PREDICTION OF MOISTURE CONTENT OF ORAL SOLID DRUGS AFTER UNIT DOSE REPACKAGING

By

Nicholas Gus Fotis

A THESIS

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

MASTER OF SCIENCE

School of Packaging

1983

ABSTRACT

PREDICTION OF MOISTURE CONTENT OF ORAL SOLID DRUGS AFTER UNIT DOSE REPACKAGING

By

Nicholas Gus Fotis

Moisture content is a significant factor in the quality of many products and protective plastic packaging is often employed to reduce the transfer of moisture between the product and the environment. In the pharmaceutical industry, new packages which offer sufficient moisture protection are designed and tested at the point of manufacture. Results of these studies are usually unavailable to hospital pharmacists who must repackage solid oral drugs into unit dose containers. A model has been proposed which combines the barrier properties of the intact package, the behavior of the product with respect to moisture, the exterior conditions of storage and distribution with established mathematical relationships for mass transfer and product moisture affinity. This study examined the usefulness of a simulation model as applied to two unit dose oral solid drug products. It was found to be an adequate tool for predicting product moisture content.

Dedication

This thesis is dedicated to my wife in appreciation of our dual burden in bearing this work. Gratitude is also extended to my parents for their commitment to education and to me.

ACKNOWLEDGEMENTS

I would like to thank Dr. Jack R. Giacin for his generous guidance. Adopting me after my first major professor changed universities, Dr. Giacin has given a great deal of time and support to this project. It is mainly through his encouragement that this paper has come into existence. I would also like to thank the other patient members of my committee: Dr. K. Jayaraman and Dr. Hugh Lockhart. Special thanks is extended to Dr. James E. Jay for his friendship and support, to Mike Irwin for assistance with the Karl Fisher apparatus, and to Terri Stevens and David Elsinger for their help in the determination of the permeation constants and moisture isotherms.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

INTRODUCTION

Degradation in pharmaceutical products is indeed a complex process. Among the more important factors are temperature of storage, length of storage, pH of formulation, ultra violet light, initial moisture content, particle size, presence of oxygen, carbon dioxide or moisture, breakdown of drug constituents, reaction with fillers, lubricants, preservatives, vaporization, sublimation, precipitation, sedimentation, cracking or creaming (United States Pharmacopeia, 1975). Among a select number of drugs, the amount of water in the tablet is a crucial test for acceptance. These drugs may be classified as being moisture sensitive.

Presently, the most frequently used method for testing new packages for moisture sensitive drug products is the long term stability study in which the drug product is packaged in the new system and then stored under typical storage conditions (i.e. months or years). Samples are taken at intervals to determine if the drug is still acceptable. These studies are expensive and expend a great deal of labor and record keeping to insure their validity, but are required by the Food and Drug Administration as part of the New Drug Application (NDA) before a new drug can be marketed. If an existing drug-package system is being modified, these studies must be underway and shown to the FDA as collateral data along with accelerated stability studies. Stability is especially important in pharmaceutical packaging where drug ingredients can be responsible for permanent benefit or detriment to the patient.

The field of simulation modeling is a quickly expanding discipline. The need for all industries to analyze new packaging systems as well as to streamline the profitability of existing systems makes modeling an advantageous route to travel.

In the area of pharmaceuticals there have been two main efforts advanced in the modeling of package/product systems, one of which is the accelerated test technique. In summary, this method seeks to predict product quality (i.e. moisture content) by subjecting the system to extreme temperature and humidity conditions for a period of time and then correlating this data with real time studies to determine a 'multiplying factor' which would equate a given amount of time at high humidity-high temperature conditions with ambient conditions. Often mistaken assumptions of the validity of utilizing 'like' products in place of the original test product yield highly questionable results. These results often point up the limited usefulness of the accelerated test model.

An alternate model has been proposed and utilizes the systems approach to package-product-environment interaction. By characterizing the barrier properties of the intact package and the behavior of the product with respect to moisture and exterior conditions, drug quality may be predicted, thus allowing for the evaluation of specific factors leading to product degradation.

