petri dishes. These petri dishes were placed in the oven. Samples were dried by placing in an oven at 85°C for an hour. Then the oven door was opened. Lids were replaced on the dishes and placed in the desiccator for cooling. These cooled dishes were reweighed to calculate the weight loss of the sample due to loss of moisture content (the weight of the petri dishes was subtracted) and IMC on a dry basis was determined. This procedure was developed after comparing oven drying, Karl Fisher method, and Brinkman apparatus, as described in the results section. A reliable, reproducible moisture content can be obtained by drying the capsule, shell, or powder in an oven for 1 hour at 85°C. This was verified with comparative determinations with researchers at Lilly, and with Karl Fisher method and Brinkman apparatus at the School of Packaging. Table 6 shows the results of the trials. We believe that the oven method and the Brinkman method (using homogenizer) release a little more water than the Karl Fisher method draws out of the product.

B. Determination of Dissolution Profile

Vankel 7000 Dissolution Test Station from Vankel was used for this study. Disposable syringes of 5 cc capacity and polyvinyl chloride Tygon tubing were used for sampling. The volume of each dissolution vessel was 1000 ml.

According to USP XXII, if capsule shells interfere with the analysis, the contents of not less than six capsules should be removed as completely as possible, and the empty capsule shells should be dissolved in the specified volume of the dissolution medium[32]. Factors such as deaeration, temperature used, position of a dosage unit, and volume must be taken into consideration while following the test method[32]. In this study, the capsule (pulvule) shells did not interfere with the analysis. One capsule per vessel per reading is used.

An acceptance table in the procedure is used based on six capsules. It allows up to twenty-four pulvules as the maximum limit. According to the USP monograph for Nizatidine capsules, the drug is considered to have passed the dissolution test if not less than 75% of the labeled amount of the drug is dissolved in 30 minutes[30].

1. Preparation for the experiment:

1) Boil distilled, and deionized water for an hour to prepare deaerated dissolution medium. Cool it to 37°C before using. Check the temperature using NST and ISTS certified thermometer with a correction factor. If this water is not boiled, air bubbles appear on the outer and inner surfaces of the vessels and we can not watch the actual dissolution. Also, temperature control is not precise. The major influence of gas or air in

media seems to be physical; i.e. , the bubbles that appear in media as the equilibrium is disturbed may alter the flow patterns as they rise to the surface, or may associate with aggregate particles, resulting in random concentrations of the particles in the solvent stream, or may attach to dosage forms before disintegration, thus altering the disintegration and deaggregation process by reducing the surface area exposed to the solvent stream and/or altering the specific gravity of the mass, resulting in a random, uncontrollable positioning of the mass in the solvent stream, or may in some cases contribute to the boundary layer at the solid-liquid interface in a random manner.[31]

2) Switch on the dissolution apparatus. Set the water-bath temperature at 37.3°C.

3) Fill the vessels with the cooled, deaerated, distilled water. Fill 900 ml of water in each vessel. Allow half an hour to reach temperature equilibrium with the water in the water bath. Check the temperature with the NST and ISTS certified thermometer with a correction factor.

4) Wash the Tygon tubing with distilled water. Cut roughly 1 cc of cotton. Wet the cotton first. Put wet cotton snugly into the tube end near the syringe. It should fit tightly in the tube so that it will not come out with air pressure during the sampling procedure. We are using the filter to remove insoluble particles which may interfere with the spectrophotometer readings.

5) Squeeze out excess water from the cotton and tube, using syringe air pressure, so that the excess water will not dilute the sample. The same syringe and tube were used for one vessel for all the time intervals. Three pulvules were tested at a time. Three vessels were active, so three syringe and tube assemblies were used.

6) Prepare two sets of clean, dry test tubes for the sampling and number them.

2. Procedure for dissolution

1) Cut heavy weight paper clips in half. Dip them into water resistant paint such as a PVC plastisol. Dry them for 2-3 hours. Put clips on the Axid pulvule lengthwise, so that the pulvule will sink to the bottom of the vessel and will stay to the bottom throughout the dissolution test procedure. Sample three vessels at 5, 10, 20, 30, 40 and 50 minutes dissolution time. Leave an interval of three minutes between a vessel to allow for sample collection.

2) Sample 2-3 ml of solution at each time interval with the syringe through the tubing. Place the sample in the first set of test tubes. After sampling, return the excess liquid in the tubing with syringe air pressure to the vessel. From the 2-3 ml sample, place 1 ml in the second set of tubes by Pipetman. Dilute that 1 ml to 20 ml with a pipette. This dilution factor is found to be appropriate for Axid in order to achieve best spectrophotometer response with our equipment. Then measure the absorbance in a UV spectrophotometer. When returning the remaining solution from the original 2-3 ml sample to the vessel, add 1 ml of previously prepared dissolution medium to the vessel to account for the sample used for absorbance reading.

3. After the dissolution procedure

1) Switch on the UV spectrophotometer. Wait for half an hour to warm it up. Press safe mode 4 times till we get C on the digital display. Press Run. Then wait until we get 0 in the place of C. Then press 314 and goto λ key.

2) Put Parafilm on the top of the tubes which have diluted samples. Invert the tube and shake it a little to mix the diluted sample.

3) Put freshly prepared dissolution medium in the cuvette for blank reading. Put sample in another. Put both the cuvettes in the frame. Put the frame in the spectrophotometer. Read the digital display for the absorbance.

4) From the reference standard curve for Nizatidine, calculate concentration for the absorbance values.

5) Calculate the concentration in 900 ml dissolution medium considering dilution factor of 20 which is described above.

6) Plot the % drug dissolved versus time (minutes) for the pulvules.

This is how we developed the procedure for collecting samples for dissolution: The problem to be solved was, what sampling device and what filter was best to take samples from the dissolution vessel. A standard solution was prepared with Nizatidine USP reference standard of concentration of 0.01 mg/ml (absorbance of 0.47) for these studies. The filtering materials chosen for comparison included wet glass wool, wet cotton, dry glass wool, dry cotton, and a Millipore 0.45 μ syringe filter. In the experiments, roughly 1 cc of cotton or glass wool was put into the tube for filtering whereas the Millipore filter was attached at the end of the tube. For wetting the cotton and glass wool, a 1 cc ball of chosen filter material was dipped in water and then squeezed to remove excess water before inserting it into the sampling tube. Table 2 lists the readings obtained and their mean and standard deviation values for experiments with cotton and glass wool. Similar experiments were conducted using a syringe and a 0.45 μ Millipore filter for each vessel. Those readings were compared with solutions sampled using a syringe and cotton and a syringe and glass wool. The readings obtained with wet cotton were closest to those for the standard solution and the cotton was more convenient and cheaper to use. Therefore, wet cotton was the filter of choice for the experiments.

Table 2. Comparison of the dry cotton, the dry glass wool, the wet cotton, the wet glass wool, for developing the sampling procedure

	Absorbance			
	Glass Wool		Cotton	
Expt. no.	Dry	Wet	Dry	Wet
1	0.464	0.458	0.463	0.469
2	0.466	0.463	0.475	0.475
3	0.463	0.463	0.473	0.473
4	0.463	0.463	0.472	0.471
5	0.463	0.463	0.471	0.469
Average	0.464	0.462	0.471	0.471
Std. Dev.	0.001	0.002	0.005	0.003

The dilution factor for spectrophotometer readings was determined by trial and error method, until the absorbance readings were within the range of the spectrophotometer.

C. Water Vapor Transmission Rate (WVTR) of Package

The three blister package materials were formed into blisters containing molecular sieve (desiccant) and sealed at the Packaging Laboratory at Lilly. These were evaluated for water vapor transmission rate at the following conditions: 18°C/89% RH; 28°C/89% RH; and 38°C/89% RH. Empty blister packs were used as controls. The individual packages were weighed and stored in a constant temperature and humidity bucket maintained at the above mentioned combinations of temperature and humidity. The packages were weighed at specific time intervals until a constant rate of moisture gain was obtained.

Average net weight gain was calculated by subtracting the weight gain of empty blisters from the weight gain of blisters containing desiccants. The moisture permeation was calculated. The net weight gain in g was plotted as a function of elapsed time (days). The slope of the straight line portion of the graph was the rate of water vapor transmission for the package. By using that, the permeability constant for the package was determined.

Chapter 5

RESULTS AND DISCUSSION

When an unpackaged product is exposed to the environment (in this case, buckets), it reaches equilibrium with the temperature and relative humidity in the buckets after a certain time interval. The relationship between the moisture content of the product and the relative humidity can be represented by the moisture equilibrium isotherm curve. As the relative humidity increases, the equilibrium moisture content increases. The higher the difference between the relative humidities of the product and the bucket, the larger the driving force, and more moisture enters the product.

In this study, we initially exposed the product to seven different humidities at three different temperatures. These initial experiments uncovered a need to add two more humidity points. Experiments were then repeated so as to have data at all nine humidities and three temperatures (see the following sections).

The time required to reach equilibrium humidity in the buckets after they were prepared was determined by taking periodic humidity readings for 48 hours after the buckets were freshly prepared. These readings are tabulated in Table 3 and plotted in Figure 1. As seen from Figure 1, the humidity reaches its final value within one hour.

Table 3. Determining time for reaching equilibrium moisture content

	Time (hrs:min)										
	1:00	2:00	2:35	3:45	4:30	6:50	12:00	16:50	48:00		
Bucket No.	Relative Humidity (%)									Average	Std. Dev.
1	10.8	10.8	10.6	10.6	10.6	10.4	10.6	10.6	10.3	10.5889	0.1616
2	21.3	21.3	21.2	21.3	21.1	21	21.2	21.2	20.8	21.1556	0.1667
3	32.8	32.8	32.5	33	32.5	32.5	32.7	32.8	32.3	32.6556	0.2186
4	42.5	43.3	42.8	43.5	42.8	42.5	43.3	43.3	42.8	42.9778	0.3768
5	51.5	51.8	51.5	52	51.8	51.3	52.5	52.5	51.8	51.8556	0.4216
6	74.7	75.2	74.7	75.2	75.2	74	75.7	75.2	75.2	75.0111	0.4833
7	87.8	88.8	89.1	90.3	89.1	89.3	89.6	89.6	88.8	89.1556	0.6912

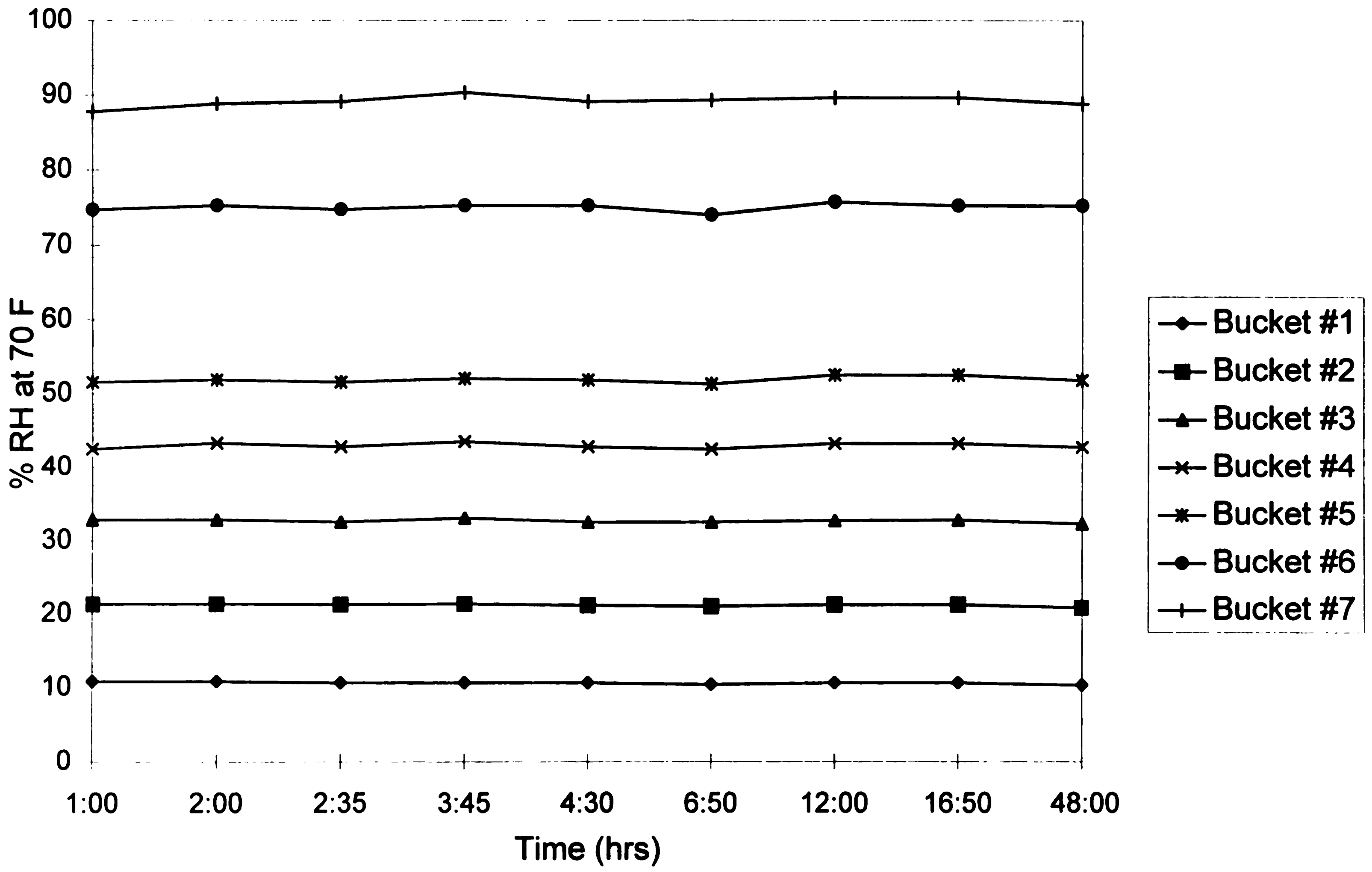

Figure 1. Equilibrium time for conditioning buckets

The temperature readings taken over time are tabulated in Table 4 for the buckets kept in the 38°C storage chamber and the corresponding humidity readings are given in Table 5. These readings were taken to verify the stability of temperature and humidity values over long periods of time, as would be required in the actual experiments with the drug product. Salt solutions used for the experiment and their actual relative humidities at 18°C, 28°C, and 38°C are given in Table 1.

Table 4. Bucket temperatures over time in the 38°C storage chamber

Relative Humidity (%RH)	Bucket Temperatures (°C)				
	3/22/94	4/1/94	4/11/94	4/14/94	4/18/94
14.20	37.8	37.8	37.8	37.8	37.8
23.60	37.8	37.8	37.8	37.8	37.8
35.25	<------- Reading could not be taken -------->				
44.50	37.8	37.8	37.8	37.8	37.8
53.75	37.8	37.8	37.8	37.8	37.8
75.70	35.6	36.7	36.7	35.6	36.7
89.80	37.8	37.8	37.8	37.8	37.8

Table 5. Relative Humidity at 38°C over time

Relative Humidity (%RH)	Relative Humidity (% RH) Readings at 38°C									
	3/22/94	4/1/94	4/11/94	4/14/94	4/18/94	4/28/94	5/2/94	5/6/94	5/10/94	5/14/94
14.20	12.40	12.20	12.40	12.40	12.40	12.60	12.60	12.60	12.60	12.20
23.60	22.60	22.20	22.40	22.80	22.20	22.40	22.40	22.40	22.20	22.40*
35.25	32.50	31.75	32.00	32.25	31.50	32.00	32.00	31.50	31.75	30.75
44.50	43.00	42.50	42.75	43.50	42.75	43.00	43.00	43.25	42.75	41.75
53.75	49.00	48.00	48.25	49.00	48.00	49.00	49.00	49.0	48.25	47.00
75.70	74.95	74.45	74.95	75.70	74.70	75.45	75.70	75.7	75.20	73.70
89.80	86.80	85.30	86.30	89.30	85.80	87.80	88.05	87.8	86.05	83.05

1. Determination of Initial Moisture Content:

To determine the isotherms, we had to develop the technique for determining initial moisture content. Lilly uses the Karl Fisher method for initial moisture content, but it does not work very well for gelatin capsules, so we developed an oven dry method for the initial moisture content. A reliable, reproducible moisture content can be obtained by drying the capsule, shell, or powder in an oven for 1 hour at 85°C. This was verified with comparative determinations with Lilly, and with Karl Fisher method at the School of Packaging. In a demonstration of Brinkmann apparatus at the School of Packaging, comparable results were obtained, but this data is not available. Table 6 shows the results of the trials run at the School of Packaging. The comparison was made to find the best technique for determining moisture content. This oven-dry method provides moisture content for powder, for capsule shell, and for capsule shell with powder in it. In the Karl Fisher method, 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 or visual 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. We believe that the oven method and the Brinkman method (using homogenizer) release a little more water than the Karl Fisher method draws out of the product.

For packaging purposes, we need moisture content of the whole product entity, i.e. capsule with powder in it. In order to understand the packaging mechanism in detail, we

Table 6.. Initial Moisture Content of Axid Pulvules

	% Initial moisture content (g water/100 g dry product)													
	Oven Dry Method										Karl fischer Method			
Temp, °C	100	100	87	85	83	85	85	85	85	85	5.19 ###	5.4 ###	4.88 ###	5.18 ###
Vacuum used	Yes	Yes	Yes	No	No	No	No	No	No	No	-	-	-	-
Time, hrs	12	1	1	1	1	2	4	14	4	13.5	-	-	-	-
Unopened (% IMC)	*	*	*	3.55 ##	-	-	-	-	-	-	1.32@	-	-	2.8 (8.12) @@
Unopened pulled apart (% IMC)	-	-	-	5.91	5.8	6.62	-	-	-	-	-	-	-	-
Unopened pulled apart and emptied (% IMC)	-	-	-	-	6.3	6.75	6.78	6.71	6.83	6.89	-	-	-	-
Empty shells (% IMC)	**	**	#	13.45	12.6	14.56	-	-	-	-	5.03@	-	10.66	-
Empty shells pulled apart (%IMC)	-	-	-	-	-	15.07	14.73	14.2	14.8	14.6	-	-	-	-
Axid Powder (% IMC)	***	***	#	4.96	4.9	5.41	5.37	5.33	5.18	5.47	4.55	5.17	-	-
Axid Powder (% IMC)	-	-	-	-	-	-	-	5.32	-	-	4.64	-	-	-
Axid Powder (% IMC)	-	-	-	-	-	-	-	-	-	-	4.55	-	-	-
Axid Powder (% IMC)	-	-	-	-	-	-	-	-	-	-	4.71	-	-	-

* Unopened pulvules pulled apart on their own because of vacuum and high temperature.

** Empty shells turned dark colored because of high temperature

*** Powder turned black because of high temperature in the oven (100°C).

Empty shells or Axid Powder did not change color because of high temperature.

Unopened pulvules did not open due to high temperature or vacuum

The titer of the Karl Fischer reagent (mg/ml)

@ In these cases unopened or empty pulvules were floating on the top of the solution.

@@ The first reading was taken immediately after adding the pulvules and second reading was taken after 2 hrs.

measured moisture content of the whole capsule, empty shell, and Axid™ powder. Procedural techniques were developed to achieve this goal. Improvements in capsule handling methods have reduced the standard deviation, and the work was done continuously to minimize the standard deviation. At first, tweezers were used to open the pulvules which resulted in some spilling of the contents, so surgical gloves were used then instead for opening the pulvules. This resulted in lower standard deviation for the opened pulvules as seen from Table 7.

Table 7. Initial moisture content of Axid pulvules on dry weight basis

Sample Number	% Moisture Content (g water/100 g dry product)			
	Opened with surgical gloves		Opened with tweezers	
	Opened	Unopened	Opened	Unopened
1	6.45	5.02	7.11	4.64
2	6.50	4.53	5.71	4.76
3	6.58	4.92	6.30	4.73
4	6.86	4.53		
5	6.53	4.92		
Average	6.59	4.78	6.37	4.71
Std. Dev.	0.16	0.23	0.70	0.06

The initial moisture content (IMC) of the product is given in Table 8, The IMC of each sample was calculated with the following formula.

$$IMC = \frac{W_i - W_f}{W_f} \times 100$$

where IMC = Initial Moisture Content of product, g H_2O/100 g dry product

W_i = Initial weight of product sample, g

W_f = Final weight of product sample, g

Table 8. Initial moisture content (IMC) of Axid capsules on dry weight basis

Expt. No.	% IMC (g water/100 g dry product)		
	Unopened Pulvules	Axid Powder	Axid Empty Shells
1	6.69	4.19	13.89
2	6.72	3.56	13.90
3	3.32	5.07	13.43
Average	5.58	4.27	13.74

The average IMC is used in all further calculations. The humidity buckets were kept in constant temperature chambers at three temperatures of 18°C, 28°C, and 38°C in order to cover the entire temperature range the product is likely to encounter. Once the buckets were kept at a particular temperature setting, equilibrium was attained after one hour. Temperature and humidity readings were taken periodically to confirm the equilibrium.

2. Determination of Moisture Isotherm

The equilibrium moisture isotherm was determined by a gravimetric method. The difference in the moisture content of the product and the external environment acts as a driving force, and the product absorbs moisture till the moisture content reaches equilibrium with the moisture content of the outside environment. The equilibrium moisture content (EMC) is expressed on a dry product weight basis. The initial moisture content was measured by the oven dry method. The equilibrium moisture content was determined by exposing pulvules to seven different relative humidities at three different temperatures. The relative humidities used ranged from 11 to 90% relative humidity.

The equilibrium moisture content of the samples was calculated with the following formula.

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

where,

P_f = Final Product Weight, g

P_i = Initial Product Weight, g

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

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

To establish the time period in which the equilibrium was reached, %EMC was calculated every 3-5 days for a 25-30 day period at 38°C for unopened pulvules, empty gelatin shells, and Axid™ powder. These readings are tabulated in Table 9 for unopened pulvules, in Table 10 for empty gelatin shells, and in Table 11 for Axid™ powder. The corresponding plots are depicted in Figure 2 for unopened pulvules, in Figure 3 for empty gelatin shells and in Figure 4 for Axid™ powder. As seen from the figures, the % EMC was constant for the entire period after 3 days. Therefore, it was decided to take two readings for each temperature-humidity combination: one at 3 days and another at 6 days to confirm equilibrium.

Table 9. Variation of %EMC with time for seven different humidities for unopened pulvules at 38°C

Time -> (days)	3.83	6.83	9.9	12.8	15.8	18.9	23.0	25.9	28.4	31.5
AVG % RH	% EMC (g water/100 g dry product)									
12.53	4.13	4.00	3.98	3.96	3.91	3.93	3.92	3.91	3.88	3.88
22.33	5.08	5.23	5.26	5.29	5.25	5.23	5.27	5.21	5.16	5.11
31.58	6.10	6.02	6.03	6.03	5.99	5.97	6.01	6.02	5.95	5.93
42.71	6.86	6.86	6.88	6.87	6.82	6.88	6.91	6.88	6.86	6.79
48.38	7.28	7.27	7.32	7.32	7.24	7.25	7.33	7.30	7.26	7.24
75.15	9.79	10.00	10.08	10.02	9.96	10.09	10.13	9.95	9.93	9.94
86.43	13.20	13.02	13.10	13.05	12.95	13.21	13.65	12.88	11.29	13.43

Table 10. Variation of %EMC with time for seven different humidities for empty gelatin shells at 38°C

Time -> (days)	3	7	10	13	17	20	22.5	25.6
AVG RH	% EMC (g water/100 g dry product)							
12.53	7.54	9.62	7.38	7.38	7.20	7.22	7.16	7.13
22.33	10.54	10.43	10.26	10.32	10.30	10.13	9.97	9.73
31.58	12.21	12.21	12.12	11.99	11.94	11.92	11.72	11.59
42.71	13.87	13.84	13.64	13.73	13.78	13.55	13.44	13.35
48.38	14.32	14.09	14.05	14.05	14.21	14.07	13.91	13.84
75.15	19.41	19.41	18.50	19.21	19.48	18.57	19.12	18.95
86.43	29.04	28.21	27.56	29.35	30.35	27.45	22.40	29.74

Table 11. Variation of %EMC with time for seven different humidities for Axid Powder at 38°C

Time -> (days)	3	7	10	13	17	20	22.5	25.6
AVG % RH	% EMC (g water/100 g dry product)							
12.53	3.19	3.23	3.18	3.19	3.21	3.15	3.15	3.10
22.33	4.26	4.61	4.21	4.23	4.25	4.20	4.17	4.12
31.58	4.75	4.80	4.73	4.75	4.79	4.75	4.69	4.69
42.71	5.40	5.34	5.28	5.36	5.37	5.31	5.28	5.28
48.38	5.73	5.67	5.64	5.73	5.80	5.81	5.76	5.75
75.15	8.09	8.06	7.77	8.04	8.03	8.56	8.49	8.46
86.43	9.94	9.91	9.63	10.13	10.24	9.73	8.85	10.17

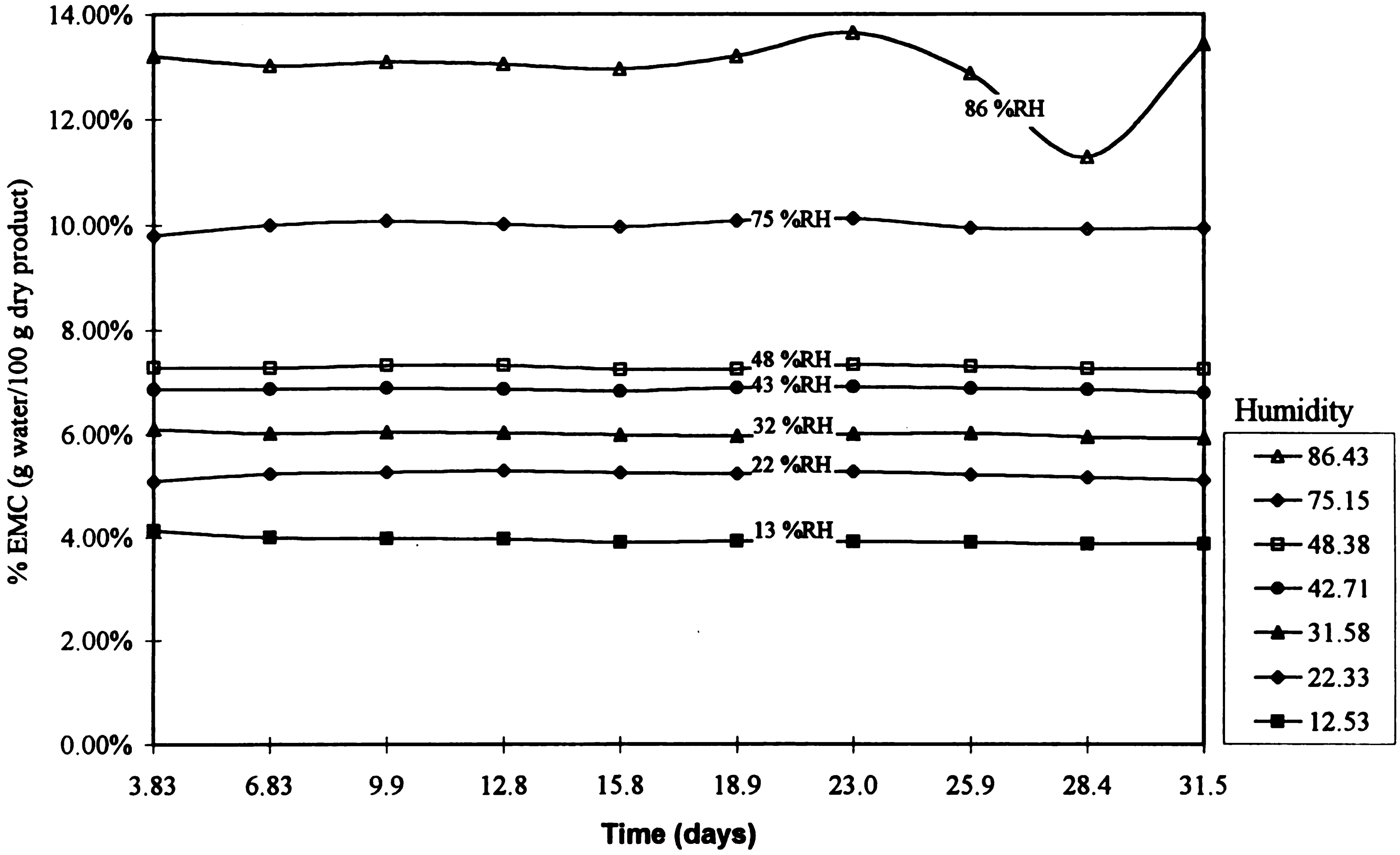

Figure 2. Variation of %EMC with time for seven different humidities for unopened pulvules at 38°C

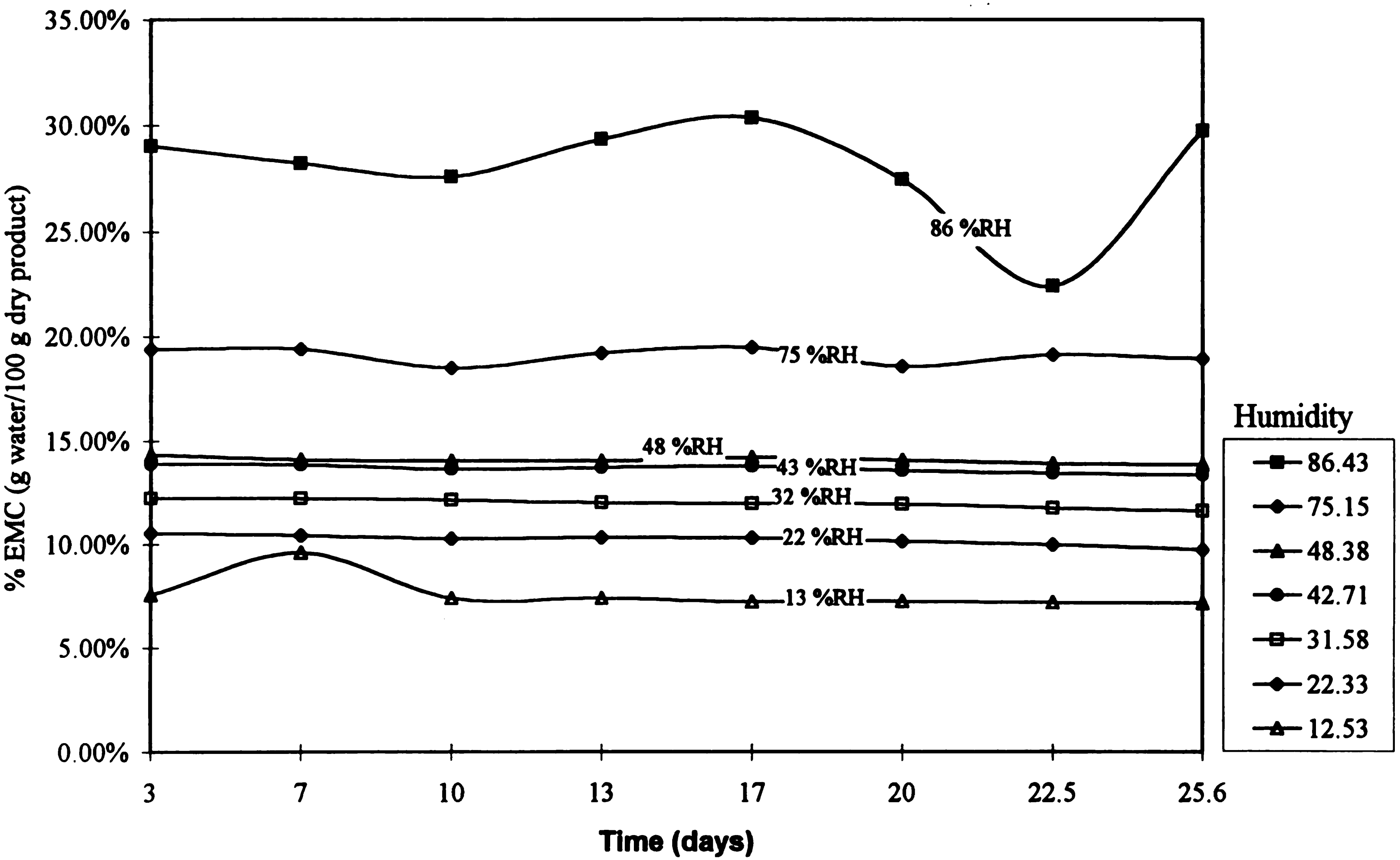

Figure 3. Variation of %EMC with time for seven different humidities for empty gelatin shells at 38°C

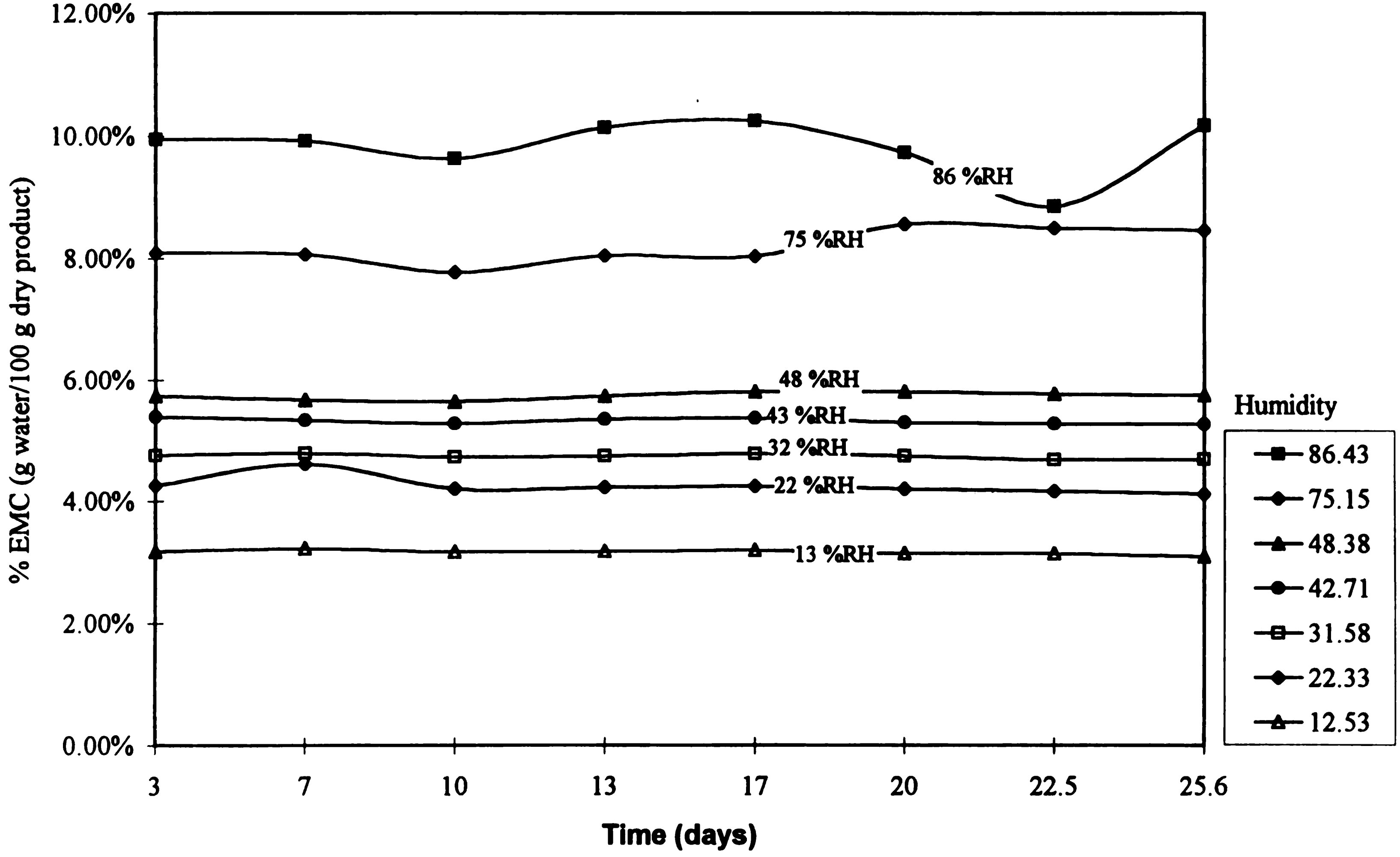

Figure 4. Variation of %EMC with time for seven different humidities for Axid™ powder at 38°C

Moisture Isotherm at 28°C:

The equilibrium isotherm on a dry basis was determined at 8, 10, and 17 days as seen from Table 12 for unopened pulvules, Table 13 for Axid™ powder, and Table 14 for empty gelatin shells. The values are also plotted in Figure 5, Figure 6, and Figure 7. We can see from the figures that the equilibrium moisture content was constant over the period and that the equilibrium was reached at or before 8 days.

Table 12. Equilibrium moisture content for unopened pulvules at seven humidities at 28°C

Time (days) ->	8	10	17
AVG % RH	% EMC (g water/100 g dry product)		
12.10	4.10	4.06	4.00
22.00	5.49	5.47	5.39
32.50	6.48	6.45	6.42
43.75	7.18	7.18	7.16
51.50	7.89	7.88	7.85
67.00	-	-	-
75.20	10.78	10.73	10.65
79.20	-	-	-
91.00	16.39	16.34	16.88

The experiments at 28°C at 8, 10, and 17 days and those at 38°C at time points from 3 to 30 days (reported earlier in Tables 9-11) were carried out simultaneously. The purpose of these experiments was to determine the time to reach equilibrium as the first step in developing a new procedure for determination of equilibrium moisture content of Axid™ pulvules. From these experiments at 28°C and 38°C, it was clear that the equilibrium was reached after 3 days. Thus, it was decided to take the reading at 3 days and a confirmatory reading at 6 days for all experiments from this point forward and to use a period of 6 days for the dissolution experiments as well.

Table 13. Equilibrium moisture content for Axid™ powder at seven humidities at 28°C

Time (days) ->	8	10	17
AVG % RH	% EMC (g water/100 g dry product)		
12.10	3.27	3.15	3.06
22.00	4.30	4.25	4.16
32.50	4.99	4.95	4.88
43.75	5.84	5.75	5.70
51.50	6.22	6.19	6.14
67.00	-	-	-
75.20	8.61	8.54	8.42
79.20	-	-	-
91.00	12.03	11.97	12.28

Table 14. Equilibrium moisture content for empty gelatin shells at seven humidities at 28°C

Time (days) ->	8	10	17
AVG % RH	% EMC (g water/100 g dry product)		
12.10	7.71	7.60	7.00
22.00	11.20	10.89	10.56
32.50	13.19	13.01	12.81
43.75	14.38	13.98	13.93
51.50	15.35	15.17	14.94
67.00	-	-	-
75.20	20.51	20.42	20.00
79.20	-	-	-
91.00	36.86	36.69	38.16

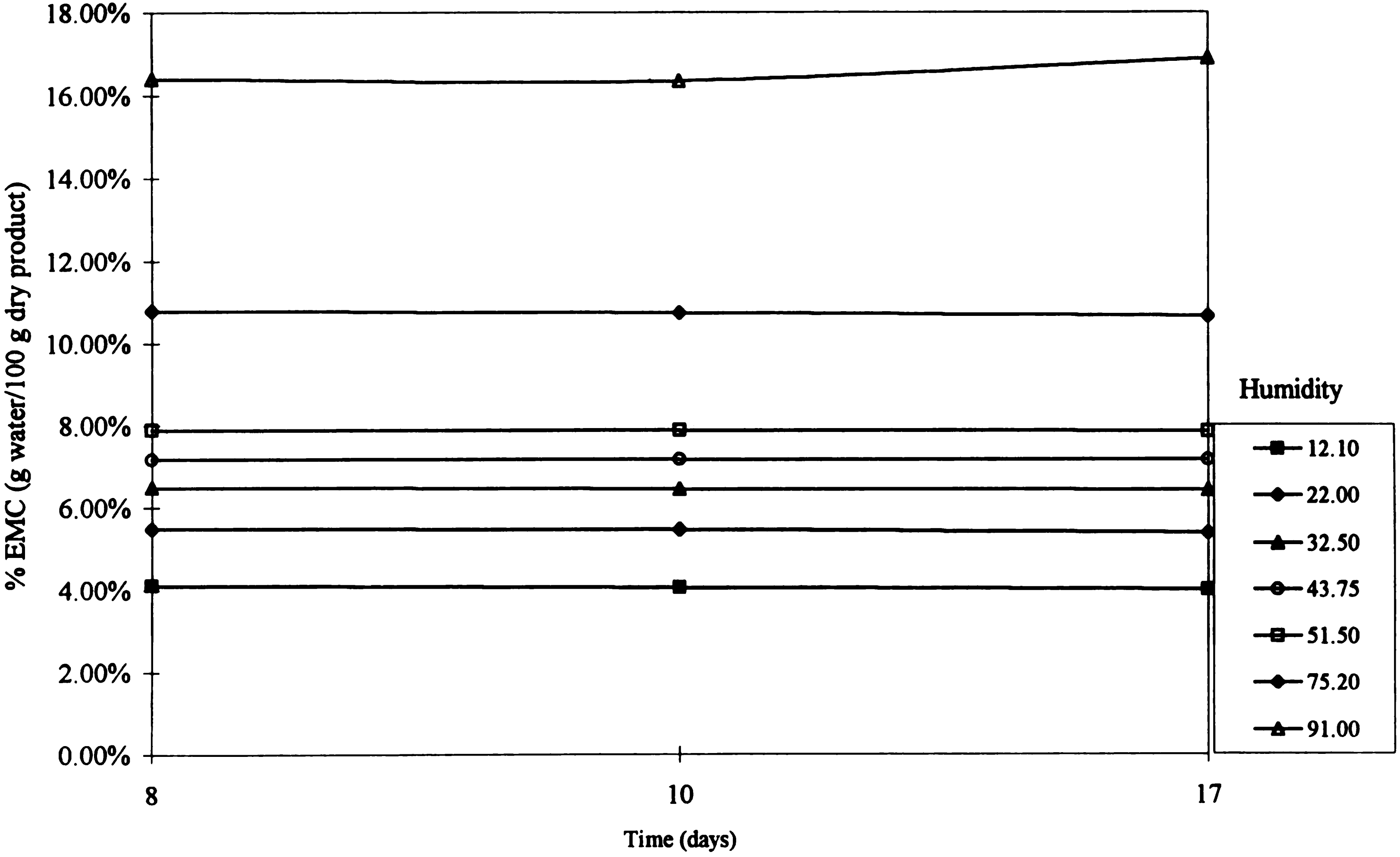

Figure 5. Variation of EMC with time for unopened pulvules at seven humidities at 28°C

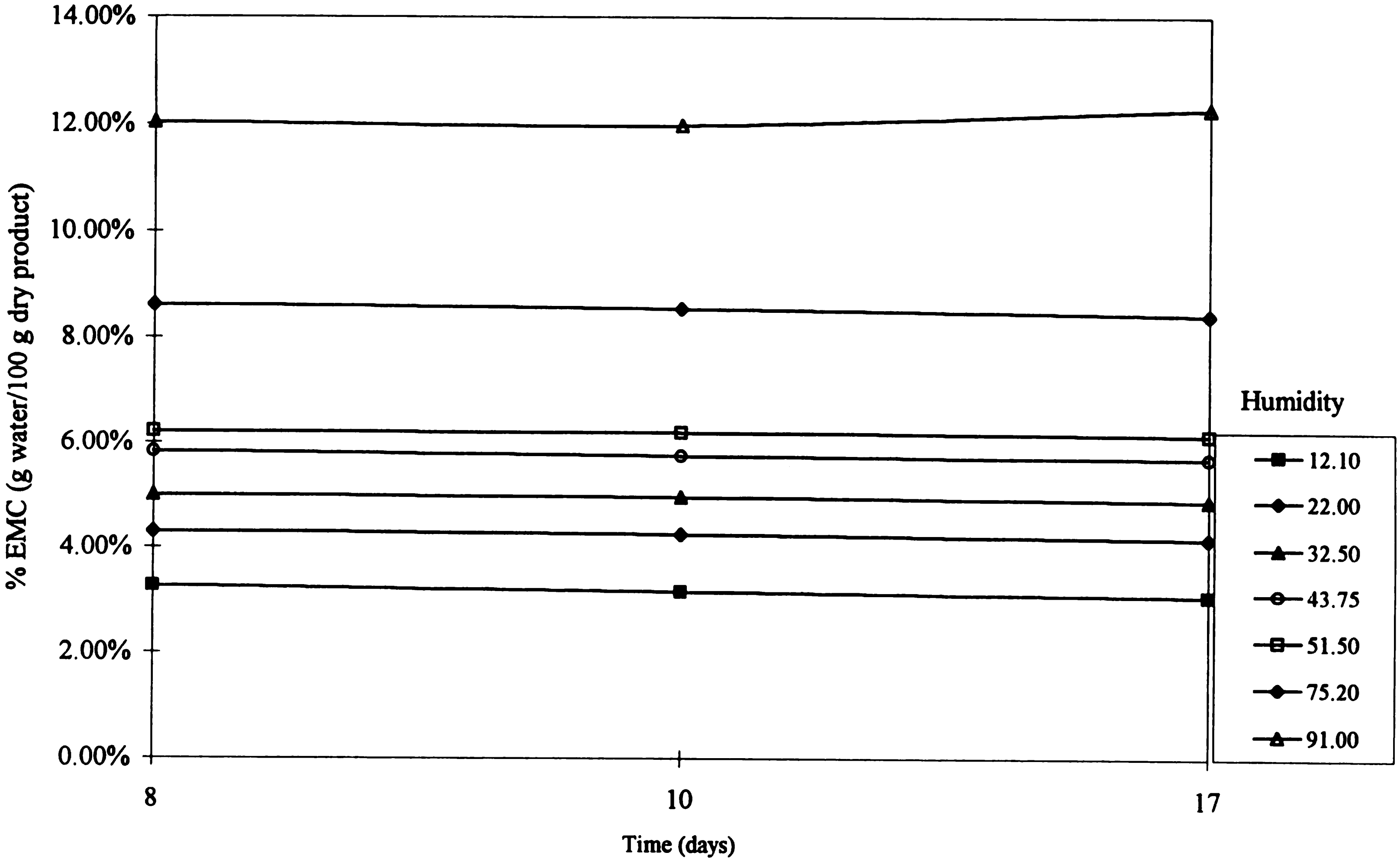

Figure 6. Variation of EMC with time for Axid^{TM} powder at seven humidities at 28°C

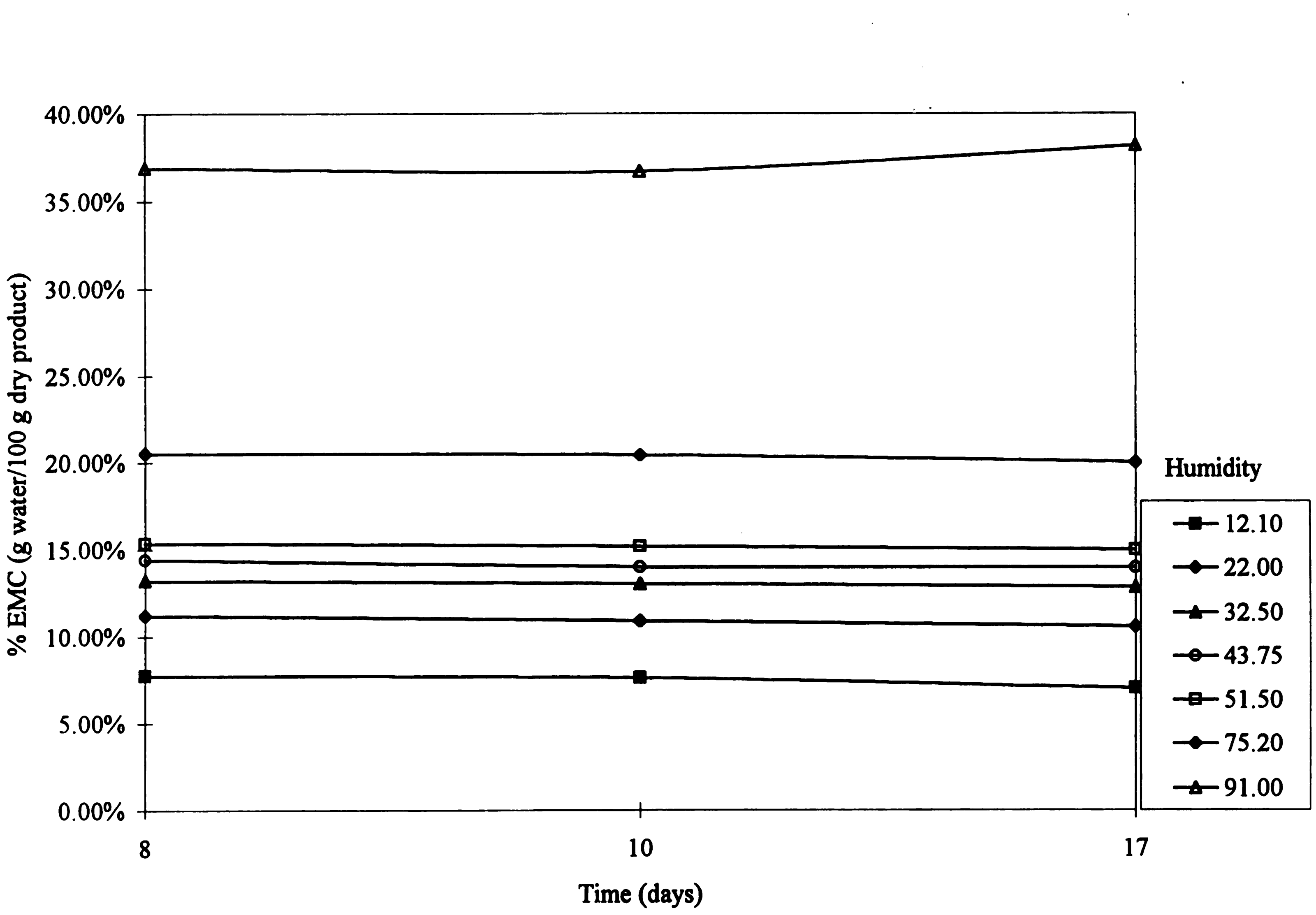

Figure 7. Variation of EMC with time for empty gelatin shells at seven humidities at 28°C

Since this research was undertaken to develop a new procedure for studying the effect of humidity and temperature on shelf-life, one set of pulvules (at 28°C) was monitored for long-term study (90 days). When the dissolution was conducted on the 90 day samples (see Table 21 in this chapter), insolublization was observed for the samples kept at 75.20 RH. Therefore, two humidity points were added - one on each side of 75.20 %RH point - to study this phenomenon in greater detail. Both short-term and long-term studies were planned and this research was focused on the short-term study, whereas the long-term study was planned as a separate project. The isotherm experiments were repeated at 28°C to gather data for all nine humidity values at 6 days, which would be required for the dissolution experiments. From Table 15, we can see that equilibrium is reached after 6 days and is stable even after 90 days.

The values from Table 15 are plotted in Figure 8. From Figure 8, we can see that as the relative humidity increases, equilibrium moisture content increases. We can also see the different behavior pattern for each component separately. It appears that the unopened pulvules represent an additive response of empty shells and Axid™ powder. As the time passes, particularly in the high humidity conditions the pulvules become sticky. They are difficult to handle. Gelatin of the capsules partially dissolves in the petri dish. At the highest humidity conditions, microbial growth was observed in empty shell and unopened pulvule dishes, whereas the powder turned pale yellow at the two highest humidities.