The purpose of this thesis is to examine the usefulness of the calculation method based on a simulation model, as it applies to a unit dose oral solid drug product. Packaging of oral solid drugs into unit dose containers is performed at either the manufacturing plant or at local hospital pharmacies. The manufacturer of the drug often has a staff of packaging professionals available to design the optimal package to protect the product at the lowest cost. The local pharmacist does not have such a staff and often does not even have adequate data concerning product protection requirements or packaging material specifications. In recent years it has been shown that errors in predicting shelf life may arise through the lack of expertise at the hospital pharmacy in repackaging oral solid drugs (Reamer, et al., 1977). For this reason, data concerning the validity of utilizing a moisture content simulation model would provide the pharmacist with a tool for quickly and accurately specifying packaging materials and design at the local hospital. In addition to its application in community pharmacies, this work can also be shown to provide a foundation for developing models for other moisture sensitive products.

REVIEW OF LITERATURE

A review of the significant literature impacting the topic under discussion can best be done by first examining the development of shelf life simulation models in general. Second, by looking at specific articles in the field of shelf life simulation for the pharmaceutical industry, and finally by focusing on the shelf life research done in the repackaging of unit dose oral solid drugs.

Modern day simulation modeling techniques have their origin in the early 1950's. At this time, engineering principles were beginning to be applied in nearly all disciplines. Most researchers acknowledge that Easter (1953) was one of the fathers of accelerated test techniques for food products. He described an accelerated test where the food product was subjected to accelerated and normal conditions and in which a correlation could be established. Often, as has been noted by Manathunya (1976) and Kliment (1979), the accelerated test method is pressed beyond its usefulness by applying the same accelerated test conclusions to different products which appear to be similar.

By incorporating a more engineering-like perspective on the problem of food degradation, a number of researchers have proposed models for food spoilage based on kinetic data and mass transfer properties of packaging materials. A number of models evolved throughout the past 40 years. At first, studies were done which outlined the adsorption of water to critical moisture contents (Oswin, 1945). Critical moisture content is defined as that amount of moisture in a product, beyond which the product becomes unsalable. In the pharmaceutical industry this is generally given to be the point at which the drug is at 90% of its initial potency (Connors, 1979). This method was extended to other food products (Felt et al., 1945; Charie et al., 1963). This model was amplified to include non-enzymatic browning of selected dehydrated foods and a computer model was developed for the spoilage of cabbage (Mizrahi et al., 1970). This model has since been extended to other food systems (Labuza et al., 1972). Similar work was done with dried potatoes and seed (Aguilera et al., 1975; Harrington, 1973). Labuza (1968, 1971) published extensively on the stability of food products based on their moisture content and the kinetic/mass transfer concept of simulation modeling. Later, food degradation modeling was expanded to include oxidative degradation (Simon et. al, 1971). Quast and Karel (1972) developed a mathematical model which examined and predicted the breakdown of potato chips. This model utilizes a computer to aid in the calculation of the interaction of two degradation mechanisms simultaneously. A unique model was proposed by Labuza (1972) that predicted packaging film requirements based on physical and chemical properties of certain space rations. Articles have been written by Karel (1973, 1975), Labuza (1973) and Gyeszly (1980) which describe many of these shelf life concepts and studies.

In 1977 Mizrahi and Karel outlined a model which was not based on information about the kinetic model of food spoilage. Afterwards known as the "no model" method, this process was expanded to describe storage at varying temperatures (1977). Chirife and Iglesias (1978) and Boquet et al. (1978) published studies which described the most common equations for equilibrium moisture isotherms of foods. Resnick and Chirife worked in the area of non-enzymatic browning and published their study in 1979.

The pharmaceutical industry, like all health industries, is especially cautious of relying on a model for prediction of shelf life. The liability of drug products is at least equal to, if not greater than, the liability and assurance level necessary for food products. This industry is, however, just as concerned with quick and labor efficient development and analysis of drug products in order to maximize profits and minimize costs.

Accelerated testing in the pharmaceutical industry began in the 1950's along with food products. A significant advance came with the integration of the Arrhenius equation to the thermodegredation rates of vitamins (Garrett, 1955, 1956). This method was simplified by graphical calculation (Campbell, 1958). The work with vitamin stability was extended and was shown to be reliable (Tardif, 1965). In 1965 a quick method of designing stability charts was described by Lordi and an accelerated test technique to determine appearance changes was described by Catstensen et al. (1964). A 1980 study by Davies examined the errors associated with the accelerated test technique and cautioned on temperature and assay errors becoming significant if the experiment is not properly designed.