Table 15. Equilibrium moisture content at nine humidities for three product forms of Axid™ pulvules at 28°C

	% EMC (g water/100 g dry product)					
	Unopened pulvules		Axid™ powder		Empty gelatin shells	
AVG % RH	6 days	90 days	6 days	90 days	6 days	90 days
12.10	4.58	4.30	3.51	3.57	9.03	9.24
22.00	5.95	5.74	4.49	4.61	12.57	12.31
32.50	6.66	6.53	5.13	5.20	13.67	14.06
43.75	7.13	7.26	5.63	5.84	14.89	15.45
51.50	8.01	8.02	6.38	6.43	15.95	16.37
64.00	8.83	8.88	7.04	7.08	17.21	17.37
75.20	10.87	10.85	8.66	8.74	21.28	21.72
80.00	11.61	11.51	9.02	9.08	23.71	23.59
91.00	17.26	16.95	12.92	10.41	40.82	41.31

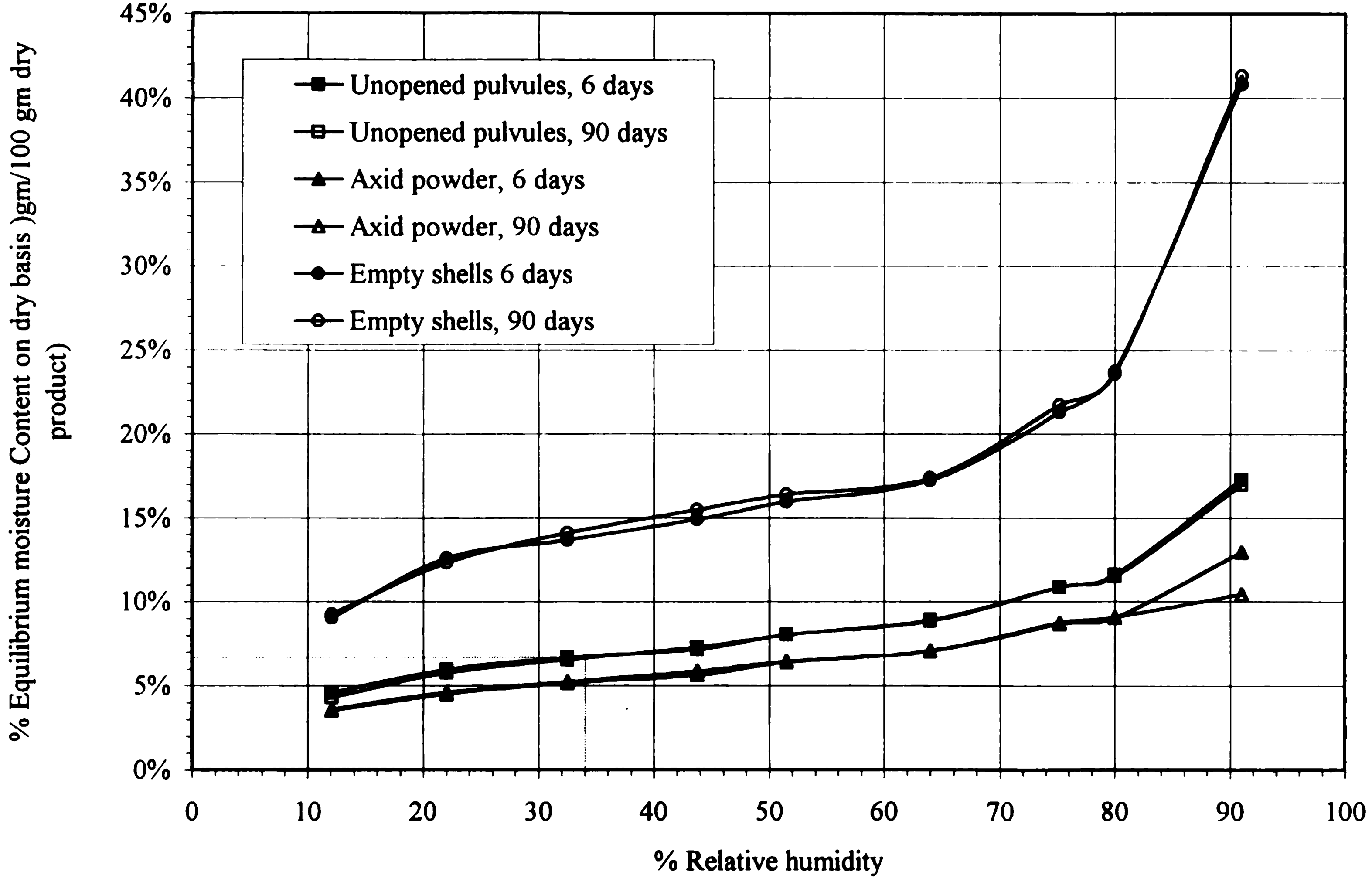

Figure 8. Equilibrium moisture content isotherm on dry weight basis at 28°C for three product forms of Axid™ pulvules at nine different humidities

Moisture Isotherm at 38°C:

It was decided from the previous moisture isotherm experiments to take readings at 3 and 6 day periods for determination of %EMC and to take the 6 day readings for dissolution experiments. As a result, experiments were repeated at 38°C to take readings at 3 and 6 days. Also, two humidity points were added on either side of 75.70 %RH to cover the entire range from 15 %RH to 90 %RH more uniformly. The %EMC values obtained from these experiments are tabulated in Table 16 for unopened pulvules, empty gelatin shells, and Axid™ powder. The data is also plotted in Figure 9 which shows that as the relative humidity increases the equilibrium moisture content increases. As the time passes, the pulvules, particularly in the high humidity conditions, become sticky and difficult to handle because the gelatin of the pulvules partially dissolves and sticks to the petri dish. As with 28°C, from Figure 9, we can see that unopened pulvules have an additive response of empty gelatin shells and Axid™ Powder.

Table 16. Equilibrium moisture content at nine humidities for three product forms of Axid™ pulvules at 38°C

	% EMC (g water/100 g dry product)					
	Unopened pulvules		Axid™ powder		Empty gelatin shells	
AVG % RH	3 days	6 days	3 days	6 days	3 days	6 days
14.20	4.32	4.21	3.34	3.20	8.19	7.78
23.60	5.55	5.47	4.31	4.23	11.11	10.70
35.25	6.35	6.31	4.87	4.82	12.94	12.76
44.50	6.92	6.92	5.35	5.30	13.97	13.64
53.75	7.60	7.54	5.85	5.80	14.47	14.35
63.25	8.36	8.31	6.54	6.57	16.01	15.75
75.70	10.20	10.23	7.88	7.76	19.30	17.64
80.20	11.21	11.15	8.69	8.93	23.28	22.60
89.80	13.93	14.26	10.27	10.44	30.27	31.33

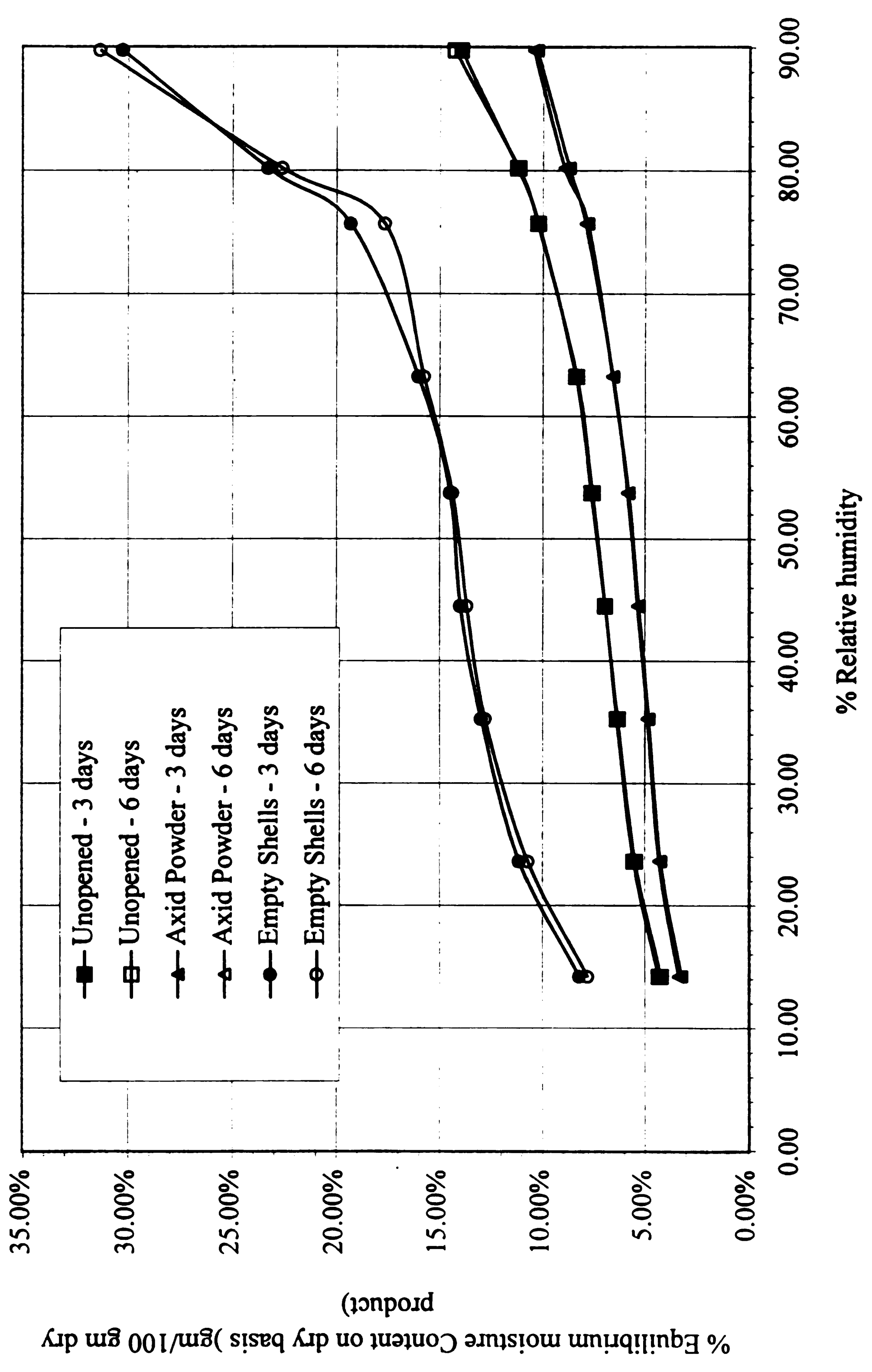

Figure 9. Equilibrium moisture content isotherm on dry weight basis at 38°C for three product forms of Axid$^{\text{TM}}$ pulvules at nine different humidities

Moisture Isotherm at 18°C:

Initially, equilibrium moisture content data was collected after 3 and 6 days at seven humidities as given in Table 17 for all three product forms. Once it was decided to add one humidity point on either side of 74.40 %RH point, the entire experiment was repeated at 28°C and nine humidity values. The data collected in this case is tabulated in Table 18. By comparing the EMC obtained at the common seven humidity values in these two tables, we can see that the experiment is very well reproducible. As a result, the average values of EMC for the seven common humidities were used in all calculations. These values are listed in Table 19 for all three product forms and are also plotted in Figure 10. From Figure 10, we can see that as the relative humidity increases, equilibrium moisture content increases.

Table 17. Equilibrium moisture content for three product forms of Axid™ pulvules at seven humidities at 18°C, after 3 and 6 days

	% EMC (g water/100 g dry product)					
	Unopened pulvules		Axid™ powder		Empty gelatin shells	
AVG %RH	3 days	6 days	3 days	6 days	3 days	6 days
16.10	5.50	5.38	4.04	4.02	11.25	11.10
22.50	6.20	6.15	4.76	4.72	13.04	13.01
36.75	6.83	6.81	5.23	5.23	14.06	13.94
45.75	7.15	7.22	5.57	5.65	14.52	14.58
55.00	7.94	8.21	6.43	6.54	15.51	15.96
67.00	-	-	-	-	-	-
74.40	10.69	11.15	8.73	8.48	21.84	21.72
79.20	-	-	-	-	-	-
92.80	13.47	16.35	11.27	12.76	34.71	39.61

Table 18. Equilibrium moisture content for three product forms of Axid™ pulvules at nine humidities at 18°C, after 3 and 6 days (repeated experiment)

	% EMC (g water/100 g dry product)					
	Unopened pulvules		Axid™ powder		Empty gelatin shells	
AVG %RH	3 days	6 days	3 days	6 days	3 days	6 days
16.10	5.62	5.54	4.22	4.16	11.98	11.78
22.50	6.27	6.31	4.76	4.78	13.14	13.14
36.75	6.83	6.82	5.27	5.26	14.15	14.18
45.75	7.20	7.50	5.63	5.69	14.83	14.71
55.00	8.26	8.42	6.61	6.66	16.13	16.49
67.00	9.69	9.78	7.71	7.70	18.72	18.97
74.40	11.31	11.32	8.85	8.87	22.42	22.20
79.20	11.74	12.28	9.23	9.45	24.02	24.86
92.80	18.32	19.32	13.82	14.49	47.23	46.16

Table 19. Average equilibrium moisture content for three product forms of Axid™ pulvules at nine humidities at 18°C after 3 and 6 days (combined data)

	% EMC (average) (g water/100 g dry product)					
	Unopened pulvules		Axid™ powder		Empty gelatin shells	
AVG %RH	3 days	6 days	3 days	6 days	3 days	6 days
16.10	5.56	5.46	4.13	4.09	11.62	11.44
22.50	6.23	6.23	4.76	4.75	13.09	13.08
36.75	6.83	6.82	5.25	5.24	14.10	14.06
45.75	7.17	7.36	5.60	5.67	14.68	14.65
55.00	8.10	8.32	6.52	6.60	15.82	16.23
67.00	9.69	9.78	7.71	7.70	18.72	18.97
74.40	11.00	11.23	8.79	8.67	22.13	21.96
79.20	11.74	12.28	9.23	9.45	24.02	24.86
92.80	15.89	17.84	12.55	13.62	40.97	42.89

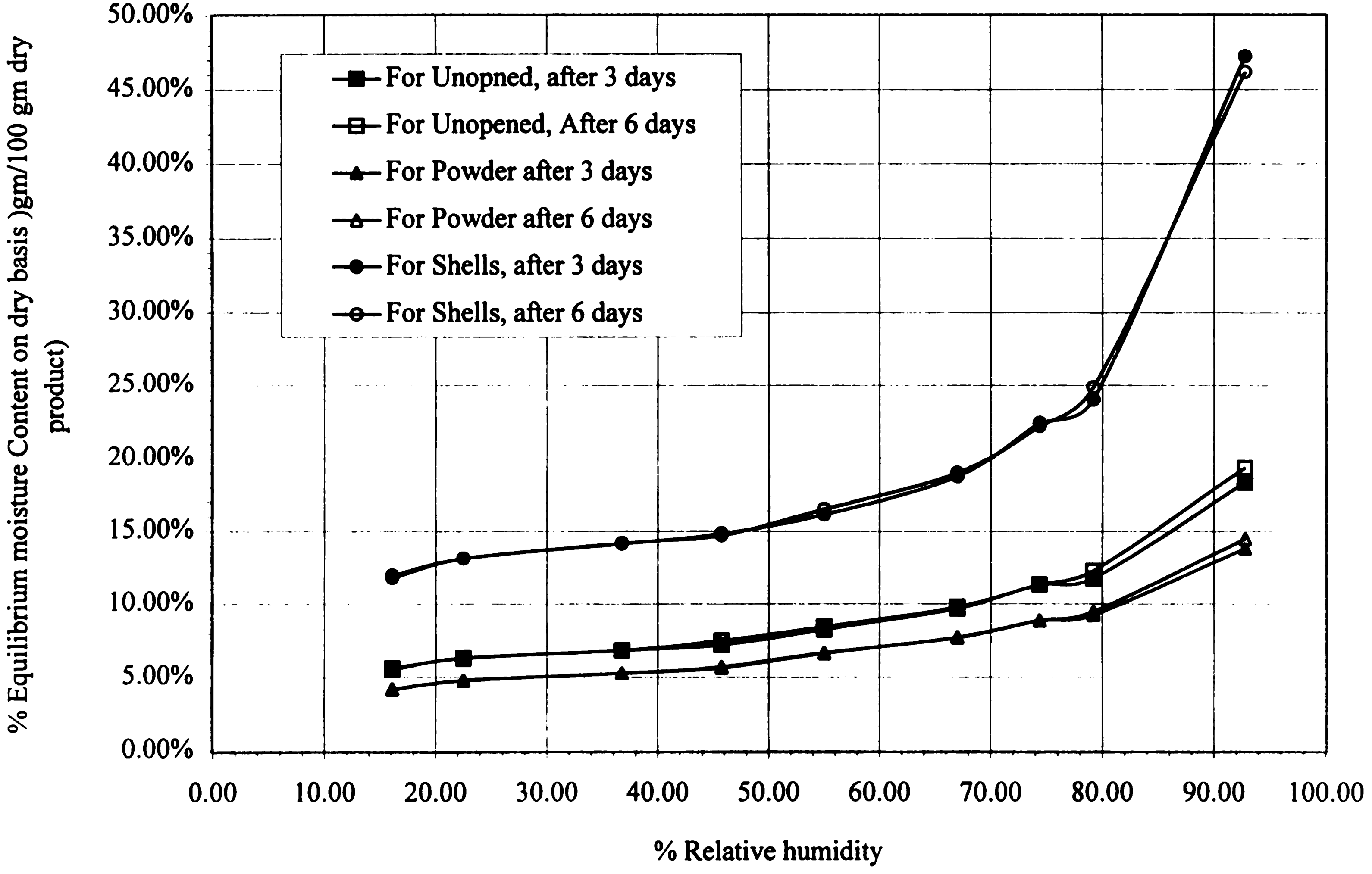

Figure 10. Average equilibrium moisture content isotherm for three product forms of Axid^{TM} pulvules at nine different humidities at 18°C after 3 and 6 days

3. Dissolution Profiles for Axid Pulvules at 18°C, 28°C, and 38°C

Calibration of the dissolution apparatus

The dissolution apparatus was calibrated with USP Prednisone Tablets RS (Dissolution Calibrator, Disintegrating). Prednisone 50 mg tablets were used from Lot K. This USP Dissolution Calibrator is provided for the Apparatus Suitability Test in the General Chapters <711> and <724> of U.S. Pharmacopoeia[32]. The quantity of Prednisone, dissolved at 30 mins, for each spindle in percent of the labeled amount was determined. The amount of Prednisone in solution in filtered portions of the Dissolution medium (suitably diluted with fresh Dissolution Medium) was measured at the wavelength of maximum absorbance at about 242 nm in comparison with a solution of known concentration of USP Prednisone Reference Standard. The apparatus is suitable if each of the individual calculated values for each apparatus at all indicated speeds is within the specified ranges. The profile obtained is tabulated in Table 20, and plotted in Figure 11. From Figure 11, we can see that about 60% of the Prednisone tablets dissolved in 45 minutes.

Table 20. Dissolution data for Prednisone

Time (min)	Drug dissolved, (%)		
	Vessel I	Vessel II	Vessel III
0	0	0	0
10	31	27	27
20	42	41	38
30	52	51	50
45	62	60	59

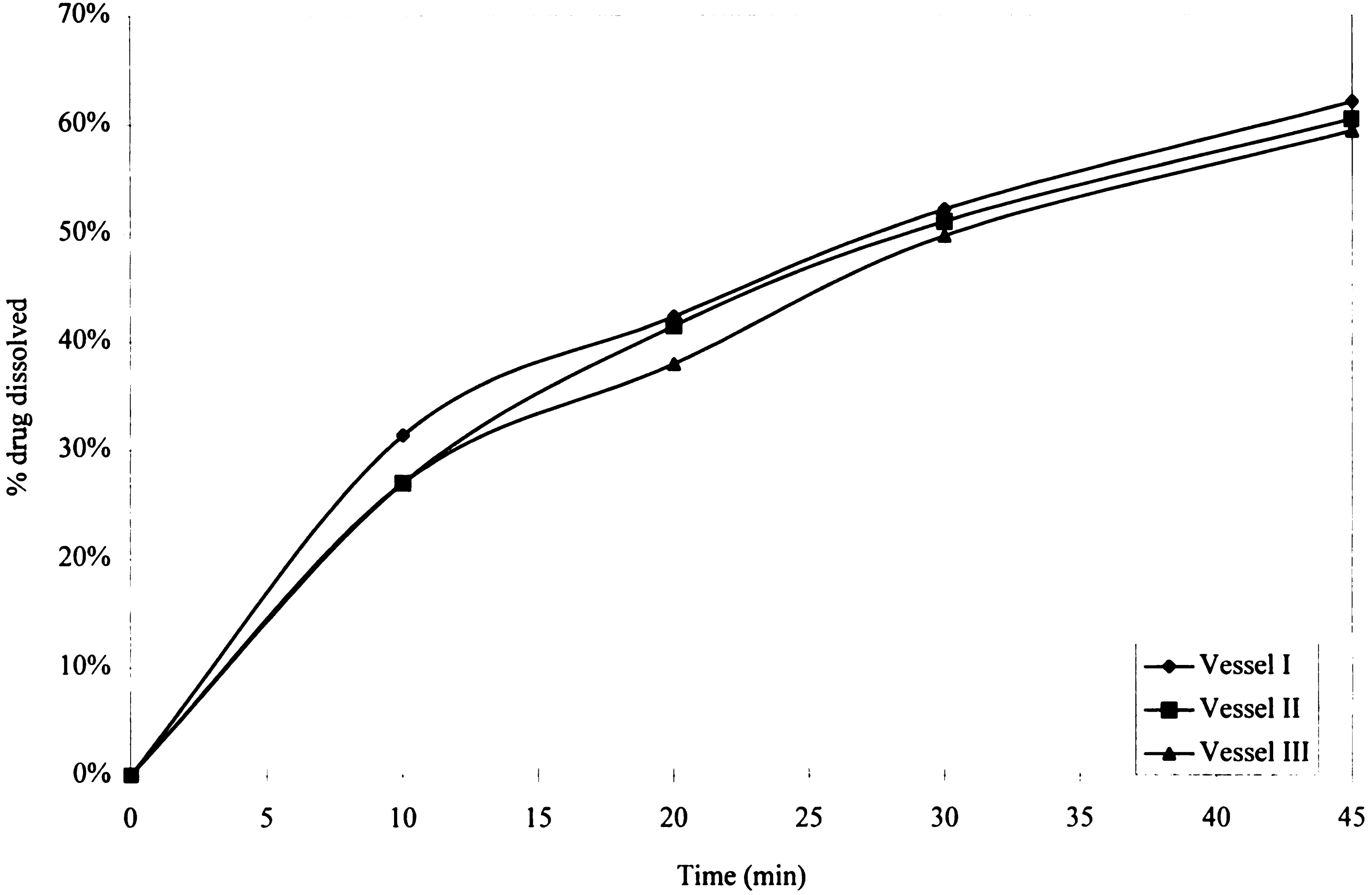

Figure 11. Dissolution profiles obtained for Prednisone using USP Dissolution Calibrator, (disintegrating type), 50 mg, Lot K

The concentration of the drug dissolved at each time point in a dissolution study was calculated from absorbance measurements. The spectrophotometer used for this purpose was calibrated using Prednisone. The calibration curve is depicted in Figure 12. The calibration curve for Nizatidine (Axid™), depicted in Figure 13, was obtained on the same spectrophotometer and matched with the reference standard curve from USP. This calibration curve was used to calculate concentration in all the dissolution experiments.

Dissolution study of Axid™ pulvules

The dissolution test is provided to determine compliance with dissolution requirements stated in the individual monograph for a tablet or a capsule dosage form. The dissolution test was conducted for Axid™ pulvules according to its USP monograph. Dissolution measurements were performed after storage at three temperatures 18°C, 28°C, and 38°C at nine different relative humidities for various time intervals from 6 to 90 days.

According to USP Vol. XXII Supplement Seven monograph for Nizatidine capsules, not less than 75% of the labeled amount of Nizatidine should be dissolved in water in 30 minutes in the dissolution test[30]. Experiments were carried out with 900 ml of water as the dissolution medium and 50 rpm speed for the stirrer. The amount of Nizatidine is determined from ultraviolet absorbance measurements at the wavelength of maximum absorbance, at about 314 nm, using a filtered portion of the solution under test. The solution is diluted with water and is compared with a standard solution having a known concentration of USP Nizatidine RS in the same medium.

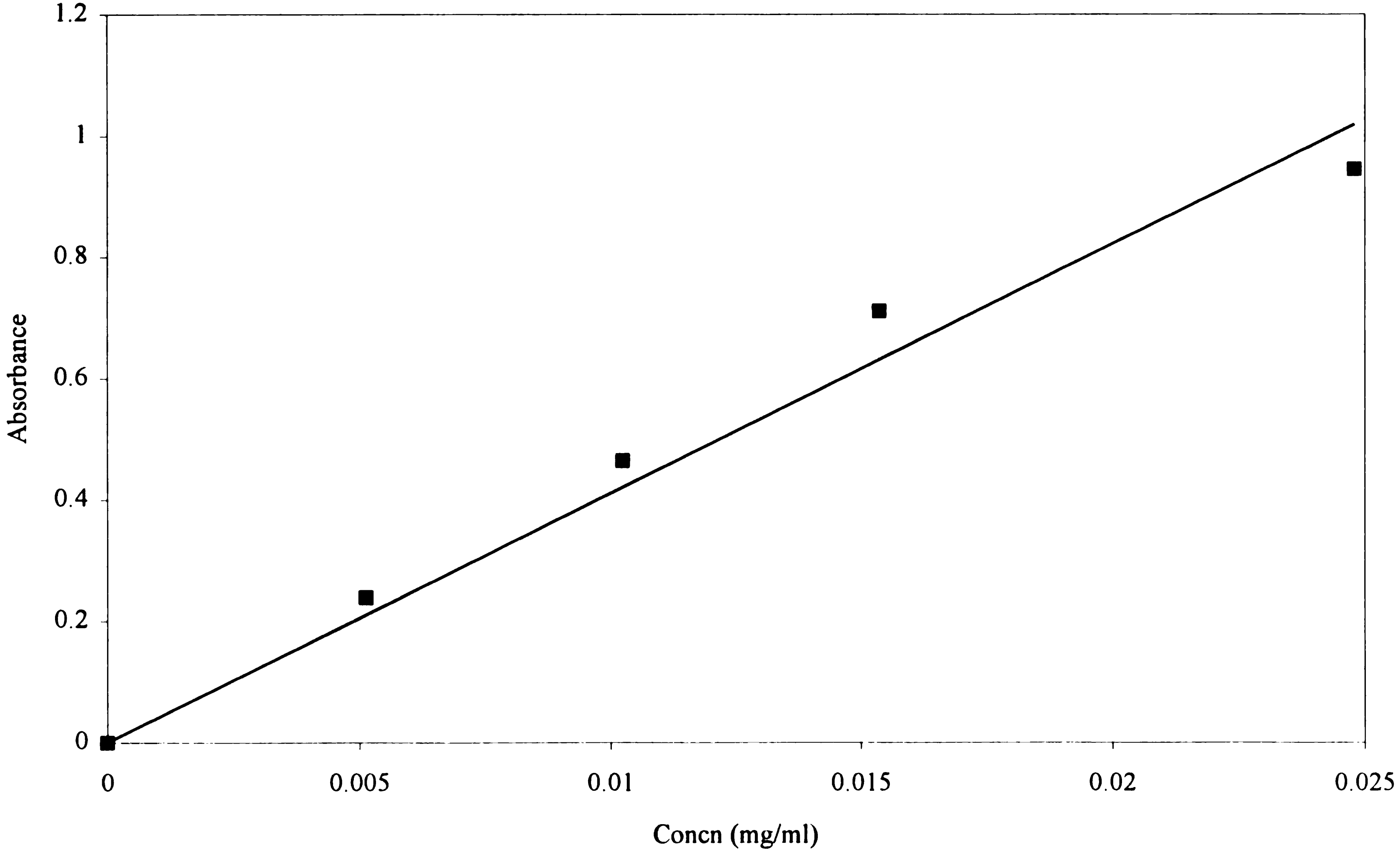

Figure 12. Calibration curve for the spectrophotometer using Prednisone

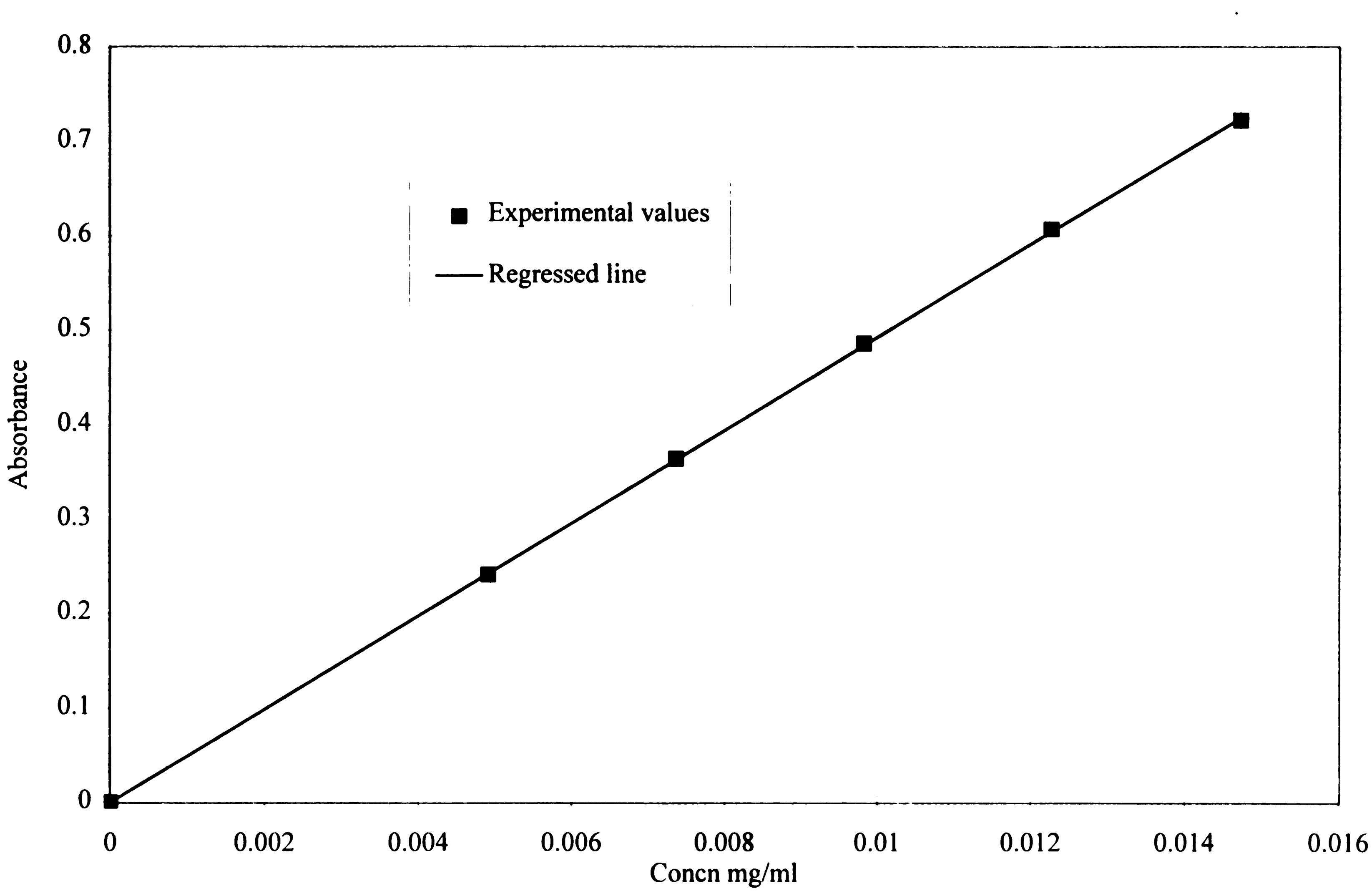

Figure 13. Calibration curve for nizatidine refernce standard after drying for 1 hr at 100°C

In order to study the dissolution mechanism in detail, we collected samples at 5, 10, 20, 30, 40, and 50 min time interval. Then the sample was diluted 20 fold (determined previously - see Chapter 3, section B.2, page 19), with distilled water for the spectrophotometer reading. From the absorbance, and from the USP Nizatidine Standard Solution graph, concentration of the drug in the sample in mg/ml was calculated. From this value, the amount of drug in 900 ml and subsequently, the % drug dissolved was calculated. One capsule was used per vessel and three vessels were used for each storage humidity and temperature combination. The tables in the following sections report data which is the mean and standard deviation of the readings from three vessels. The raw data for individual vessels is given in Appendix A.

For all dissolution studies, open-dish storage conditions were used. We measured the performance of the product which was not packaged. The goal of these dissolution studies was to establish product behavior as this information is not available in the open literature.

Drug dissolved at 28°C at seven different relative humidities after 90 days storage

The amount of drug dissolved with time at 28°C after 90 days storage at 7 different humidities is given in Table 21 and is plotted in Figure 14. From the table we can see that the amount of drug dissolved during the dissolution test increases with time in the vessel. The standard deviation is generally low, especially at higher time points with the exception of data at 75.20 %RH.

We saw a difference between the dissolution test of capsules exposed to 75.20 %RH and 28°C for 90 days and the dissolution tests of capsules exposed to lower

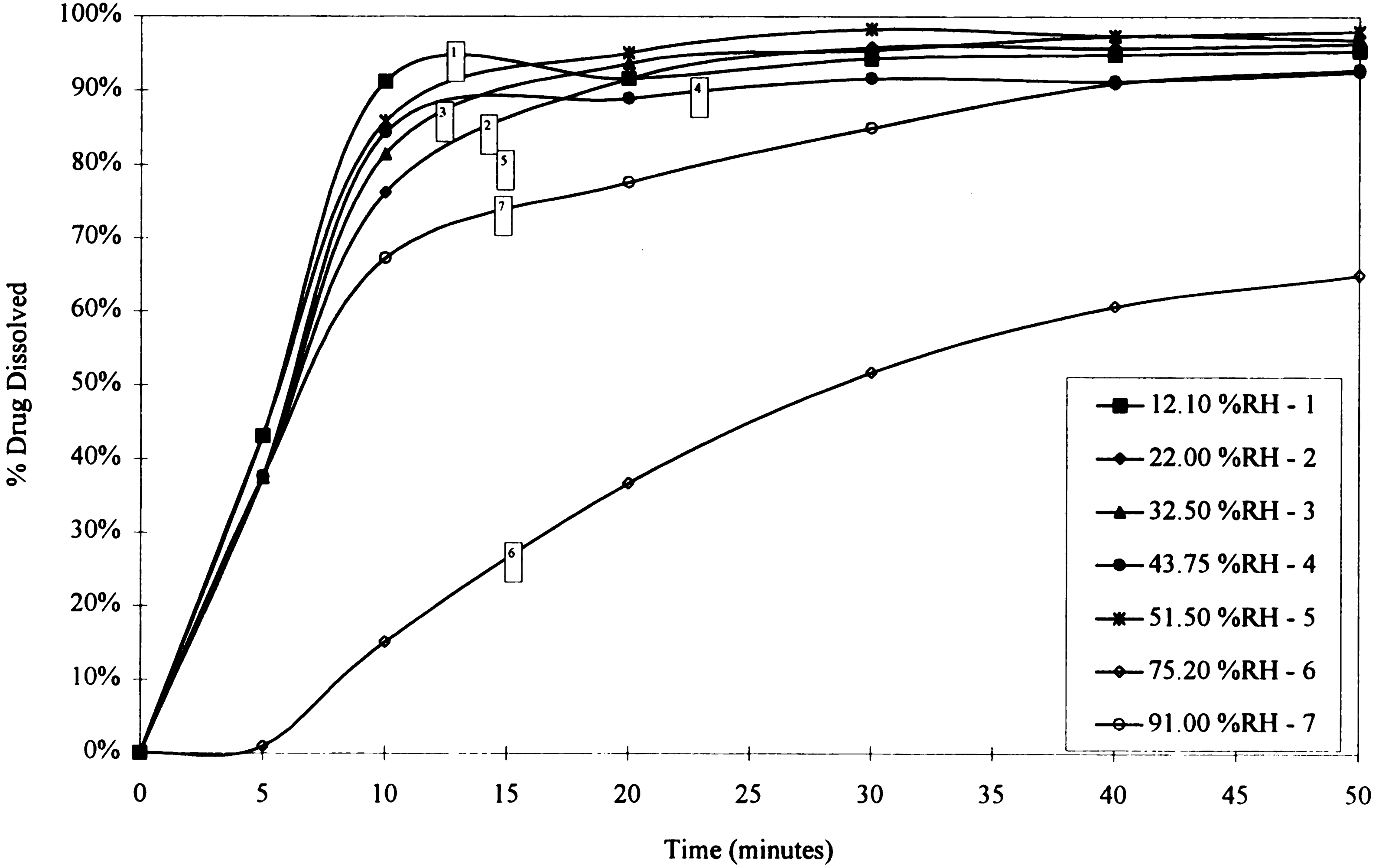

Figure 14. Dissolution profiles at 28°C after 90 days storage at 9 different humidities

humidity conditions at 28°C for 90 days. At humidities below 75%, capsules behave in a normal manner. For the "normal" capsules, first an air bubble was formed at the orange-colored end of the capsules. Then the capsules burst open, the powder started spilling out and dissolving, and then the entire capsules dissolved completely. On the other hand, the capsules exposed to 75.20 %RH and 28°C for 90 days did not dissolve completely but formed sacks/bubbles. In this case, only 52% of the drug was dissolved after 30 minutes and the capsule failed the dissolution test. In one dissolution run, the powder was clumped on the paddle of the dissolution apparatus. The capsules in this case are said to get crosslinked[4,33]. When the capsule gets crosslinked, it shrinks, it becomes dense, and becomes insoluble. In the dissolution test, hydrogen bonds are broken. Crosslinking makes the pulvule insoluble. Crosslinking/insolubilization can happen by many factors, such as high temperature, high humidity, and chemical agents like formaldehyde.

It is important to note that at 91 %RH, microbial growth was observed, and the capsule shells were sticky, and the gelatin had dissolved and stuck to the glass dish. These factors might have helped to dissolve the capsule in the dissolution tests, although the amount dissolved was lower than the corresponding values at lower humidities at each time point. Thus, even though the amount of drug dissolved after 30 minutes was higher than the required amount in the monograph (which would indicate compliance with the dissolution test), the capsules failed the test based on physical appearance and structural failure.

To study the capsule behavior observed at 75 %RH in greater detail, two humidity points were added on either side of the 75 %RH humidity point. It was decided to conduct short-term (6 days) and long-term (90 days) experiments at nine humidities and three temperatures. The six-day study was added to the current research objectives whereas the long-term study will be conducted in the future by another researcher.

Table 21. Drug dissolved with time at 28°C after 90 days storage at 7 different humidities

	% Drug dissolved (mean ± std dev)					
Average % RH Storage Humidity	5 minutes	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes
12.10	43 ±7.3	91 ±9.1	92 ±0.9	94 ±0.7	95 ±1.8	95 ±1.6
22.00	37 ±13.7	76 ±2.9	92 ±2.4	96 ±0.5	96 ±1.0	96 ±1.3
32.50	37 ±9.7	81 ±3.8	94 ±1.1	95 ±1.4	97 ±0.9	97 ±1.2
43.75	38 ±9.9	84 ±4.7	89 ±1.9	92 ±4.2	91 ±0.5	92 ±5.5
51.50	43 ±16.2	86 ±8.5	95 ±3.6	98 ±2	97 ±1.1	98 ±1.6
64.00	-	-	-	-	-	-
75.20	1 ±0.1	15 ±13.7	37 ±18.1	52 ±13.5	61 ±13.6	65 ±13.6
80.00	-	-	-	-	-	-
91.00	38 ±10.4	67 ±3.7	78 ±4	85 ±2.9	91 ±4.2	93 ±3.6

Drug dissolved at 28°C at nine different relative humidities after 6 days storage

The drug dissolved with time at 28°C after 6 days storage at 9 different humidities is given in Table 22 and is plotted in Figure 15. In this case, the physical appearance of all the capsules was "normal" except at the highest humidity. (see the description above for 90 day study at 28°C) and all of them passed the dissolution test. In the case of the

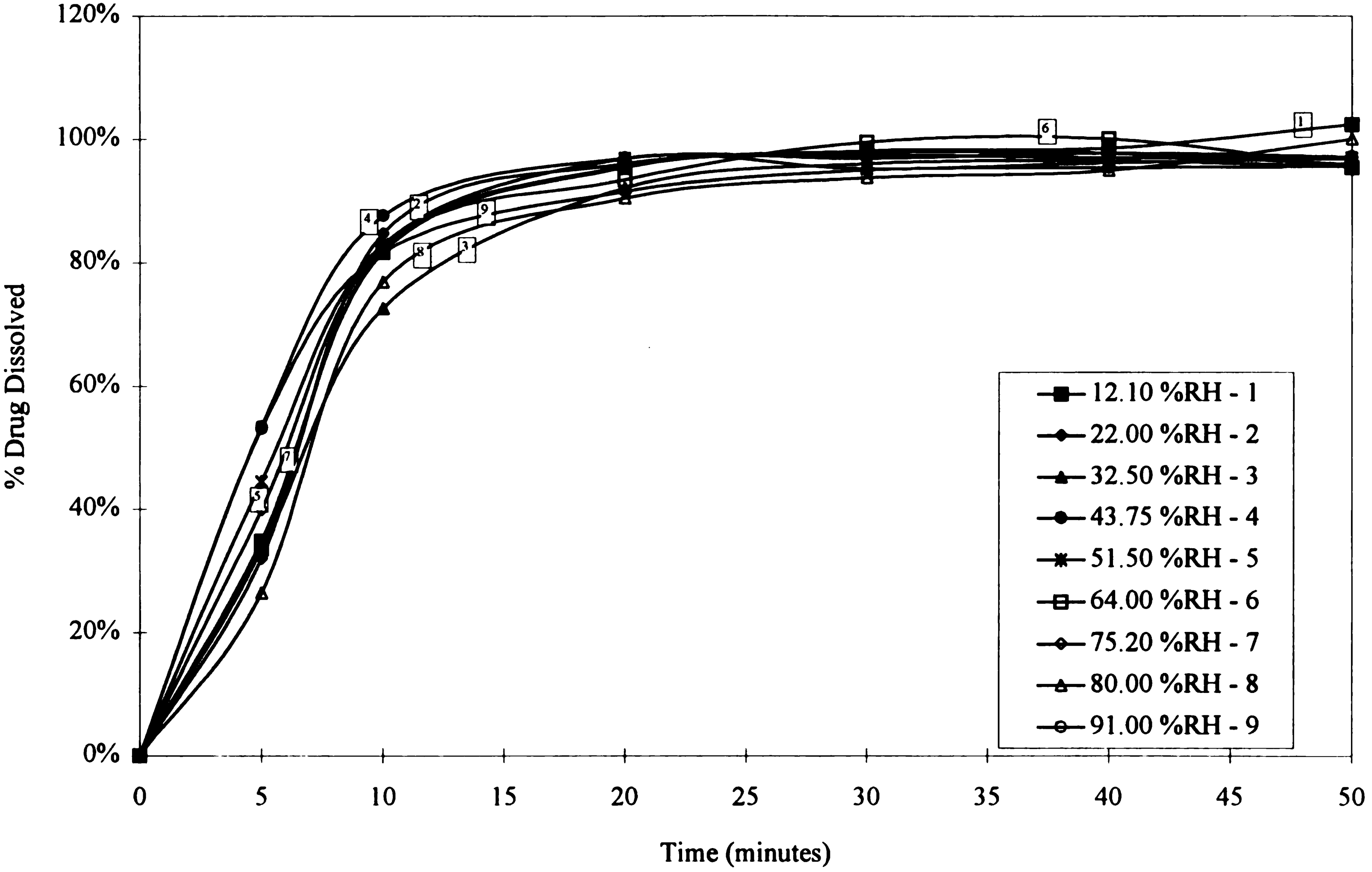

Figure 15. Dissolution profiles at 28°C after 6 days storage at 9 different humidities

highest humidity, capsules were stuck to the dish. Gelatin of the capsule became soft and started dissolving. The amount of drug dissolved in the dissolution experiment increases with time, but there is no trend in the amount of drug dissolved with increasing humidities at the same time point. The standard deviation values were generally low with a mean standard deviation of about 4%, but the values ranged from 2% to 16%.

Table 22. Drug dissolved with time at 28°C after 6 days storage at 9 different humidities

	% Drug dissolved (mean ± std dev)					
Average % RH Storage Humidity	5 minutes	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes
12.10	35 ±16.0	82 ±11.3	95 ±3.0	98 ±0.5	99 ±2.5	102 ±7.4
22.00	32 ±5.1	85 ±7.6	96 ±2.8	97 ±2.9	97 ±1.3	97 ±1.8
32.50	33 ±3.2	73 ±3.6	92 ±2.8	96 ±0.2	96 ±1.4	96 ±0.2
43.75	53 ±2.3	88 ±2.4	97 ±1.8	97 ±1.0	98 ±1.9	97 ±0.6
51.50	44 ±10.9	83 ±1.6	97 ±3.2	95 ±1.2	96 ±1.2	97 ±1.2
64.00	33 ±5.6	82 ±5.4	93 ±3.4	100 ±9.4	100 ±8.9	95 ±0.4
75.20	40 ±12.0	83 ±7.2	96 ±1.7	98 ±2.1	98 ±0.4	96 ±0.4
80.00	26 ±14.5	77 ±10.0	90 ±3.6	94 ±1.1	95 ±0.5	100 ±8.9
91.00	53 ±14.1	82 ±2.3	92 ±1.6	95 ±1.6	95 ±1.8	96 ±1.1

Drug dissolved at 38°C at nine different relative humidities after 6 days storage

The drug dissolved with time at 38°C after 6 days storage at 9 different humidities is given in Table 23 and is plotted in Figure 16. In this case, the physical appearance of all the capsules was "normal" (see the description above for 90 day study at 28°C) and all of them passed the dissolution test. However, the percent drug dissolved at 5 minutes at 80% and 90% RH humidity is significantly lower than the rest of the data points at 5 minutes. In fact, these two data points resemble the 5 minute data point at 75% RH in Figure 14. Thus, these two data points may indicate the potential failure of the pulvule after longer term storage such as that at 75% RH at 28°C after 90 days of storage.

Table 23. Drug dissolved with time at 38°C after 6 days storage at 9 different humidities

	% Drug dissolved (mean ± std dev)					
Average % RH Storage Humidity	5 minutes	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes
14.20	36 ± 4.3	84 ± 6.2	97 ± 2.7	98 ± 1.6	98 ± 0.9	98 ± 1.0
23.60	33 ± 9.3	81 ± 1.6	96 ± 4.1	99 ± 1.5	98 ± 1.1	98 ± 1.1
35.25	40 ± 9.1	86 ± 5.5	96 ± 1.8	98 ± 0.6	97 ± 0.4	97 ± 0.6
44.50	39 ± 7.5	86 ± 4.6	96 ± 0.9	97 ± 0.6	98 ± 0.9	97 ± 0.5
53.75	31 ± 9.6	74 ± 8.9	93 ± 1.6	99 ± 3.1	98 ± 0.1	97 ± 0.5
63.25	38 ± 9.1	86 ± 6.6	95 ± 1.9	101 ± 6.8	98 ± 1.7	97 ± 1.1
75.70	34 ± 10.5	84 ± 4.0	95 ± 0.9	96 ± 1.0	98 ± 1.1	96 ± 1.0
80.20	6 ± 0.2	67 ± 4.0	88 ± 4.1	94 ± 2.1	95 ± 1.1	96 ± 2.1
89.80	20 ± 10.8	76 ± 5.4	92 ± 1.7	96 ± 1.7	97 ± 1.6	96 ± 0.5

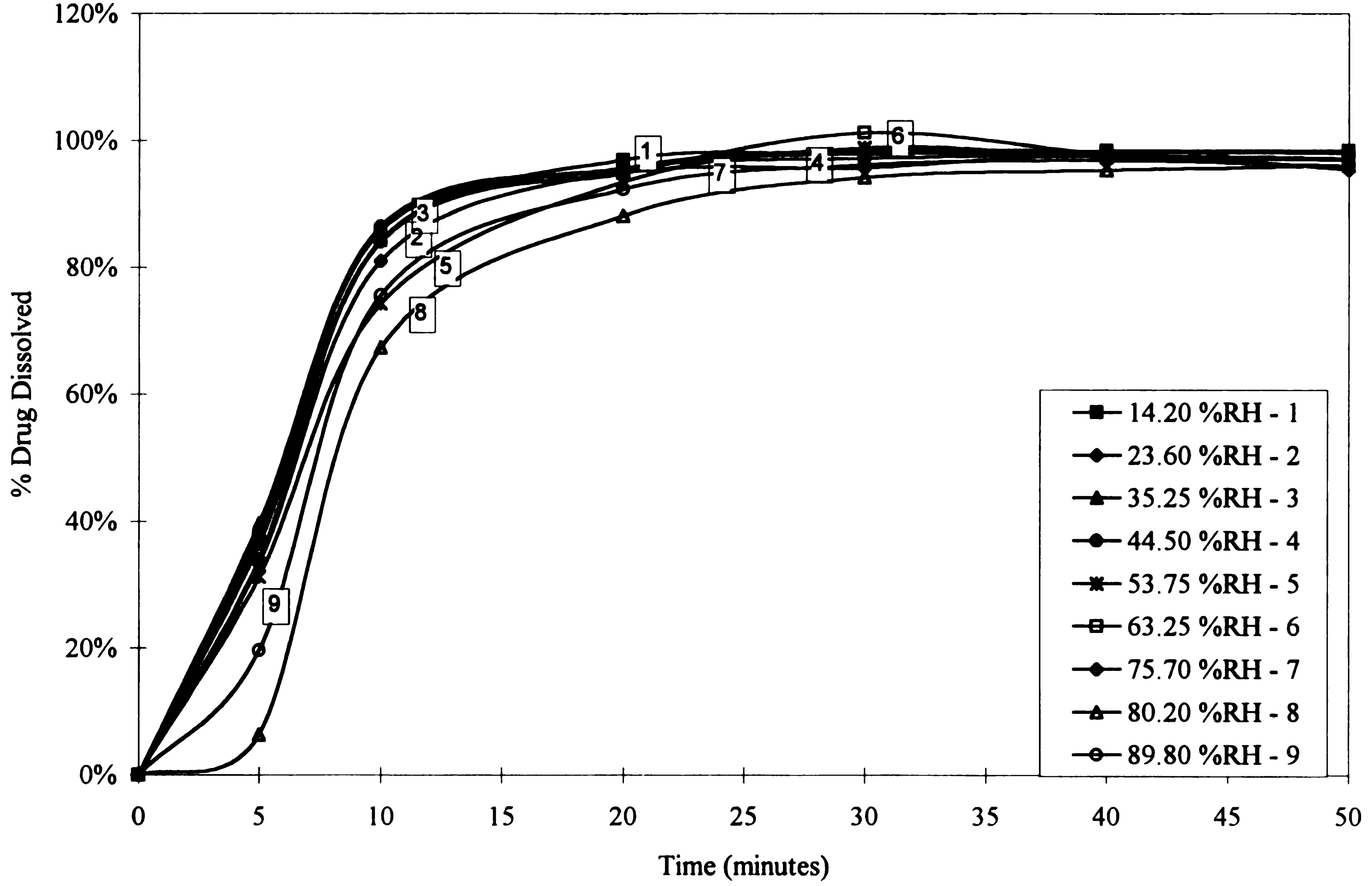

Figure 16. Dissolution profiles at 38°C after 6 days storage at 9 different humidities

The amount of drug dissolved increases with time, but there is no trend in the amount of drug dissolved with increasing humidities at the same time point. The standard deviation values were generally low with a mean standard deviation of about 4% but the values ranged from 2% to 16%. Microbial growth was observed in the pulvules stored at 89.80 %RH and the pulvules were stuck to the petri dish.

Drug dissolved at 18°C at nine different relative humidities after 6 days storage

The average percent drug dissolved at 5, 10, 20, 30, 40, and 50 minutes interval at 18°C after six days storage at nine different humidities is given in Table 24. We can see from the readings that the amount of drug dissolved increases with time. At the 10 minute interval, 82% of the drug was dissolved in the water. At the 30 minute interval, 95% of the drug was dissolved in water. From the table we can see that after 10 minutes,

Table 24. Drug dissolved with time at 18°C after 6 days storage at 9 different humidities

	% Drug dissolved (mean ± std dev)					
Average % RH Storage Humidity	5 minutes	10 minutes	20 minutes	30 minutes	40 minutes	50 minutes
16.10	39 ± 5.6	82 ± 6.4	93 ± 1.6	95 ± 0.1	92 ± 2.1	95 ± 1.2
22.50	40 ± 2.5	82 ± 3.9	93 ± 2.1	95 ± 1.4	93 ± 3.3	96 ± 0.6
36.75	40 ± 8.9	79 ± 8.0	91 ± 5.3	94 ± 3.3	94 ± 0.2	96 ± 0.8
45.75	38 ± 5.0	85 ± 7.3	94 ± 3.7	96 ± 0.6	96 ± 0.4	96 ± 0.5
55.00	36 ± 8.2	76 ± 7.1	88 ± 7.2	95 ± 1.5	94 ± 1.8	96 ± 1.0
67.00	36 ± 8.7	79 ± 0.5	95 ± 3.6	95 ± 2.0	96 ± 1.6	96 ± 1.9
74.40	42 ± 5.1	83 ± 4.6	89 ± 5.9	93 ± 2.7	94 ± 1.6	95 ± 1.1
79.20	42 ± 9.5	80 ± 7.3	95 ± 11.3	94 ± 1.6	99 ± 8.9	94 ± 0.6
92.80	51 ± 12.1	83 ± 7.2	92 ± 2.5	95 ± 1.1	95 ± 1.2	95 ± 1.2

humidity of storage environment does not have any effect on the amount of drug dissolved. The amount of drug dissolved after 5 minutes increases slightly at the highest humidity value tested, but this trend is not seen at longer dissolution times. Table 24 and Figure 17 show the amount of drug dissolved at 18°C after 6 days storage at 9 different humidities was more than that required by the USP monograph. No physical change was observed in the capsules at this stage except at the highest humidity. In case of the highest humidity, capsule shells were stuck to the dish. Gelatin of the capsule started dissolving in the dish itself.

The amount of drug dissolved at 30 minutes is tabulated in Table 25 and is plotted in Figure 18 for all three temperatures after 6 days storage and for 28°C after 90 days storage. At 28°C, data were available for 6 days as well as 90 days storage and dissolution profiles were determined for both.