Accelerated studies have long been part of the pharmaceutical industry's standard operations. Kinetic information is valuable not only in the stability of the drug product, but also in the effectiveness of the drug once administered. As early as 1965, Lee showed that moisture isotherms are appropriate descriptions for drug products. The Arrhenius technique is prevalent throughout the literature and often drug-specific in the type and method of breakdown (Garrett, 1965; Bentley, 1970; Lachman, 1976). In general, this technique uses the dependence of the rate of degradation of a drug on the storage temperature. The rate of degradation is expressed as a constant 'k' determined by use of the following equation:

$$k = (2.303/t)\log(Co/c) \qquad (1)$$

where Co is the original concentration and c is the concentration at time t. The logarithm of the rate constant (log k) is proportional to absolute (Kelvin) temperature. By determining the rate constants for two or more elevated temperatures, and by plotting log k versus absolute temperature, the rate constant for any temperature can be predicted (Kleinberg, 1980).

Until recently very little application of the above accelerated-kinetic studies have been combined with information concerning packaging and mass transfer properties.

Unit dose packaging of drug products is a relatively new phenomenon. Introduced in the early 1960's, this method quickly gained acceptance as being more convenient for use and dispensing. The repackaging of bulk oral solid drugs into unit dose containers at hospital pharmacies followed closely behind the introduction of manufactured unit dose products. This increase in use was documented in an article by Rhomberg in 1979.

As early as 1972, Grover Bowles warned that care in selecting packaging materials at the hospital pharmacy level must be taken to insure the validity of expiration dates for repackaged drugs. Late in 1977 the American Society of Hospital Pharmacies (ASHP) established guidelines for repackaging of oral solids in single and unit dose packages. One section of the guidelines read as follows:

> The expiration date applied to the package should not be that of the manufacturer's original container but rather should be based on a study of the stability of the drug as repackaged. In the absence of valid stability data, an arbitrary expiration date of not more than 60 days from the date of repackaging, or as defined by FDA or USP, should be used (ASHP, 1977).

In 1977 Reamer and Grady et al. published a report on moisture permeation of selected unit dose repackaging materials. Their study outlined the properties of several unit dose packaging systems in terms of permeability and concluded that none prevented moisture permeation. By the end of 1977 an article by Nold pointed up the significance of this problem at Ohio State University Hospital. In 1978 Reamer and Grady evaluated newer unit dose packaging materials and found that certain materials did give adequate protection, while others, introduced since their 1977 article were much more permeable.

They pointed out the fact that the fabrication of a good unit dose package is not only dependent on materials, but also on maintenance of the equipment, skill of the operator and efficacy of heat or adhesive seals.

In 1979, the ASHP saw fit to revise their guidelines on repackaging of unit dose drug products and eliminated the arbitrary 60 day expiration dating. Gupta et al. published a study in 1980 which showed that, under their conditions of test, two drug products (Mycifradin and Aminophyllin) had gained a significant amount of moisture and changed color before 30 days had elapsed. This study yielded mixed results and was not conclusive. Also in 1979, Veillard related hardness to moisture content in blister packaged unit dose drugs and proposed a method for determining the diffusion coefficient of the blister film, based on the moisture adsorption curves.

A series of studies was published in 1980 and 1981 by Nakabayashi of Takedo Chemical Industries. In these articles he outlined a shelf life prediction method not too unlike the one described in the following pages. Nakabayashi extended this concept to storage stability of sugar coated tablets, aspirin aluminum tablets and to prediction of the aging and disintegration properties of the respective tablets. Finally, a report was presented of work with packaged prednisolone tablets in relation to dissolution properties (Nakabayashi, 1981). Similar work with prednisolone tablets was undertaken and published in 1981 by Taborsky-Urdinola in which the effects of packaging and storage are shown to impact dissolution.

DISCUSSION OF THE CALCULATION BASED ON SIMULATION

The intact package may be thought of as a system consisting of four parts:

1) the exterior environment
2) the package itself
3) the internal environment
4) the product.

Part one, the external environment, is usually in constant flux unless specifically maintained at a particular temperature or relative humidity. Part two is the package itself which is usually made up of material, design, and closure. The package acts as a barrier between the internal and external environments. With polymers, this barrier is semi-permeable and allows moisture to travel through in each direction. This characteristic is described by the water vapor transmission rate (WVTR).