Table 25. Drug dissolved after 30 minutes at three temperatures at nine different relative humidities after 6 and 90 days storage

Relative Storage Humidity	% Drug dissolved (mean ± std. dev.)			
	18°C	28°C		38°C
	6 days	6 days	90 days	6 days
12.10	95 ± 0.1	98 ± 0.5	94 ± 0.7	98 ± 1.6
22.00	95 ± 1.4	97 ± 2.9	96 ± 0.5	99 ± 1.5
32.50	94 ± 3.3	96 ± 0.2	95 ± 1.4	98 ± 0.6
43.75	96 ± 0.6	97 ± 1.0	92 ± 4.2	97 ± 0.6
51.50	95 ± 1.5	95 ± 1.2	98 ± 2	99 ± 3.1
64.00	95 ± 2.0	100 ± 9.4	-	101 ± 6.8
75.20	93 ± 2.7	98 ± 2.1	52 ± 13.5	96 ± 1.0
80.00	94 ± 1.6	94 ± 1.1	-	94 ± 2.1
91.00	95 ± 1.1	95 ± 1.6	85 ± 2.9	96 ± 1.7

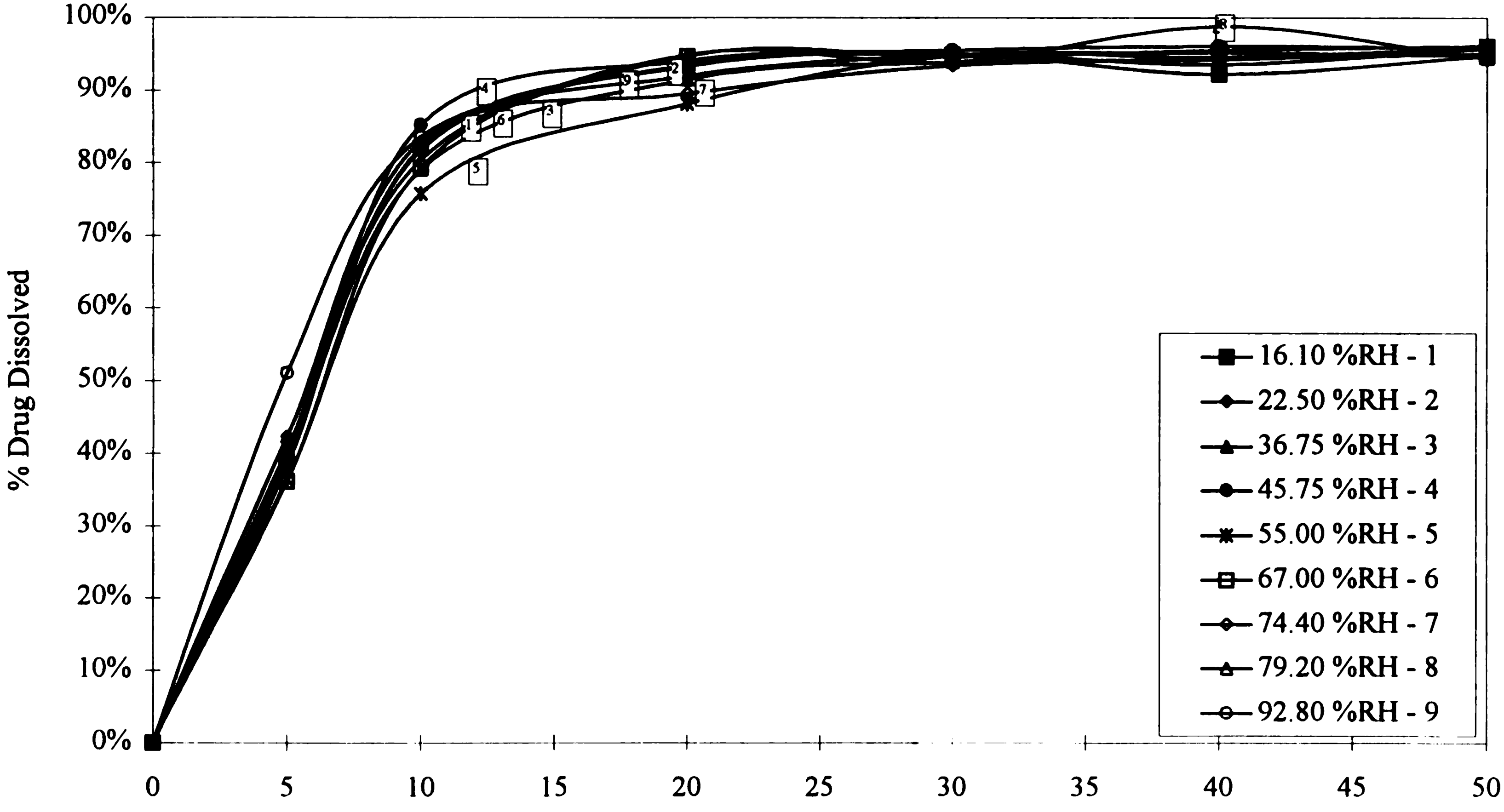

Figure 17. Dissolution profiles at 18°C after six days storage at 9 different humidities

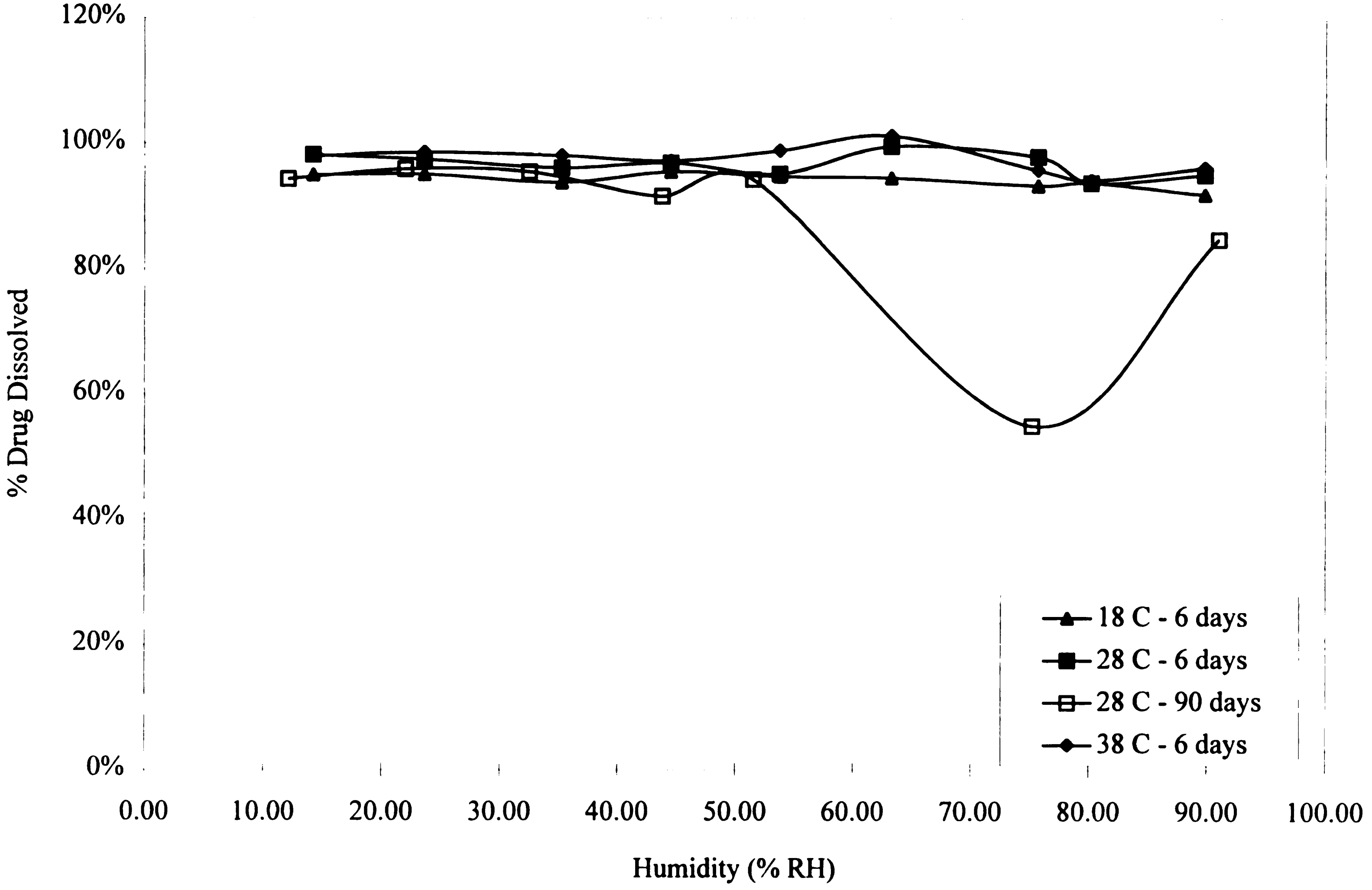

Fig. 18. Dissolution profiles after 30 minutes of dissolution time at three temperatures at nine different relative humidities after 6 and 90 days storage

For each data point in Table 25, three dissolution profiles were determined and the numbers reported in Table 25 are the mean and standard deviation of those three runs. From the profiles for different humidities we can see that the drug starts dissolving in the first 5-10 mins. The physical observations and dissolution behavior for each temperature/humidity combination are summarized in Table 26.

Table 26. Dissolution and physical change behavior at different humidity/temperature combinations over time

Temperature (^{o}C)	Time of Exposure (days) [No. of humidity Buckets tested]	Dissolution Behavior	Physical Observation (before dissolution)
18	6 [9]	Passed test for all nine humidities	Normal, except for 92.8 %RH - capsule shells stuck to dish
28	6 [9]	Passed test for all nine humidities	Normal, except for 91 %RH - capsules were stuck to dish
28	90 [7]	Passed test except for 75.2 %RH	Normal except for 91 %RH - microbial growth, sticky capsules
38	6 [9]	Passed test for all nine humidities. Dissolution data at 5 minutes at 80 & 90 %RH may be indicative of potential failure after extended storage (similar to failure observed at 75% RH at 28^{o}C after 90 days)	Normal except for 91 %RH - microbial growth, sticky capsules

There were two notable departures from normal behavior at 28°C and 90 days: For the case of 75.2 % RH, no change was observed in the capsule before starting the dissolution, but while dissolving bubbles were formed at the end of the capsule and insolubilization was observed. For the case of 91 % RH, microbial growth was observed in the stored capsules before starting the dissolution. Some insolubilization was observed.

4. Water Vapor Transmission Rate (WVTR) of the Package

4.1 WVTR at three temperatures and 91% RH for PVC alone

Table 27 contains the WVTR data obtained for PVC blisters at three temperatures. By subtracting the weight gained by empty blister from the weight gained by blister with a desiccant, the net weight gain was calculated and tabulated in Table 27.

Table 27. Net weight gain with time for PVC blisters at three temperatures and at 91% relative humidity

Temperature = 18°C		Temperature = 28°C		Temperature = 38°C	
Time (days)	Net Wt. Gain (g)	Time (days)	Net Wt. Gain (g)	Time (days)	Net Wt. Gain (g)
0	0.000	0	0.000	0	0.000
1	0.011	1	0.017	0.50	0.022
2	0.014	2	0.026	0.67	0.032
3	0.024	3	0.054	1.17	0.045
6	0.049	6	0.098	1.58	0.057
8	0.063	8	0.129		

The raw data for the actual weights of empty blisters and blisters with desiccants are given in Appendix B. The net weight gain was plotted versus time, as depicted in

Figure 19. We can see from Table 27 that as the temperature increases the net weight gain increases. The net weight gain also increases with time.

For experiments conducted at 18°C and 28°C, six time points were used. After statistical regression of these data, the calculated R^2 values were 0.994 and 0.995 for 18°C and 28°C, respectively. For experiments conducted at 38°C, five time points were used, and after the statistical regression, an R^2 of 0.977 was calculated.

Due to thermal energy, segments of a polymer chain move with respect to one another. The greater thermal energy at higher temperatures increases the frequency and amplitude of the motion. Permeation of the water vapor increases as the polymer molecular motion increases. Whenever there is a difference in the relative humidity between the inside and outside of a package, there will be a difference in partial pressure of water from one side of the barrier layer to the other. High relative humidities in storage result in high partial pressure differences. Moisture flows through the barrier layer until an equilibrium is reached and a pressure difference no longer exists.

4.2 WVTR at three temperatures and 91% RH for PVC/0.6 mil Aclar

Table 28 contains the net weight gained at each time interval for PVC/0.6 mil Aclar blisters at three temperatures and at 91 % relative humidity. By subtracting the weight gained by empty blister from the weight gained by blister with a desiccant, the net weight gain for each time period was obtained and tabulated in Table 28. The raw data for the actual weights of the empty blisters and blisters with desiccants is given in Appendix B. The net weight gain was plotted versus time as depicted in Figure 20.

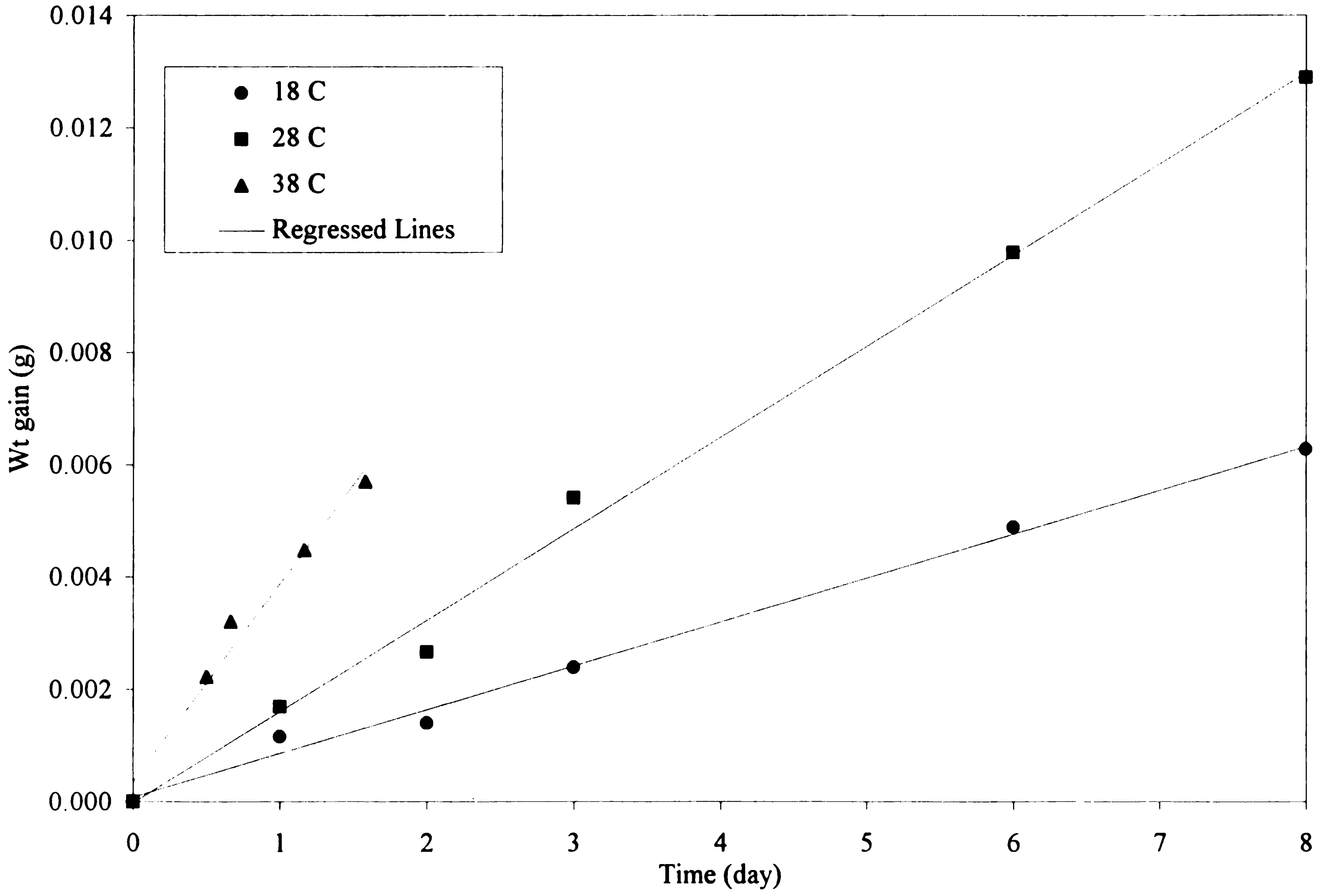

Figure 19. Net weight gain with time for PVC blisters at three temperatures and at 91% relative humidity

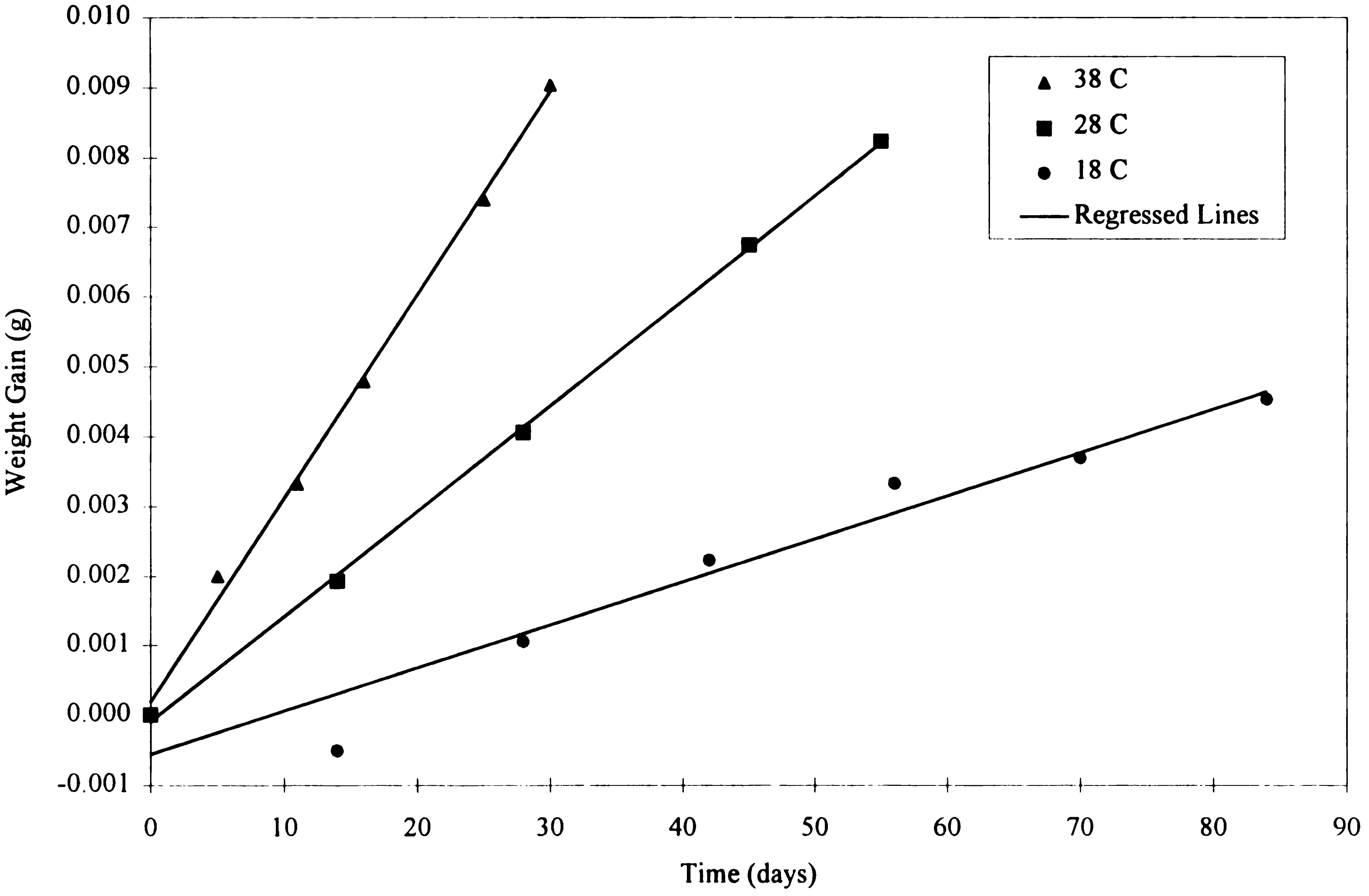

Figure 20. Net weight gain with time for PVC/0.6 mil ACLAR blisters at three temperatures and at 91% relative humidity

As described above, we can see that net weight gain increases as the temperature increases. At higher temperature less time was required to gain weight. As discussed above, polymer molecular motion increases as the temperature increases and this leads to increased permeation to water vapor. From Table 27 and Table 28, we can see that the net weight gain was less with PVC/0.6 mil Aclar than with PVC alone. Therefore, PVC/0.6 mil Aclar is a better water vapor barrier than PVC alone. Similarly, from Table 28 and Table 29, we can see that the net weight gain was higher with PVC/0.6 mil Aclar than with PVC/2 mil Aclar. Therefore, PVC/2 mil Aclar is a better water vapor barrier than both PVC and PVC/0.6 mil Aclar.

Table 28. Net weight gain with time for PVC/0.6 mil Aclar blisters at three temperatures and at 91% relative humidity

Temperature = 18°C		Temperature = 28°C		Temperature = 38°C	
Time (days)	Net Wt. Gain (g)	Time (days)	Net Wt. Gain (g)	Time (days)	Net Wt. Gain (g)
0	0.000	0	0.000	0	0.000
14	-0.005	14	0.019	5	0.019
28	0.010	28	0.040	11	0.033
42	0.022	45	0.067	16	0.048
56	0.033	55	0.082	25	0.074
70	0.037			30	0.090
84	0.045				

For experiments conducted at 18 °C, 28°C, and 38°C, seven, five, and six time points, respectively, were used. After statistical regression, the corresponding R^2 values for the three temperatures were 0.944, 0.999, and 0.997, respectively.

4.3 WVTR at three temperatures and 91% RH for PVC/2 mil Aclar

Net weight gain with time for PVC/2 mil Aclar blisters at three temperatures and at 91% relative humidity is given in Table 29 and plotted in Figure 21. We can see from the table that net weight gain increases with time and temperature, as seen before with PVC and PVC/0.6 mil Aclar. As discussed above, polymer molecular motion at the molecular level increases as the temperature increases and this leads to increased permeation to water vapor. From Table 27, Table 28, and Table 29 we can see that PVC/2 mil Aclar is a better water vapor barrier than both PVC alone and PVC/0.6 mil Aclar.

From Figure 22, we can see that blank i.e. empty blisters behaved erratically at 18°C. This erratic behavior was carried over to the net weight gain reading (which is calculated by subtracting the weight of empty blister from the weight of blister containing desiccant) for PVC/2 mil Aclar. Therefore, it was decided to drop PVC/2 mil Aclar material from further consideration in this study. The study was then focused only on PVC and PVC/0.6 mil Aclar as the packaging materials.

Table 29. Net weight gain with time for PVC/2.0 mil Aclar blisters at three temperatures and at 91% relative humidity

Temperature = 18°C		Temperature = 28°C		Temperature = 38°C	
Time (days)	Net Wt. Gain (g)	Time (days)	Net Wt. Gain (g)	Time (days)	Net Wt. Gain (g)
0	0.000	0	0.000	0	0.000
14	-0.007	14	0.002	5	0.007
28	-0.002	28	0.012	11	0.012
42	0.013	45	0.020	16	0.016
56	0.039	55	0.021	25	0.027
70	0.005			30	0.032
84	0.018				

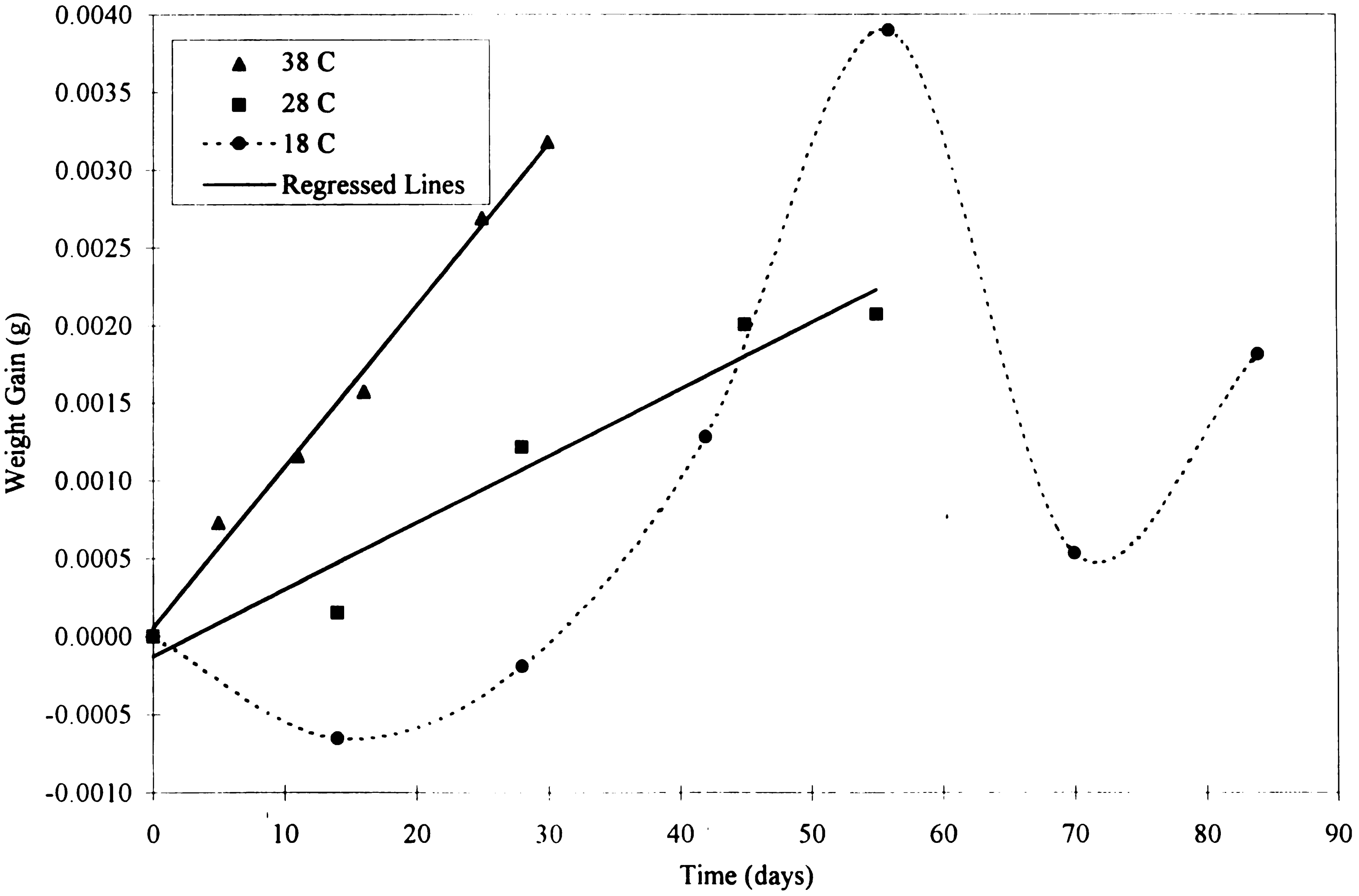

Figure 21. Net weight gain with time for PVC/2.0 mil ACLAR at three temperatures and at 91% relative humidity

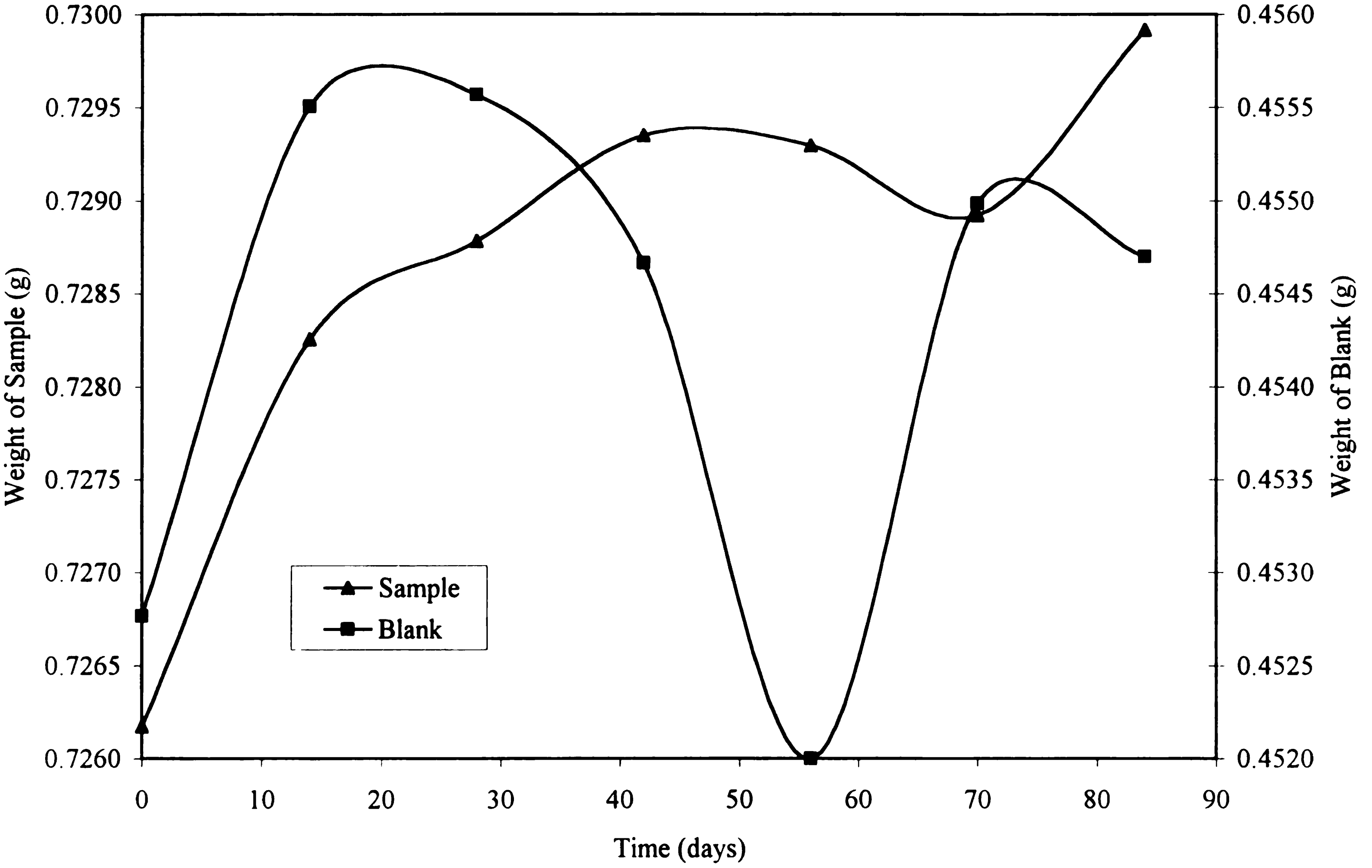

Figure 22. Net weight versus time for blank and sample for PVC/ 2 mil ACLAR blisters at 18°C and 91% relative humidity

The linear portion of the curve in Figure 22 was used to calculate the slope which is the WVTR for the package at that specific temperature. The regression tool in Microsoft Excel (Microsoft Corporation, Redmond, WA) was used to find the best linear fit to the data. The results of the regression are shown in Appendix B. From the regression output, the slope of the regressed line using least squares fit was calculated.

Table 30. WVTR, Permeability Constant, and Activation Energy for PVC and PVC/0.6 mil Aclar blisters

	Temp (^oC)	WVTR (g/day/package)	Permeability Constant (gm-mil/day-mm Hg-package)	Activation Energy (cal/mol)
PVC	18	0.0078	0.00562	3027
	28	0.0163	0.00638	
	38	0.0352	0.00787	
PVC/0.6 mil Aclar	18	0.00062	2.67E-05	3467
	28	0.00151	3.55E-05	
	38	0.00292	3.91E-05	

Table 30 lists WVTR, Permeability constant, and Activation energy for PVC and PVC/0.6 mil Aclar for three temperatures and at 91% relative humidity. WVTR was calculated from Figure 19 and Figure 20 for PVC and PVC/0.6 mil Aclar respectively. The Arrhenius plot for PVC and PVC/0.6 mil Aclar is plotted in Figure 23. We can see from Table 30 that WVTR increases with temperature as mentioned above. As PVC/0.6 mil Aclar is a better moisture vapor barrier than PVC alone, WVTR for PVC alone is higher than WVTR for PVC/0.6 mil Aclar. The permeability constant increases with temperature and is dependent on the characteristics of the package material. In this case, the permeability constant is higher for PVC alone than for PVC/0.6 mil Aclar.

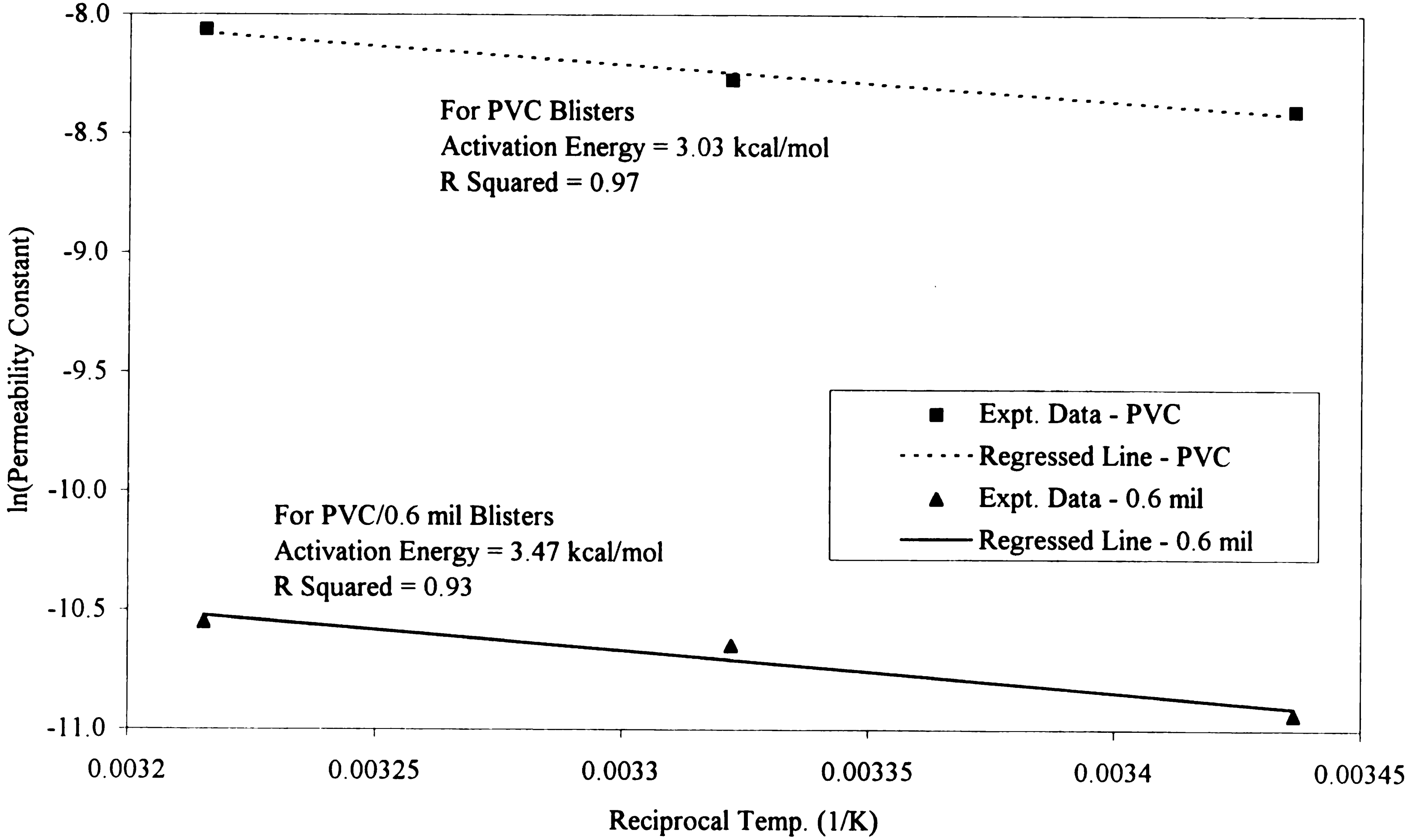

Figure 23. Arrhenius plot for permeability constants for PVC and PVC/0.6 mil Aclar

A very effective way to control moisture permeation, and probably the most common method, is the correct selection of a material or combinations of the materials to form the structural layers of a package. When choosing these materials, the water vapor transmission rate is an important criteria to consider.

The barrier properties of a material can be expressed in terms of permeability and permeability constant. Permeability of a material is the flux or the rate at which a quantity of permeant gas or vapor, in this case water vapor, passes through unit surface area in unit time, dependent upon partial pressure, and film thickness. The permeability constant of a specimen is the steady state mass or volume rate constant of permeant gas or vapor passing from one side to the other of the specimen times the thickness, per unit of time and pressure differential of the permeant through the specimen per unit surface area. The permeability constant, $\bar{P}$, is calculated with the following equation:

$$\bar{P}\left[\frac{\mathrm{g} \cdot \mathrm{mil}}{\mathrm{m}^2 \cdot \mathrm{mm\ Hg} \cdot \mathrm{day}}\right] = \frac{\mathrm{WVTR} \cdot l}{S\left(\frac{R_1 - R_2}{100}\right)}$$

where l = Film thickness

S = Saturation vapor pressure at 27.8°C

R_1, R_2 = % Relative humidity of external and internal environments, respectively

Permeability depends on permeant partial pressure, surface area of the material, thickness of the material, and temperature of the material. It is a characteristic of the material and the test conditions. Permeability constant depends on temperature, properties of the penetrant molecules (size, shape), properties of the polymer e.g. % crystallization, interaction between penetrant and a polymer, and environment factors e.g. temperature, relative humidity, etc.

Effect of temperature on permeability can be expressed by an Arrhenius plot. Here E_a is the Arrhenius activation energy, the difference between the average energy of the reactive molecules and the average energy of all molecules. From Table 30, we can see that PVC/0.6 mil Aclar has a higher activation energy than PVC. In any reaction, the colliding molecules must possess at least the amount of energy E_a before reaction can occur. This energy called, the activation energy, must be sufficient to overcome the mutual repulsion of the interacting molecules and enable them to approach each other close enough to effect certain bond ruptures and simultaneously establish new bonds characteristic of the products. The greater this energy requirement is, the smaller the proportion of colliding molecules that will have the necessary energy and the slower will be the reaction. So in this case, PVC/0.6 mil Aclar will be a better water vapor barrier than PVC.

The WVTR is then calculated with the following equation:

$$WVTR\left[\frac{g}{m^2 \cdot day}\right] = \frac{g\ water\ gained \big/ day}{Surface\ Area\ of\ Blister\ Cavity,\ m^2}$$

The numerator is the slope of the graph of weight gain versus time, which for 28°C for PVC/0.6 mil Aclar blisters (Figure 20) is 0.000151 g/day.

Figure 24 shows the schematic of the blister cavity studied. Since one side of the blister cavity is lined with impermeable material, the effective surface area of the blister cavity in a strip is calculated as follows:

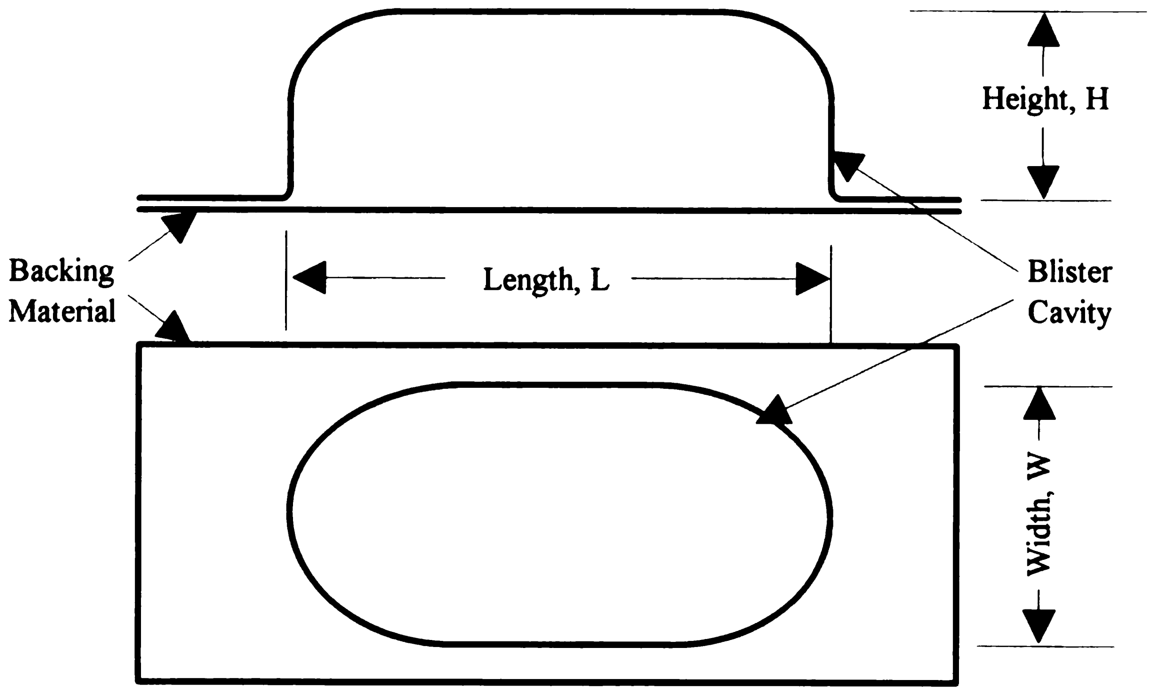

Figure 24. Schematic showing measurement of dimensions of a blister cavity

A = 2 (L x H) + 2 (W x H) + (L x W)

where, L = Length of blister cavity = 21 mm

H = Height of blister cavity = 9.4 mm

W = Width of blister cavity = 10.9 mm

Substituting these values, we obtain,

$$A = 828\ \text{mm}^2 = 0.00083\ \text{m}^2.$$

Substituting these values in above equation, we obtain,

$$WVTR\left[\frac{g}{m^2 \cdot day}\right]_{28^\circ C,\, 91\%\, RH} = \frac{0.000151\ {}^{g}\!/_{day}}{0.00083\ m^2} = 0.182\left[\frac{g}{m^2 \cdot day}\right]$$

The film thickness is 10.1 mil (7.5 mil PVC + 2 mil PE + 0.6 mil Aclar) for the film before making it into blisters. Once the blisters are formed, the film thickness varies along the surface of the blisters. The minimum film thickness of the blister was estimated to be approximately 4 mil (based on studies conducted in a separate project at the School of Packaging at Michigan State University). This thickness is used in our calculations.

The relative humidity values are $R_1 = 91\%$, $R_2 = 0$, and the saturation vapor pressure, S at 27.8°C is 28.021 mm Hg. Substituting these values in the above equation for permeability constant, we obtain,

$$\overline{P} = \frac{0.182\ \frac{g}{m^2 \cdot \text{day}} \times 4\ mil}{28.021\ \text{mm Hg}\left(\frac{91-0}{100}\right)} = 0.0286\ \frac{g \cdot mil}{m^2 \cdot mm\ Hg \cdot day}$$

5. Prediction of Shelf Life

A computer simulation model was used to estimate the shelf-life (storage stability) of the product/package system, as described in Chapter 4. The input data to the computer model is given below which is a print-out of the program.

The shelf-life was computed in two other ways: (1) using a permeability constant based on unit surface area and unit film thickness, and (2) using a permeability constant based on the blister cavity without reducing the constant to unit area or thickness. In the first case, the permeability constants for PVC and PVC/0.6 mil Aclar used in the model were $6.378\text{x}10^{-5}$ g/day-mm Hg-blister cavity and $5.921\text{x}10^{-6}$ g-mil/day-mm Hg-blister cavity, respectively. Using these permeability constants with unity for surface area and film thickness in the model, we obtain shelf-lives of 1843.8 days for PVC and 19861 days for PVC/0.6 mil Aclar blisters at 28°C and 91 %RH. For the second case, as the computer output below shows, the shelf-life for the given product/package system under the input conditions was calculated to be 199 days for PVC/0.6 mil Aclar blisters (shown below) and 18.4 days for PVC blisters at 28°C and 91 %RH (not shown below).

There is a large difference in the shelf-life predicted by the model in two cases above. Using unit thickness for multi-layer structures and unit area for blisters introduces inaccuracy into the calculation. The shelf-life model calculated for the blister cavity should be the more accurate one. However, further research will be needed to decide which value is closer to the correct answer.

We know from the moisture isotherms that the product passes dissolution test after being stored at the critical humidity for six days. Thus, the actual shelf-life of the drug would be greater than the sum of the time required for the drug to reach critical humidity and the known time for which the drug is stable (based on dissolution) at that humidity. For example, the shelf-life would be at least 24 (18 + 6) and 205 (199 + 6) days, for PVC and PVC/0.6 mil Aclar, respectively, at 28°C and 91 %RH. Further research needs to be done to get precise information[34,35].

From Table 25 at 28°C after 90 days, we can see that at 75.2% RH the product failed the dissolution test. So we have considered the EMC corresponding to this relative humidity as the critical moisture content (CMC). Therefore, this humidity value is used as "the critical relative humidity when the product is about to spoil" for calculations in the model below.

Print-out of the computer simulation program

The following values were used for PVC/0.6 mil Aclar package at 28°C and 91 %RH:

```
Enter the temperature in Celsius under which the product's sorption isotherm is studied
? 27.8
Enter the moisture content of the product in grams of water per 100 grams of solids when
the product is fresh
? 6.7
Enter the equilibrium relative humidity in % for the above product
? 34
Enter the moisture content of the product in grams of water per 100 grams of solids when
the product is about to spoil
? 10.87
Enter the equilibrium relative humidity in % for the above product
? 75.2
Enter the weight in grams of the product in the package
```

```
? 0.27025
Enter the permeability constant of the packaging material in
g * mil/day * 100 SQ.IN * mm Hg
? 0.001844
Enter the thickness of the packaging material in mil
? 4
Enter the area of the packaging material used in the package in SQ.INCHES
? 1.2844
Enter the relative humidity for the environment where the packaged product is
 stored
? 91

TEMPERATURE =  27.8
INITIAL MOISTURE CONTENT =  6.7
ERH =  34
FINAL MOISTURE CONTENT =  10.87
ERH =  75.2
PRODUCT WEIGHT =  0.27025
PERMEABILITY CONSTANT =  0.001844
FILM THICKNESS =  4
AREA OF PACKAGE =  1.2844
RH IN STORAGE ENVIRONMENT =  91

DOUBLE CHECK THE VALUES YOU HAVE ENTERED, ENTER  Y  TO
PROCEED; ENTER  N  TO RE-ENTER ALL THE VALUES.
?Y
The maximum shelf life of the product is 199.1 days.
```

Calculation of shelf-life from dissolution experiments

Although the shelf life of a drug product depends on many other factors, dissolution is used in the pharmaceutical industry as the only criterion for determining the shelf life. Therefore, this study uses dissolution as the sole criterion for determining shelf life. A procedure is outlined below which could be used to determine shelf life from dissolution experiments and may obviate the need for lengthy long-term stability experiments and the collection and analysis of weight gain data compiled from such long-term experiments.

Table 31, Table 32, and Table 33 depict the dissolution profile at 30 minutes at 18°C, 28°C, and 38°C respectively. The three columns in these tables, EMC, RH, and Drug Dissolved could be plotted on two graphs; Figure 25 depicts the graph of drug dissolved versus relative humidity and Figure 26 shows the graph of relative humidity versus equilibrium moisture content at 28°C. In addition, Figure 27 shows the plot of moisture content versus time which would be used to predict shelf-life, once the critical moisture content is obtained from the dissolution studies. From these graphs, it will be possible to determine the shelf life just by conducting dissolution experiments. The drug dissolved at critical relative humidity, which indicates dissolution failure, can be determined by performing dissolution experiments. Then, from the above two graphs, the corresponding equilibrium moisture content can be obtained and by using the moisture gain curve, the shelf life can be determined.

Table 31. Drug dissolved at 30 minutes at 18°C after six days for nine humidities and corresponding EMC

Bucket	% RH	EMC g water/100 g dry product	% Drug Dissolved
1	16.1	0.055	94.9
2	22.5	0.063	95.0
3	36.8	0.068	93.8
4	45.8	0.074	95.5
5	55.0	0.083	94.8
5a	67.0	0.098	94.5
6	74.7	0.112	93.3
6a	79.2	0.123	93.8
7	92.8	0.178	91.9