Part three is the internal environment. At first the internal environment is dictated by the conditions under which the package was sealed, but very quickly the internal environment becomes the subject of two forces. One, the water vapor coming into or leaving the internal environment via the package material or seal and two, the controlling effect of the product to either adsorb or desorb water. Part four is the product itself. Originally manufactured with some initial moisture content, the product comes into equilibrium with the internal environment through the gain or loss of water vapor. This equilibrium is described by an equilibrium moisture isotherm which gives the relationship between a particular product moisture content and relative humidity in the internal environment, at a specific temperature.

The driving force for the system is the water vapor partial pressure difference between the internal and external environments. As the low partial pressure seeks to raise itself and the high partial pressure seeks to lower itself by permeation though the package wall, the product gains or loses moisture depending on the relative humidity inside of the package.

Now that a basic understanding of the system has been obtained, the mathematics of permeation and adsorption can be examined and a model constructed.

The total amount of moisture in the package can be described by M1, the moisture in the product and M2 the moisture in the internal environment.

$$MT = M1 + M2 \tag{2}$$

The moisture in the product is described by an equilibrium moisture isotherm (EMI). The isotherm is a curvilinear relationship between the product moisture content and a corresponding relative humidity at a constant temperature. The EMI generally spans the entire range of relative humidities and is linear for most products through the middle regions (i.e. 30% relative humidity to 70% relative humidity). It must be noted, however, that this linearity is entirely product dependent. If the EMI is found to be linear the isotherm can then be described by the equation

$$m = a + b\ (Hi) \tag{3}$$

where m is the moisture content of the product, a is the y intercept of the EMI, b is the slope of the linear portion of the EMI and Hi is the internal relative humidity. The actual amount of moisture in the product is then

$$M1 = m \times (W / 100) \tag{4}$$

where W is the dry weight of the product. Combining equations 3 and 4 gives:

$$M1 = (a + b\ Hi) \times (W / 100) \tag{5}$$

The total amount of moisture in the headspace can be approximated by using the ideal gas law. (Although water vapor is not an ideal gas, the error introduced here is minimal.)

$$M2 = 18 \times (P \times V / R \times T) \tag{6}$$

Where P is the pressure, V is the volume, T is the temperature and R is the ideal gas constant. Since relative humidity is much easier to measure than pressure, one can use the following equation to substitute into the above

$$P = Ps\ (Hi/100) \tag{7}$$

Where Ps is the saturation vapor pressure of water at the given temperature of the test. Substituting we have:

$$M2 = (18 \times V/ R \times T) \times Ps \times (Hi/100) \tag{8}$$

By substituting back into the original equation we have:

$$M_{(t)}=[(a+b \times Hi)\times(W/100)] + [(18\times V/R/T) \times Ps\times(Hi_{(t)}/100)] \tag{9}$$

Where $M_{(t)}$ is the total moisture content at time equals t.

Leaving the total moisture content, and turning to the permeation, by Fick's law we have

$$dQ/dt = (P/l) \times A \times (Pe - Pi) \tag{10}$$

Where dQ is the amount of moisture permeated in terms of time, P is the permeability constant of the material, l is the thickness, A is the area of the package and Pe and Pi are the partial pressures, external and internal respectively.

Substituting the package permeation constant, P_p for (P/l)xA and the relative humidity equivalents for the partial pressure we have

$$DQ = P_p \times (Ps/100) \times (He - Hi) \times Dt \tag{11}$$

Dt is the time step of the equation and must be small.

At any time in the future, the total moisture will be the moisture present in the product and headspace, plus that which permeates in.

$$M_{(t + Dt)} = M_{(t)} + DQ \tag{12}$$

Now substituting the equations for $M_{(t)}$ and $M_{(t+Dt)}$ into the above equation and solving for the internal relative humidity at time (t + Dt) gives

$$Hi_{(t+Dt)} = Hi + (DQ/[(Wxb/100)+(18xVxPs/RxTx100)]) \tag{13}$$

This completes the derivation. By finding the initial relative humidity using the equation

$$Hi\ (0) = (mi - a)/b \tag{14}$$

and then substituting DQ into the above equation the new internal relative humidity can be calculated. This will then become the relative humidity at time t=t as a new calculation is made.