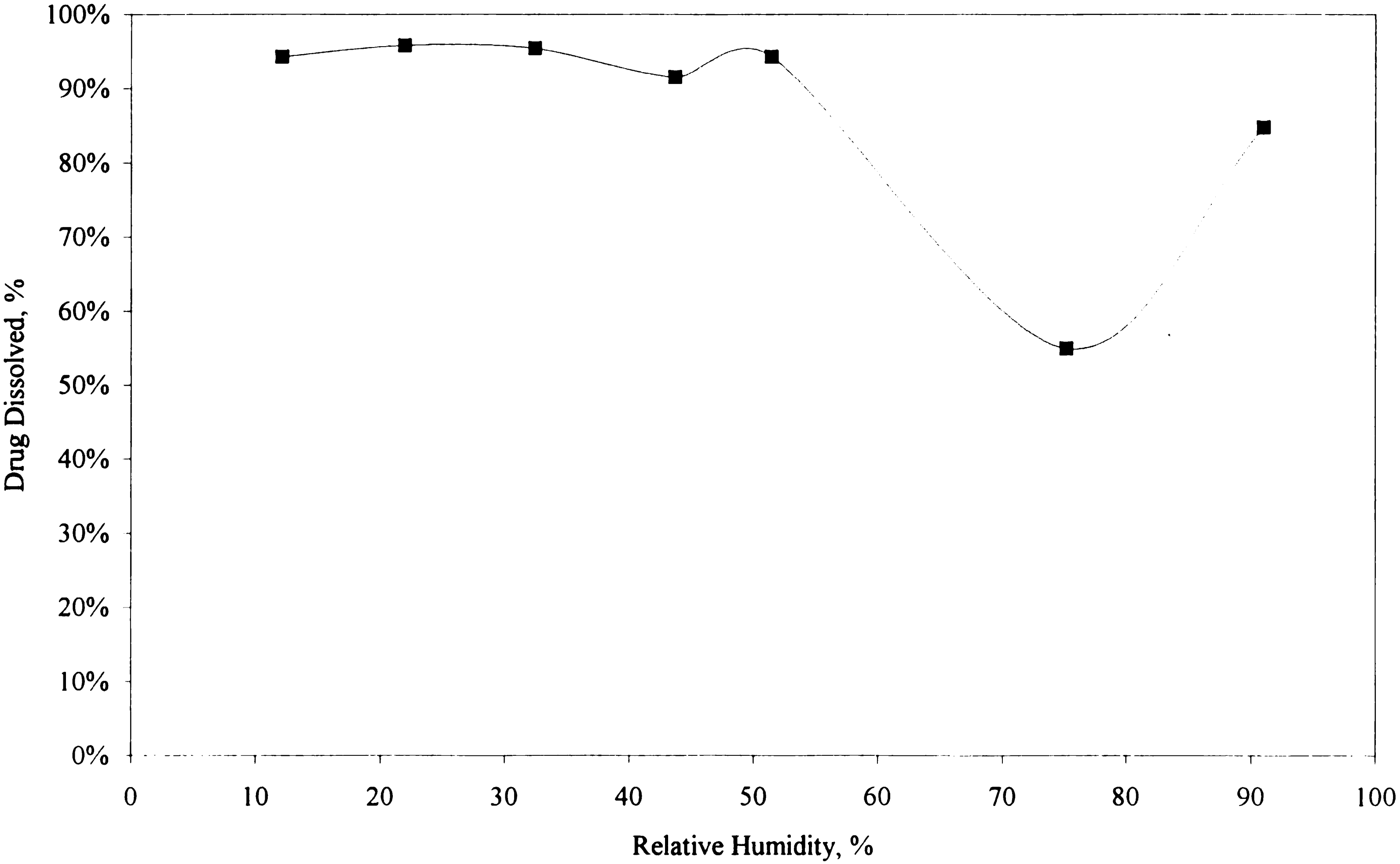

Figure 25. Drug dissolved versus relative humidity at 28°C after 90 days

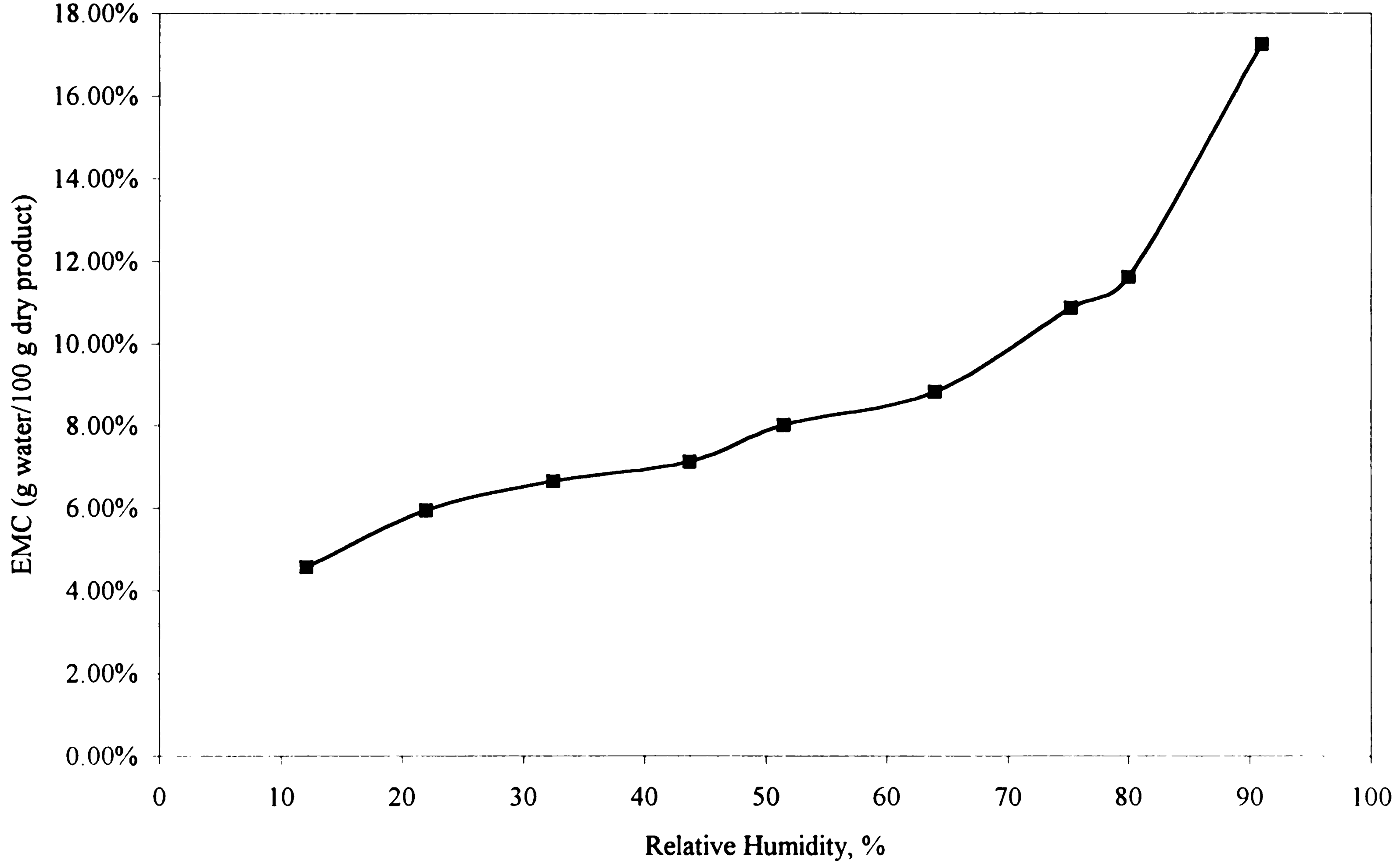

Figure 26. Relative Humidity versus Equilibirum Moisture Content at 28°C

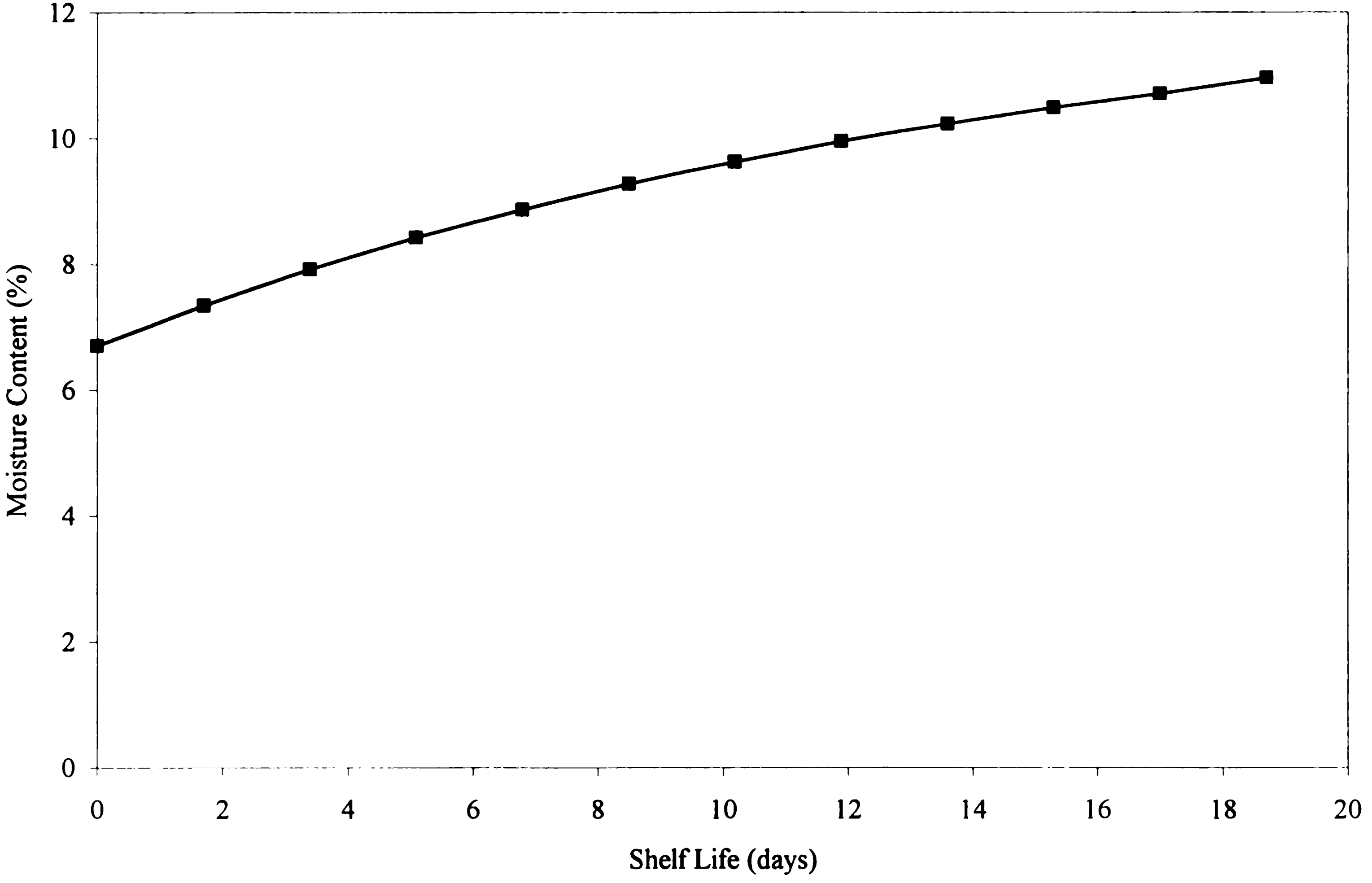

Figure 27. Moisture content versus time for PVC Blisters at 28°C and 91% RH, determined from the Shelf-Life Model

Table 32. Drug dissolved at 30 minutes at 28°C after 6 and 90 days for nine and seven humidities respectively and corresponding EMC.

Bucket No	% RH	EMC g water/100 g dry product	% Drug Dissolved	
			90 days	6 days
1	12.10	0.046	94.3	98.1
2	22.00	0.059	95.8	97.4
3	32.50	0.067	95.4	96.1
4	43.75	0.071	91.6	96.9
5	51.50	0.081	94.3	95.2
5a	64.00	0.088	-	99.6
6	75.20	0.109	54.9	97.88
6a	80.00	0.116	-	93.8
7	91.00	0.173	84.8	95.0

Table 33. Drug dissolved at 30 minutes at 38°C after 6 days for nine humidities and corresponding EMC.

Bucket No	% RH	EMC 6 days g water/100 g dry product	% Drug Dissolved
1	14.2	0.041	97.9
2	23.6	0.054	98.5
3	35.25	0.062	98.0
4	44.5	0.069	97.2
5	53.75	0.074	98.9
5a	63.25	0.083	101.2
6	75.7	0.101	95.8
6a	80.2	0.112	94.2
7	89.8	0.136	96.2

Chapter 6

CONCLUSIONS AND RECOMMENDATIONS

The objective of this work was to obtain experimental data for verification of a shelf-life computer model developed by the School of Packaging. The equilibrium moisture isotherms, the package permeability, and storage conditions were used in the model to predict the time required to reach a critical moisture content.

For the dissolution studies, open dish storage was used without any packaging. Thus, we measured the performance of the product without any packaging. Such information is not available anywhere in the open literature. All three Axid pulvule product forms were used for the experiments. The initial moisture content of the unopened pulvules, empty gelatin shells, and powder was calculated to be 5.58 g water/100 g dry product, 13.74 g water/100 g dry product, and 4.27 g water/100 g dry product respectively Equilibrium sorption isotherms were determined for all three product forms for Axid pulvule at 18°C, 28°C, and 38°C for nine relative humidities. The equilibrium moisture content (EMC) increases with relative humidity slowly at low humidities and linearly at high relative humidity values.

The shelf-life for the given product/package system under the input conditions was predicted to be 199.1 days for PVC/0.6 mil Aclar blisters at 28°C and 91 %RH. The model predicted a shelf-life of 18.4 days for PVC blisters at 28°C and 91 %RH. Accounting for the fact that the drug passes dissolution tests after six days storage at 91% RH, the shelf-life is at least equal to the predicted shelf-life plus six days. When permeability constant per cavity was used with unit surface area and unit film thickness, the model predicted shelf-lives of 1843.8 days and 19861 days for PVC and PVC/0.6 mil Aclar, respectively. This indicates that the model does not account for all the complexities involved in shelf-life estimation and further research needs to be conducted.

The model can be used to reduce the time required for actual stability testing of a product/package system and it can also be useful in rejecting certain packaging options early on before performing time-consuming experiments.

This is an example of computer simulation model for the shelf life of moisture sensitive product. This estimation technique is less costly and more rapid than the actual storage testing. But it is not a substitute for actual testing. From the outline of the simulation model, it can be seen that, by considering product characteristics (moisture isotherm), package characteristics (permeability constant, WVTR, area, thickness, etc.), and environmental conditions (temperature, relative humidity) it can calculate shelf life of a product. It can be used to select product formulation, packaging materials, and storage conditions.

This preliminary research was undertaken to study the behavior of unpackaged product. The results of this research show that dissolution can be used as a tool to predict shelf life in conjunction with the shelf-life model. In order to validate the model further, it is recommended to conduct longer-term experimental study which would provide EMC data with time that could be compared with model predictions.

APPENDIX A

Dissolution Experiments - Raw Data

Humidity bucket No.1 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Absorban	Concn	Total amt	% drug	Absorban	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved	Reading	mg/ml	in 900 ml	dissolved	Reading	mg/ml	in 900 ml	dissolved
Blank												
0				0%				0%				0%
5	0.133	0.05433	48.89744	33%	0.164	0.066994	60.29459	40%	0.178	0.072713	65.44169	44%
10	0.309	0.126226	113.6038	76%	0.361	0.147468	132.7216	88%	0.333	0.13603	122.4274	82%
20	0.373	0.15237	137.1334	91%	0.384	0.156864	141.1776	94%	0.384	0.156864	141.1776	94%
30	0.388	0.158498	142.6482	95%	0.387	0.158089	142.2805	95%	0.387	0.158089	142.2805	95%
40	0.385	0.157272	141.5452	94%	0.375	0.153187	137.8687	92%	0.368	0.150328	135.2952	90%
50	0.381	0.155638	140.0746	93%	0.387	0.158089	142.2805	95%	0.391	0.159723	143.7511	96%

Humidity bucket No.2 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel VI				Vessel V				Vessel IV			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.176	0.071896	64.70639	43%	0.163	0.066585	59.92694	40%	0.156	0.063726	57.35339	38%
10	0.321	0.131128	118.0156	79%	0.351	0.143383	129.0451	86%	0.327	0.133579	120.2215	80%
20	0.371	0.151553	136.3981	91%	0.387	0.158089	142.2805	95%	0.385	0.157272	141.5452	94%
30	0.381	0.155638	140.0746	93%	0.392	0.160132	144.1188	96%	0.39	0.159315	143.3835	96%
40	0.386	0.157681	141.9129	95%	0.366	0.149511	134.5599	90%	0.392	0.160132	144.1188	96%
50	0.392	0.160132	144.1188	96%	0.388	0.158498	142.6482	95%	0.392	0.160132	144.1188	96%

Humidity bucket No.3 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.124	0.050654	45.58859	30%	0.166	0.067811	61.02989	41%	0.196	0.080066	72.05939	48%
10	0.291	0.118873	106.9861	71%	0.319	0.130311	117.2803	78%	0.356	0.145426	130.8834	87%
20	0.355	0.145017	130.5157	87%	0.367	0.149919	134.9275	90%	0.397	0.162174	145.957	97%
30	0.37	0.151145	136.0305	91%	0.381	0.155638	140.0746	93%	0.397	0.162174	145.957	97%
40	0.383	0.156455	140.8099	94%	0.384	0.156864	141.1776	94%	0.385	0.157272	141.5452	94%
50	0.387	0.158089	142.2805	95%	0.392	0.160132	144.1188	96%	0.393	0.16054	144.4864	96%

Humidity bucket No.4 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel VI				Vessel V				Vessel IV			
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.179	0.073121	65.80934	44%	0.143	0.058415	52.57394	35%	0.144	0.058824	52.94159	35%
10	0.313	0.12786	115.0744	77%	0.365	0.149102	134.1922	89%	0.364	0.148694	133.8246	89%
20	0.384	0.156864	141.1776	94%	0.368	0.150328	135.2952	90%	0.398	0.162583	146.3247	98%
30	0.39	0.159315	143.3835	96%	0.387	0.158089	142.2805	95%	0.392	0.160132	144.1188	96%
40	0.391	0.159723	143.7511	96%	0.394	0.160949	144.8541	97%	0.391	0.159723	143.7511	96%
50	0.389	0.158906	143.0158	95%	0.393	0.16054	144.4864	96%	0.39	0.159315	143.3835	96%

Humidity bucket No.5 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorban Reading	Concn mg/ml			Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.123	0.050245	45.22094	30%	0.135	0.055147	49.63274	33%	0.186	0.075981	68.38289	46%
10	0.283	0.115605	104.0449	69%	0.303	0.123775	111.3979	74%	0.34	0.13889	125.001	83%
20	0.328	0.133988	120.5892	80%	0.364	0.148694	133.8246	89%	0.386	0.157681	141.9129	95%
30	0.381	0.155638	140.0746	93%	0.386	0.157681	141.9129	95%	0.393	0.16054	144.4864	96%
40	0.385	0.157272	141.5452	94%	0.378	0.154413	138.9717	93%	0.393	0.16054	144.4864	96%
50	0.387	0.158089	142.2805	95%	0.392	0.160132	144.1188	96%	0.395	0.161357	145.2217	97%

Humidity bucket No.5 (a) at 18 degrees C.(09/01/95), After 6 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.177	0.072304	65.07404	43%	0.108	0.044118	39.70619	26%	0.156	0.063726	57.35339	38%
10	0.325	0.132762	119.4862	80%	0.321	0.131128	118.0156	79%	0.324	0.132354	119.1186	79%
20	0.4	0.1634	147.06	98%	0.388	0.158498	142.6482	95%	0.371	0.151553	136.3981	91%
30	0.393	0.16054	144.4864	96%	0.387	0.158089	142.2805	95%	0.377	0.154004	138.604	92%
40	0.397	0.162174	145.957	97%	0.388	0.158498	142.6482	95%	0.384	0.156864	141.1776	94%
50	0.401	0.163808	147.4276	98%	0.389	0.158906	143.0158	95%	0.386	0.157681	141.9129	95%

Humidity bucket No.6 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel VI				Vessel V				Vessel IV			
	Absorbanc	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.151	0.061683	55.51514	37%	0.193	0.07884	70.95644	47%	0.173	0.07067	63.60344	42%
10	0.321	0.131128	118.0156	79%	0.358	0.146243	131.6187	88%	0.334	0.136439	122.7951	82%
20	0.338	0.138073	124.2657	83%	0.384	0.156864	141.1776	94%	0.373	0.15237	137.1334	91%
30	0.368	0.150328	135.2952	90%	0.387	0.158089	142.2805	95%	0.387	0.158089	142.2805	95%
40	0.38	0.15523	139.707	93%	0.381	0.155638	140.0746	93%	0.392	0.160132	144.1188	96%
50	0.383	0.156455	140.8099	94%	0.392	0.160132	144.1188	96%	0.388	0.158498	142.6482	95%

Humidity bucket No.6 (a) at 18 degrees C.(09/01/95), After 6 days of storage

Time	Vessel I		Total amt	% drug	Vessel II				Vessel III			
	Absorbanc	Concn	in 900 ml	dissolved	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml				mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.216	0.088236	79.41239	53%	0.142	0.058007	52.20629	35%	0.159	0.064951	58.45634	39%
10	0.36	0.14706	132.354	88%	0.301	0.122958	110.6626	74%	0.322	0.131537	118.3833	79%
20	0.435	0.177697	159.9277	107%	0.343	0.140115	126.1039	84%	0.383	0.156455	140.8099	94%
30	0.387	0.158089	142.2805	95%	0.375	0.153187	137.8687	92%	0.386	0.157681	141.9129	95%
40	0.445	0.181782	163.6042	109%	0.382	0.156047	140.4423	94%	0.382	0.156047	140.4423	94%
50	0.387	0.158089	142.2805	95%	0.385	0.157272	141.5452	94%	0.382	0.156047	140.4423	94%

Humidity bucket No.7 at 18 degrees C.(07/30/95), After 9 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorbanc	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.223	0.091095	81.98594	55%	0.153	0.0625	56.25044	38%	0.248	0.101308	91.17718	61%
10	0.367	0.149919	134.9275	90%	0.309	0.126226	113.6038	76%	0.346	0.141341	127.2069	85%
20	0.386	0.157681	141.9129	95%	0.366	0.149511	134.5599	90%	0.373	0.15237	137.1334	91%
30	0.391	0.159723	143.7511	96%	0.382	0.156047	140.4423	94%	0.388	0.158498	142.6482	95%
40	0.393	0.16054	144.4864	96%	0.389	0.158906	143.0158	95%	0.383	0.156455	140.8099	94%
50	0.392	0.160132	144.1188	96%	0.385	0.157272	141.5452	94%	0.383	0.156455	140.8099	94%

Humidity bucket No. 1 at 28 degrees C.(07-07-95), After 90 days

Time	Vessel I				Vessel VI				Vessel V			Time
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.156	0.063726	57.35339	38%	0.21	0.085785	77.20649	51%	0.161	0.065768	59.19164	39%
10	0.35	0.142975	128.6775	86%	0.415	0.169527	152.5747	102%	0.352	0.143792	129.4128	86%
20	0.37	0.151145	136.0305	91%	0.377	0.154004	138.604	92%	0.374	0.152779	137.5011	92%
30	0.383	0.156455	140.8099	94%	0.388	0.158498	142.6482	95%	0.383	0.156455	140.8099	94%
40	0.385	0.157272	141.5452	94%	0.395	0.161357	145.2217	97%	0.381	0.155638	140.0746	93%
50	0.396	0.161766	145.5894	97%	0.388	0.158498	142.6482	95%	0.383	0.156455	140.8099	94%

Humidity bucket No.2 at 28 degrees C.(07-13-95), After 90 days

Time	Vessel I				Vessel II				Vessel III			Time
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.111	0.045343	40.80914	27%	0.131	0.053513	48.16214	32%	0.216	0.088236	79.41239	53%
10	0.301	0.122958	110.6626	74%	0.307	0.125409	112.8685	75%	0.324	0.132354	119.1186	79%
20	0.362	0.147877	133.0893	89%	0.379	0.154821	139.3393	93%	0.379	0.154821	139.3393	93%
30	0.389	0.158906	143.0158	95%	0.391	0.159723	143.7511	96%	0.393	0.16054	144.4864	96%
40	0.387	0.158089	142.2805	95%	0.39	0.159315	143.3835	96%	0.395	0.161357	145.2217	97%
50	0.39	0.159315	143.3835	96%	0.39	0.159315	143.3835	96%	0.399	0.162991	146.6923	98%

Humidity bucket No.3 at 28 degrees C.(07-13-95)

Time	Vessel VI				Vessel V				Vessel IV			Time
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.198	0.080883	72.79469	49%	0.132	0.053922	48.52979	32%	0.127	0.051879	46.69154	31%
10	0.336	0.137256	123.5304	82%	0.315	0.128677	115.8097	77%	0.345	0.140932	126.8392	85%
20	0.377	0.154004	138.604	92%	0.385	0.157272	141.5452	94%	0.384	0.156864	141.1776	94%
30	0.386	0.157681	141.9129	95%	0.396	0.161766	145.5894	97%	0.386	0.157681	141.9129	95%
40	0.394	0.160949	144.8541	97%	0.401	0.163808	147.4276	98%	0.396	0.161766	145.5894	97%
50	0.395	0.161357	145.2217	97%	0.4	0.1634	147.06	98%	0.39	0.159315	143.3835	96%

Humidity bucket No. 4 at 28 degrees C.(07-07-95)

Time	Vessel I				Vessel VI				Vessel V				Time
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	
Blank													
0				0%	0			0%	0			0%	
5	0.123	0.050245	45.22094	30%	0.199	0.081291	73.16234	49%	0.138	0.056373	50.73569	34%	
10	0.322	0.131537	118.3833	79%	0.358	0.146243	131.6187	88%	0.352	0.143792	129.4128	86%	
20	0.354	0.144609	130.1481	87%	0.369	0.150736	135.6628	90%	0.365	0.149102	134.1922	89%	
30	0.354	0.144609	130.1481	87%	0.383	0.156455	140.8099	94%	0.384	0.156864	141.1776	94%	
40	0.373	0.15237	137.1334	91%	0.37	0.151145	136.0305	91%	0.374	0.152779	137.5011	92%	
50	0.352	0.143792	129.4128	86%	0.385	0.157272	141.5452	94%	0.395	0.161357	145.2217	97%	

Humidity bucket No.5 at 28 degrees C.(07-08-95)

Time	Vessel I				Vessel II				Vessel III				Time
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	
Blank													
0				0%	0			0%	0			0%	
5	0.167	0.068219	61.39754	41%	0.155	0.063317	56.98574	38%	0.04	0.01634	14.706	10%	
10	0.326	0.133171	119.8539	80%	0.339	0.138481	124.6333	83%	0.294	0.120099	108.0891	72%	
20	0.373	0.15237	137.1334	91%	0.368	0.150328	135.2952	90%	0.358	0.146243	131.6187	88%	
30	0.385	0.157272	141.5452	94%	0.386	0.157681	141.9129	95%	0.383	0.156455	140.8099	94%	
40	0.384	0.156864	141.1776	94%	0.382	0.156047	140.4423	94%	0.379	0.154821	139.3393	93%	
50	0.386	0.157681	141.9129	95%	0.386	0.157681	141.9129	95%	0.382	0.156047	140.4423	94%	

Humidity bucket No.6 at 28 degrees C.(07-10-95)

Time	Vessel I				Vessel II				Vessel III				Time
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	
Blank													
0				0%	0			0%	0			0%	
5	0.003	0.001225	1.10295	1%	0.003	0.001225	1.10295	1%	0.003	0.001225	1.10295	1%	
10	0.021	0.008578	7.720649	5%	0.02	0.00817	7.352999	5%	0.007	0.002859	2.57355	2%	
20	0.276	0.112746	101.4714	68%	0.16	0.06536	58.82399	39%	0.056	0.022876	20.5884	14%	
30	0.323	0.131945	118.7509	79%	0.219	0.089461	80.51534	54%	0.131	0.053513	48.16214	32%	
40	0.347	0.141749	127.5745	85%	0.251	0.102533	92.28013	62%	0.177	0.072304	65.07404	43%	
50	0.358	0.146243	131.6187	88%	0.274	0.111929	100.7361	67%	0.207	0.084559	76.10354	51%	

Humidity bucket No.7 at 28 degrees C.(07-12-95)												Time
Time	Vessel VI				Vessel V				Vessel IV			
	Absorbanc Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.039	0.015931	14.33835	10%	0.15	0.061275	55.14749	37%	0.004	0.001634	1.4706	1%
10	0.3	0.12255	110.295	74%	0.273	0.11152	100.3684	67%	0.24	0.09804	88.23598	59%
20	0.348	0.142158	127.9422	85%	0.324	0.132354	119.1186	79%	0.313	0.12786	115.0744	77%
30	0.359	0.146651	131.9863	88%	0.335	0.136847	123.1627	82%	0.344	0.140524	126.4716	84%
40	0.375	0.153187	137.8687	92%	0.353	0.1442	129.7804	87%	0.355	0.145017	130.5157	87%
50	0.368	0.150328	135.2952	90%	0.36	0.14706	132.354	88%	0.364	0.148694	133.8246	89%

Humidity bucket No.5 at 28 degrees C.(07-16-95), Repetition												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.105	0.042892	38.60324	26%	0.236	0.096406	86.76538	58%	0.187	0.076389	68.75054	46%
10	0.311	0.127043	114.3391	76%	0.378	0.154413	138.9717	93%	0.361	0.147468	132.7216	88%
20	0.371	0.151553	136.3981	91%	0.394	0.160949	144.8541	97%	0.398	0.162583	146.3247	98%
30	0.394	0.160949	144.8541	97%	0.41	0.167485	150.7365	100%	0.399	0.162991	146.6923	98%
40	0.392	0.160132	144.1188	96%	0.4	0.1634	147.06	98%	0.4	0.1634	147.06	98%
50	0.398	0.162583	146.3247	98%	0.394	0.160949	144.8541	97%	0.407	0.166259	149.6335	100%

Humidity bucket No.6 at 28 degrees C.(07-16-95), Repetition												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.004	0.001634	1.4706	1%	0.004	0.001634	1.4706	1%	0.003	0.001225	1.10295	1%
10	0.061	0.024918	22.42665	15%	0.006	0.002451	2.2059	1%	0.118	0.048203	43.38269	29%
20	0.163	0.066585	59.92694	40%	0.07	0.028595	25.7355	17%	0.216	0.088236	79.41239	53%
30	0.207	0.084559	76.10354	51%	0.158	0.064543	58.08869	39%	0.268	0.109478	98.53018	66%
40	0.244	0.099674	89.70658	60%	0.194	0.079249	71.32409	48%	0.305	0.124592	112.1332	75%
50	0.255	0.104167	93.75073	63%	0.215	0.087827	79.04474	53%	0.325	0.132762	119.4862	80%

Humidity bucket No.7 at 28 degrees C.(07-16-95), Repetition												Time
Time	Vessel VI				Vessel V				Vessel IV			
	Absorban Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.132	0.053922	48.52979	32%	0.202	0.082517	74.26529	50%	0.125	0.051062	45.95624	31%
10	0.27	0.110295	99.26548	66%	0.291	0.118873	106.9861	71%	0.262	0.107027	96.32428	64%
20	0.3	0.12255	110.295	74%	0.333	0.13603	122.4274	82%	0.316	0.129086	116.1774	77%
30	0.347	0.141749	127.5745	85%	0.358	0.146243	131.6187	88%	0.334	0.136439	122.7951	82%
40	0.381	0.155638	140.0746	93%	0.381	0.155638	140.0746	93%	0.351	0.143383	129.0451	86%
50	0.393	0.16054	144.4864	96%	0.379	0.154821	139.3393	93%	0.364	0.148694	133.8246	89%

Humidity bucket No.1 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.079	0.032271	29.04434	19%	0.209	0.085376	76.83884	51%	0.137	0.055964	50.36804	34%
10	0.289	0.118056	106.2508	71%	0.381	0.155638	140.0746	93%	0.33	0.134805	121.3245	81%
20	0.378	0.154413	138.9717	93%	0.402	0.164217	147.7953	99%	0.388	0.158498	142.6482	95%
30	0.398	0.162583	146.3247	98%	0.401	0.163808	147.4276	98%	0.402	0.164217	147.7953	99%
40	0.391	0.159723	143.7511	96%	0.404	0.165034	148.5306	99%	0.411	0.167893	151.1041	101%
50	0.395	0.161357	145.2217	97%	0.452	0.184642	166.1778	111%	0.406	0.165851	149.2659	100%

Humidity bucket No.2 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel VI				Vessel V				Vessel IV			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.142	0.058007	52.20629	35%	0.142	0.058007	52.20629	35%	0.106	0.043301	38.97089	26%
10	0.358	0.146243	131.6187	88%	0.368	0.150328	135.2952	90%	0.31	0.126635	113.9715	76%
20	0.389	0.158906	143.0158	95%	0.404	0.165034	148.5306	99%	0.382	0.156047	140.4423	94%
30	0.392	0.160132	144.1188	96%	0.411	0.167893	151.1041	101%	0.389	0.158906	143.0158	95%
40	0.398	0.162583	146.3247	98%	0.4	0.1634	147.06	98%	0.39	0.159315	143.3835	96%
50	0.393	0.16054	144.4864	96%	0.403	0.164625	148.1629	99%	0.389	0.158906	143.0158	95%

Humidity bucket No.3 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.15	0.061275	55.14749	37%	0.134	0.054739	49.26509	33%	0.124	0.050654	45.58859	30%
10	0.3	0.12255	110.295	74%	0.28	0.11438	102.942	69%	0.309	0.126226	113.6038	76%
20	0.388	0.158498	142.6482	95%	0.366	0.149511	134.5599	90%	0.373	0.15237	137.1334	91%
30	0.393	0.16054	144.4864	96%	0.391	0.159723	143.7511	96%	0.392	0.160132	144.1188	96%
40	0.389	0.158906	143.0158	95%	0.4	0.1634	147.06	98%	0.392	0.160132	144.1188	96%
50	0.389	0.158906	143.0158	95%	0.39	0.159315	143.3835	96%	0.391	0.159723	143.7511	96%

Humidity bucket No.4 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel VI				Vessel V				Vessel IV			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.208	0.084968	76.47119	51%	0.227	0.092729	83.45653	56%	0.218	0.089053	80.14769	53%
10	0.35	0.142975	128.6775	86%	0.368	0.150328	135.2952	90%	0.353	0.1442	129.7804	87%
20	0.395	0.161357	145.2217	97%	0.403	0.164625	148.1629	99%	0.388	0.158498	142.6482	95%
30	0.4	0.1634	147.06	98%	0.392	0.160132	144.1188	96%	0.394	0.160949	144.8541	97%
40	0.408	0.166668	150.0012	100%	0.395	0.161357	145.2217	97%	0.394	0.160949	144.8541	97%
50	0.399	0.162991	146.6923	98%	0.396	0.161766	145.5894	97%	0.394	0.160949	144.8541	97%

Humidity bucket No.5 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.218	0.089053	80.14769	53%	0.132	0.053922	48.52979	32%	0.194	0.079249	71.32409	48%
10	0.345	0.140932	126.8392	85%	0.338	0.138073	124.2657	83%	0.332	0.135622	122.0598	81%
20	0.4	0.1634	147.06	98%	0.405	0.165442	148.8982	99%	0.38	0.15523	139.707	93%
30	0.393	0.16054	144.4864	96%	0.383	0.156455	140.8099	94%	0.389	0.158906	143.0158	95%
40	0.396	0.161766	145.5894	97%	0.387	0.158089	142.2805	95%	0.395	0.161357	145.2217	97%
50	0.4	0.1634	147.06	98%	0.39	0.159315	143.3835	96%	0.396	0.161766	145.5894	97%

Humidity bucket No.5a (NaNO2) at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.147	0.060049	54.04454	36%	0.152	0.062092	55.88279	37%	0.11	0.044935	40.44149	27%
10	0.356	0.145426	130.8834	87%	0.312	0.127452	114.7068	76%	0.337	0.137664	123.898	83%
20	0.39	0.159315	143.3835	96%	0.365	0.149102	134.1922	89%	0.388	0.158498	142.6482	95%
30	0.45	0.183825	165.4425	110%	0.377	0.154004	138.604	92%	0.392	0.160132	144.1188	96%
40	0.45	0.183825	165.4425	110%	0.382	0.156047	140.4423	94%	0.393	0.16054	144.4864	96%
50	0.388	0.158498	142.6482	95%	0.389	0.158906	143.0158	95%	0.391	0.159723	143.7511	96%

Humidity bucket No.6 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel VI				Vessel V				Vessel IV			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.12	0.04902	44.11799	29%	0.216	0.088236	79.41239	53%	0.151	0.061683	55.51514	37%
10	0.327	0.133579	120.2215	80%	0.37	0.151145	136.0305	91%	0.314	0.128269	115.4421	77%
20	0.386	0.157681	141.9129	95%	0.398	0.162583	146.3247	98%	0.386	0.157681	141.9129	95%
30	0.394	0.160949	144.8541	97%	0.409	0.167076	150.3688	100%	0.395	0.161357	145.2217	97%
40	0.398	0.162583	146.3247	98%	0.398	0.162583	146.3247	98%	0.401	0.163808	147.4276	98%
50	0.39	0.159315	143.3835	96%	0.391	0.159723	143.7511	96%	0.393	0.16054	144.4864	96%

Humidity bucket No.6a ((NH4)2SO4 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel VI				Vessel V				Vessel IV			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.061	0.024918	22.42665	15%	0.087	0.035539	31.98554	21%	0.174	0.071079	63.97109	43%
10	0.278	0.113563	102.2067	68%	0.305	0.124592	112.1332	75%	0.358	0.146243	131.6187	88%
20	0.355	0.145017	130.5157	87%	0.368	0.150328	135.2952	90%	0.384	0.156864	141.1776	94%
30	0.38	0.15523	139.707	93%	0.38	0.15523	139.707	93%	0.388	0.158498	142.6482	95%
40	0.389	0.158906	143.0158	95%	0.388	0.158498	142.6482	95%	0.385	0.157272	141.5452	94%
50	0.45	0.183825	165.4425	110%	0.389	0.158906	143.0158	95%	0.385	0.157272	141.5452	94%

Humidity bucket No.7 at 28 degrees C.(05/22/95), After 6 days of storage												Time
Time	Vessel I				Vessel II				Vessel III			
	Absorban	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.246	0.100491	90.44188	60%	0.253	0.10335	93.01543	62%	0.15	0.061275	55.14749	37%
10	0.343	0.140115	126.1039	84%	0.33	0.134805	121.3245	81%	0.325	0.132762	119.4862	80%
20	0.379	0.154821	139.3393	93%	0.366	0.149511	134.5599	90%	0.375	0.153187	137.8687	92%
30	0.385	0.157272	141.5452	94%	0.383	0.156455	140.8099	94%	0.395	0.161357	145.2217	97%
40	0.389	0.158906	143.0158	95%	0.382	0.156047	140.4423	94%	0.397	0.162174	145.957	97%
50	0.388	0.158498	142.6482	95%	0.387	0.158089	142.2805	95%	0.395	0.161357	145.2217	97%

Humidity bucket No.1 at 38 degrees C.(08/17/95) After 8 days of storage (13%RH)												
Time	Vessel I				Vessel II				Vessel III			
	Absorbance	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.157	0.0641345	57.72104	38%	0.128	0.052288	47.05919	31%	0.16	0.06536	58.82399	39%
10	0.323	0.1319455	118.7509	79%	0.336	0.137256	123.5304	82%	0.372	0.151962	136.7658	91%
20	0.387	0.1580895	142.2805	95%	0.392	0.160132	144.1188	96%	0.408	0.166668	150.0012	100%
30	0.395	0.1613575	145.2217	97%	0.396	0.161766	145.5894	97%	0.407	0.166259	149.6335	100%
40	0.403	0.1646255	148.1629	99%	0.397	0.162174	145.957	97%	0.404	0.165034	148.5306	99%
50	0.406	0.165851	149.2659	100%	0.398	0.162583	146.3247	98%	0.4	0.1634	147.06	98%

Humidity bucket No.2 at 38 degrees C.(08/17/95) After 8 days of storage (23.8% RH)												
Time	Vessel VI				Vessel V				Vessel IV			
	Absorbance	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.092	0.037582	33.82379	23%	0.157	0.064134	57.72104	38%	0.158	0.064543	58.08869	39%
10	0.334	0.136439	122.7951	82%	0.323	0.131945	118.7509	79%	0.335	0.136847	123.1627	82%
20	0.371	0.1515535	136.3981	91%	0.403	0.164625	148.1629	99%	0.395	0.161357	145.2217	97%
30	0.402	0.164217	147.7953	99%	0.408	0.166668	150.0012	100%	0.396	0.161766	145.5894	97%
40	0.398	0.162583	146.3247	98%	0.406	0.165851	149.2659	100%	0.398	0.162583	146.3247	98%
50	0.399	0.1629915	146.6923	98%	0.405	0.165442	148.8982	99%	0.396	0.161766	145.5894	97%

Humidity bucket No.3 at 38 degrees C.(08/18/95) After 9 days of storage												
Time	Vessel I				Vessel II				Vessel III			
	Absorbance	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.185	0.0755725	68.01524	45%	0.181	0.073938	66.54464	44%	0.119	0.048611	43.75034	29%
10	0.365	0.1491025	134.1922	89%	0.362	0.147877	133.0893	89%	0.325	0.132762	119.4862	80%
20	0.384	0.156864	141.1776	94%	0.398	0.162583	146.3247	98%	0.388	0.158498	142.6482	95%
30	0.397	0.1621745	145.957	97%	0.401	0.163808	147.4276	98%	0.402	0.164217	147.7953	99%
40	0.397	0.1621745	145.957	97%	0.399	0.162991	146.6923	98%	0.396	0.161766	145.5894	97%
50	0.396	0.161766	145.5894	97%	0.398	0.162583	146.3247	98%	0.393	0.16054	144.4864	96%

Humidity bucket No.4 at 38 degrees C.(08/18/95) After 9 days of storage												
Time	Vessel VI				Vessel V				Vessel IV			
	Absorbance	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.173	0.0706705	63.60344	42%	0.177	0.072304	65.07404	43%	0.122	0.049837	44.85329	30%
10	0.358	0.146243	131.6187	88%	0.368	0.150328	135.2952	90%	0.332	0.135622	122.0598	81%
20	0.386	0.157681	141.9129	95%	0.393	0.16054	144.4864	96%	0.392	0.160132	144.1188	96%
30	0.398	0.162583	146.3247	98%	0.394	0.160949	144.8541	97%	0.398	0.162583	146.3247	98%
40	0.402	0.164217	147.7953	99%	0.395	0.161357	145.2217	97%	0.399	0.162991	146.6923	98%
50	0.394	0.160949	144.8541	97%	0.397	0.162174	145.957	97%	0.398	0.162583	146.3247	98%

Humidity bucket No.5 at 38 degrees C.(08/18/95) After 9 days of storage												
Time	Vessel VI				Vessel V				Vessel IV			
	Absorbance	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml.	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.099	0.0404415	36.39734	24%	0.111	0.045343	40.80914	27%	0.172	0.070262	63.23579	42%
10	0.264	0.107844	97.05958	65%	0.31	0.126635	113.9715	76%	0.336	0.137256	123.5304	82%
20	0.381	0.1556385	140.0746	93%	0.375	0.153187	137.8687	92%	0.388	0.158498	142.6482	95%
30	0.416	0.169936	152.9424	102%	0.403	0.164625	148.1629	99%	0.391	0.159723	143.7511	96%
40	0.398	0.162583	146.3247	98%	0.398	0.162583	146.3247	98%	0.399	0.162991	146.6923	98%
50	0.394	0.160949	144.8541	97%	0.398	0.162583	146.3247	98%	0.395	0.161357	145.2217	97%

Humidity bucket No. 5a (NaNO2) at 38 degrees C.(09/09/95) After 6 days of storage												
Time	Vessel VI				Vessel V				Vessel IV			
	Absorbance	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug	Reading	Concn	Total amt	% drug
	Reading	mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved		mg/ml	in 900 ml	dissolved
Blank												
0				0%	0			0%	0			0%
5	0.183	0.0747555	67.27994	45%	0.166	0.067811	61.02989	41%	0.112	0.045752	41.17679	27%
10	0.362	0.147877	133.0893	89%	0.369	0.150736	135.6628	90%	0.319	0.130311	117.2803	78%
20	0.388	0.158498	142.6482	95%	0.394	0.160949	144.8541	97%	0.379	0.154821	139.3393	93%
30	0.445	0.1817825	163.6042	109%	0.396	0.161766	145.5894	97%	0.398	0.162583	146.3247	98%
40	0.392	0.160132	144.1188	96%	0.402	0.164217	147.7953	99%	0.405	0.165442	148.8982	99%
50	0.391	0.1597235	143.7511	96%	0.398	0.162583	146.3247	98%	0.399	0.162991	146.6923	98%

Humidity bucket No.6 at 38 degrees C.(08/18/95) After 9 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorbance Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Absorbanc Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Absorbanc Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%				0%				0%
5	0.14	0.05719	51.47099	34%	0.181	0.073938	66.54464	44%	0.095	0.038807	34.92674	23%
10	0.347	0.1417495	127.5745	85%	0.357	0.145834	131.251	88%	0.325	0.132762	119.4862	80%
20	0.383	0.1564555	140.8099	94%	0.39	0.159315	143.3835	96%	0.389	0.158906	143.0158	95%
30	0.393	0.1605405	144.4864	96%	0.393	0.16054	144.4864	96%	0.386	0.157681	141.9129	95%
40	0.404	0.165034	148.5306	99%	0.396	0.161766	145.5894	97%	0.397	0.162174	145.957	97%
50	0.393	0.1605405	144.4864	96%	0.385	0.157272	141.5452	94%	0.391	0.159723	143.7511	96%

Humidity bucket No. 6a (NH4)2SO4 at 38 degrees C.(09/01/95) After 6 days of storage

Time	Vessel VI				Vessel V				Vessel IV			
	Absorbance Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.025	0.0102125	9.191248	6%	0.026	0.010621	9.558898	6%	0.027	0.011029	9.926548	7%
10	0.285	0.1164225	104.7802	70%	0.284	0.116014	104.4126	70%	0.256	0.104576	94.11838	63%
20	0.348	0.142158	127.9422	85%	0.379	0.154821	139.3393	93%	0.352	0.143792	129.4128	86%
30	0.38	0.15523	139.707	93%	0.394	0.160949	144.8541	97%	0.379	0.154821	139.3393	93%
40	0.39	0.159315	143.3835	96%	0.393	0.16054	144.4864	96%	0.384	0.156864	141.1776	94%
50	0.398	0.162583	146.3247	98%	0.396	0.161766	145.5894	97%	0.382	0.156047	140.4423	94%

Humidity bucket No.7 at 38 degrees C.(08/18/95) After 9 days of storage

Time	Vessel I				Vessel II				Vessel III			
	Absorbance Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Absorbanc Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved	Absorbanc Reading	Concn mg/ml	Total amt in 900 ml	% drug dissolved
Blank												
0				0%	0			0%	0			0%
5	0.053	0.0216505	19.48545	13%	0.131	0.053513	48.16214	32%	0.056	0.022876	20.5884	14%
10	0.294	0.120099	108.0891	72%	0.334	0.136439	122.7951	82%	0.298	0.121733	109.5597	73%
20	0.379	0.1548215	139.3393	93%	0.382	0.156047	140.4423	94%	0.369	0.150736	135.6628	90%
30	0.39	0.159315	143.3835	96%	0.4	0.1634	147.06	98%	0.387	0.158089	142.2805	95%
40	0.4	0.1634	147.06	98%	0.398	0.162583	146.3247	98%	0.388	0.158498	142.6482	95%
50	0.391	0.1597235	143.7511	96%	0.394	0.160949	144.8541	97%	0.39	0.159315	143.3835	96%

APPENDIX B

Weight gain experiments - raw data.

Regression analysis for net weight gain with time obtained for PVC/0.6 mil Aclar blisters at 18°C and 91% RH

SUMMARY OUTPUT

Regression Statistics	0
Multiple R	0.97173466
R Square	0.94426825
Adjusted R Square	0.9331219
Standard Error	0.00497704
Observations	7

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.002098485	0.002098	84.71546	0.0002541
Residual	5	0.000123855	2.48E-05		
Total	6	0.002222339			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%	Upper 95.0%
Intercept	-0.0056239	0.003391284	-1.65833	0.158149	-0.0143414	0.0030937	-0.01434142	0.0030937
X Variable 1	**0.00061837**	6.71838E-05	9.2041	0.000254	0.0004457	0.00079107	0.000445665	0.00079107

Calculation of the Permeability Constant (18°C, PVC/0.6 mil Aclar)

WVTR and P bar is calculated for 1 cavity

WVTR= 0.00061837 gm/day/cavity Humidity = 91% RH

One Package = 10 cavities.

Therefore, WVTR = 6.1837E-05 gm/day/cavity

Saturation Vapor pressure at 17.8 C = 15.284 mm of Hg

Film thickness= 4 mil

Permeability Constant = 1.77839E-05 gm.mil/day.mm Hg.cavity

Regression analysis for net weight gain with time obtained for PVC/0.6 mil Aclar blisters at 28°C and 91% RH

SUMMARY OUTPUT

Regression Statistics	0
Multiple R	0.99970293
R Square	0.99940596
Adjusted R Square	0.99920794
Standard Error	0.00094973
Observations	5

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.004552471	0.004552	5047.13	6.146E-06
Residual	3	2.70598E-06	9.02E-07		
Total	4	0.004555177			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%
Intercept	-0.000991	0.000738013	-1.3428	0.271897	-0.0033397	0.00135769	-0.00333969
X Variable 1	**0.00150978**	2.12515E-05	71.04315	6.15E-06	0.0014421	0.00157741	0.001442145

Calculation of the Permeability Constant (28°C, PVC/0.6 mil Aclar)

WVTR and P bar is calculated for 1 package-> 12.844 sq. in. area

WVTR= 0.00150978 gm/day/package Humidity = 91% RH

One Package = 10 cavities. 1 cavity = 1.2844 sq. in. area

Therefore, WVTR = 0.00015098 gm/day/cavity

Saturation Vapor pressure at 28 C = 28.021 mm of Hg

Film thickness= 4 mil ---> Minimum thickness based on studies.

Permeability Constant = 2.36836E-05 gm.mil/day.mm Hg.cavity

Regression analysis for net weight gain with time obtained for PVC/0.6 mil Aclar blisters at 38°C and 91% RH

SUMMARY OUTPUT

Regression Statistics	0
Multiple R	0.99839034
R Square	0.99678328
Adjusted R Square	0.99597909
Standard Error	0.00213866
Observations	6

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.005669298	0.005669	1239.501	3.884E-06
Residual	4	1.82954E-05	4.57E-06		
Total	5	0.005687593			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%
Intercept	0.0018454	0.001485704	1.242107	0.282047	-0.0022796	0.00597039	-0.00227958
X Variable 1	0.00291871	8.29024E-05	35.20655	3.88E-06	0.0026885	0.00314888	0.002688533

Calculation of the Permeability Constant (38°C, PVC/0.6 mil Aclar)

WVTR and P bar is calculated for 1 package

WVTR= 0.00291871 gm/day/package Humidity = 91% RH

One Package = 10 cavities.

Therefore, WVTR = 0.00029187 gm/day/cavity

Saturation Vapor pressure at 37.8 C = 49.157 mm of Hg

Film thickness= 4 mil

Permeability Constant = 2.6099E-05 gm.mil/day.mm Hg.cavity

Regression analysis for net weight gain with time obtained for PVC blisters at 18°C and 91% RH

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.99707664
R Square	0.99416183
Adjusted R Square	0.99270228
Standard Error	0.00205935
Observations	6

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.002888674	0.002889	681.1459	1.28066E-05
Residual	4	1.69636E-05	4.24E-06		
Total	5	0.002905638			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%
Intercept	0.00077029	0.001304736	0.590379	0.586677	-0.002852245	0.004392823	-0.002852245
X Variable 1	**0.00781206**	0.000299327	26.09877	1.28E-05	0.006980997	0.00864313	0.006980997

Calculation of the Permeability Constant (18°C, PVC)

WVTR and P bar is calculated for 1 package
WVTR= 0.00781206 gm/day/package Humidity = 91% RH
One Package = 10 cavities.
Therefore, WVTR = 0.00078121 gm/day/cavity
Saturation Vapor pressure at 17.8 C = 15.284 mm of Hg
Film thickness= 4 mil
Permeability Constant = 0.000224671 gm.mil/day.mm Hg.cavity

Regression analysis for net weight gain with time obtained for PVC blisters at 28°C and 91% RH

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.99737101
R Square	0.99474893
Adjusted R Square	0.99343616
Standard Error	0.00406455
Observations	6

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.012518466	0.012518	757.7489	1.03583E-05
Residual	4	6.60824E-05	1.65E-05		
Total	5	0.012584548			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%
Intercept	-0.0001923	0.002575171	-0.07466	0.944072	-0.00734209	0.006957583	-0.00734209
X Variable 1	**0.01626268**	0.000590785	27.52724	1.04E-05	0.014622391	0.017902961	0.014622391

Calculation of the Permeability Constant (28°C, PVC)

WVTR and P bar is calculated for 1 package
WVTR= 0.01626268 gm/day/package Humidity = 91% RH
One Package = 10 cavities.
Therefore, WVTR = 0.00162627 gm/day/cavity
Saturation Vapor pressure at 28 C = 28.021 mm of Hg
Film thickness= 4 mil
Permeability Constant = 0.00025511 gm.mil/day.mm Hg.cavity

Regression analysis for net weight gain with time obtained for PVC blisters at 38°C and 91% RH

SUMMARY OUTPUT

Regression Statistics	
Multiple R	0.98828144
R Square	0.97670021
Adjusted R Square	0.96893362
Standard Error	0.00383921
Observations	5

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.001853593	0.001854	125.7565	0.001520128
Residual	3	4.42186E-05	1.47E-05		
Total	4	0.001897812			

	Coefficients	Standard Error	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0%
Intercept	0.0035724	0.002999981	1.190807	0.319363	-0.005974889	0.013119685	-0.005974889
X Variable 1	**0.03521822**	0.003140524	11.21412	0.00152	0.025223659	0.045212773	0.025223659

Calculation of the Permeability Constant (38°C, PVC)

WVTR and P bar is calculated for 1 package

WVTR= 0.03521822 gm/day/package Humidity = 91% RH

One Package = 10 cavities.

Therefore, WVTR = 0.00352182 gm/day/cavity

Saturation Vapor pressure at 37.8 C = 49.157 mm of Hg

Film thickness= 4 mil

Permeability Constant = 0.00031492 gm.mil/day.mm Hg.cavity

Regression analysis for calculation of the activation energy for experiments conducted with PVC blisters

Arrhenius Plot (PVC)

1/T	Ln(K)	Regressed
0.003215434	-8.06319	-8.07951
0.003322259	-8.27382	-8.24223
0.003436426	-8.40087	-8.41614

SUMMARY OUTPUT 0

Regression Statistics	
Multiple R	0.987051
R Square	0.97427
Adjusted R Square	0.94854
Standard Error	0.03869
Observations	3

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.056681	0.056681	37.86522	0.10256
Residual	1	0.001497	0.001497		
Total	2	0.058178			

	Coefficient	Standard	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0	Upper 95.0%
Intercept	-3.18151	0.823327	-3.86421	0.161211	-13.6428	7.279802	-13.6428	7.279802
X Variable 1	**-1523.28**	247.5477	-6.15347	0.10256	-4668.66	1622.1	-4668.66	1622.1

Slope = -E/R

R = 1.987 cal/mol-K

Act. Energy, E = 3026.75 cal/mol

Regression analysis for calculation of the activation energy for experiments conducted with PVC/0.6 mil Aclar blisters

Arrhenius Plot (0.6 mil)

1/T	Ln(K)	Regressed
0.003215434	-10.5536	-10.5232
0.003322259	-10.6507	-10.7096
0.003436426	-10.9372	-10.9088

SUMMARY OUTPUT 0

Regression Statistics	
Multiple R	0.966779
R Square	0.934662
Adjusted R Square	0.869324
Standard Error	0.072096
Observations	3

ANOVA

	df	SS	MS	F	Significance F
Regression	1	0.074355	0.074355	14.30505	0.164554
Residual	1	0.005198	0.005198		
Total	2	0.079553			

	Coefficient	Standard	t Stat	P-value	Lower 95%	Upper 95%	Lower 95.0	Upper 95.0%
Intercept	-4.91334	1.534198	-3.20255	0.192678	-24.4071	14.58041	-24.4071	14.58041
X Variable 1	**-1744.67**	461.2837	-3.7822	0.164554	-7605.81	4116.472	-7605.81	4116.472

Slope = -E/R

R = 1.987 cal/mol-K

Act. Energy, E = 3466.656 cal/mol

APPENDIX C

PRINT-OUT OF THE COMPUTER SIMULATION PROGRAM

Print-out of the Computer Simulation Program

```
Enter the temperature in Celsius under which the product's sorption isotherm is studied
? 27.8
Enter the moisture content of the product in grams of water per 100 grams of solids when
the product is fresh
? 6.7
Enter the equilibrium relative humidity in % for the above product
? 34
Enter the moisture content of the product in grams of water per 100 grams of solids when
the product is about to spoil
? 10.87
Enter the equilibrium relative humidity in % for the above product
? 75.2
Enter the weight in grams of the product in the package
? 0.27025
Enter the permeability constant of the packaging material in
g * mil/day * 100 SQ.IN * mm Hg
? 0.01986
Enter the thickness of the packaging material in mil
? 4
Enter the area of the packaging material used in the package in SQ.INCHES
? 1.2844
```

```
Enter the relative humidity for the environment where the packaged product is stored

?.91


TEMPERATURE =  27.8

INITIAL MOISTURE CONTENT =  6.7

ERH =  34

FINAL MOISTURE CONTENT =  10.87

ERH =  75.2

PRODUCT WEIGHT =  .27025

PERMEABILITY CONSTANT =  .01986

FILM THICKNESS =  4

AREA OF PACKAGE =  1.2844

RH IN STORAGE ENVIRONMENT =  91



DOUBLE CHECK THE VALUES YOU HAVE ENTERED, ENTER  Y  TO

PROCEED; ENTER  N  TO RE-

ENTER ALL THE VALUES.

?

Y


The maximum shelf life of the product is  18.4 days.
```

```
Enter  Y  if you would like to work some more, enter  N  if you've had enough
?
Y


1. Find shelf life, given a different final moisture content of the product
2. Find the permeability constant, given a shelf life and final moisture
   content of the product
3. Find the film thickness, given a shelf life, permeability constant,
   and final moisture content of the product
4. Find relative humidity inside the package and the moisture content of the
   product, given days the packaged product has been stored
5. Find saturation water vapor pressure, given temperature in Celsius
6. To start all over again
7. Quit


Enter the item number of your choice
?
4
Enter the desired shelf life in days
? 17
Enter the number of intervals desired
? 10
```

```
MC = MOISTURE CONTENT      RH = RELATIVE HUMIDITY

SL = SHELF LIFE (IN DAYS)

THE STORAGE CONDITION IS  91 %RH

THE TEMPERATURE OF THIS STUDY IS  27.8  DEGREES CELSIUS

#INCREMENT       RH%          MC           SL

-----------------------------------------------------------------

     0           34           6.7          0

     1           40.4         7.34         1.7

     2           46           7.92         3.4

     3           51           8.42         5.1

     4           55.5         8.87         6.8

     5           59.4         9.28         8.5

     6           63           9.63         10.2

     7           66.1         9.95         11.9

     8           68.9         10.23        13.6

     9           71.3         10.48        15.3

     10          73.5         10.7         17



Enter  Y  if you like to work some more, enter  N  if you had enough

?
```

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