The model makes use of time steps to approximate reality. During a single time step the temperature and relative humidity are assumed to remain constant. By using time steps it is easy to see how temperatures and relative humidities may be changed throughout the product/package storage time and these changes be reflected in the calculation based on simulation equations.

MATERIALS AND METHODS

Materials

Two different commercial drug products were selected for this study, Aminophyllin T-200 which is a bronchodilator and Mycifradin T-500 which is an antibiotic. Both of these drug products are moisture sensitive and both are often repackaged in hospital pharmacies. The package selected for this study was a strip pack fabricated on an In-Pack System III (In-Pack Systems, Mount Vernon, Ohio). This package is a form-fill-and-seal style with a paper/poly/foil/poly bottom and a clear saran coated cellophane/poly top. See Table 1 and Table 2 for specification.

Table 1. Bottom layer material specification

Raw Material	Caliper (inch)
25 # MG paper	.002 +/- 10%
LDPE	.0005 +/- 10%
.00035 Foil	.00025 +/-10%
RB 7 Primer	-
LDPE	.001 +/- 10%

Finished Target Caliper = .00385

Table 2. Top layer material specification

Raw Material	Caliper (inch)
Saran Coated Cellophane	.0007 +/- 10%
RB 7 Primer	-
LDPE	.0015 +/- 10%

Finished Target Caliper = .0022

Determination of initial moisture content (IMC)

The initial moisture content can be defined as the amount of moisture in the product at the time of packaging. There are many different methods used to determine the initial moisture content, some of which are: (i)drying with $P_2 O_5$ desiccant; (ii)extracting or volatilizing the water in the product with an organic solvent; (iii)freeze drying at room temperature; (iv)hot air oven or vacuum oven drying; or (v) physical-chemical techniques. Most of these methods are based on determining the weight before processing, driving off the water, and then reweighing to determine the amount of weight lost. In this study a vacuum oven was used to determine initial moisture content and then these values were confirmed by a series of Karl Fischer titrations.

No less than six samples of each drug product were placed in aluminum containers and weighed. Approximately 3 grams of Mycifradin and 2 grams of Aminophyllin were used. The containers were then placed in a National vacuum oven at 100° C and 25 mm Mercury for 2.5 hours. The percentage of moisture content on a dry weight basis was then determined from the amount of weight lost by using the following equation

$$IMC\ (\%\ dry) = [\ (Wi - Wf)/Wf\ ] \times 100 \qquad (15)$$

where Wi is the initial weight of the product sample and Wf is the final weight of the product sample after drying.

Since the true initial moisture content figure is critical to the correct application of the simulation model, the Karl Fischer titration technique for determining moisture content was also used to verify the results from the gravimetric method. The Karl Fischer technique is based on the reaction of a reagent with water to produce a distinct chemical change which is then electrochemically detected by an aquameter. The Titration was performed on a Precision Scientific Co. Aquatrator Model TS-68810 according to the procedure given in the manufacturer's manual. In summary, the water in a sample dispersed in an anhydrous solvent such as methanol is titrated directly with a reagent containing iodine, sulfur dioxide, pyridine, and methanol (Mitchell, 1948). A simplified stoichiometry of the reaction is shown below:

$$2\ H_2O + SO_2 + I_2 \longrightarrow H_2SO_4 + 2\ HI$$

In the presence of pyridine, added to combine with the acid to make the equation one way, we have:

$$2\ H_2O + (C_5H_5N)_2 \cdot SO_2 + I_2 + 2\ C_5H_5N \dashrightarrow (C_5H_5N_2) \cdot H_2SO_4 + 2\ C_5H_5N \cdot HI$$

Equilibrium Moisture Isotherms

Equilibrium moisture isotherms, also called sorption isotherms, describe a relationship between the relative humidity of the system and the moisture content of the product. One increasingly popular way of establishing constant relative humidities is with the use of saturated aqueous salt solutions. The characteristics of the salt regulates the water vapor pressure in the environment surrounding the saltwater slush. By carefully selecting different salts, a complete range of relative humidities may be created. Certain care must be taken in the preparation of the saturated salt solution so that no salt is left unsaturated above the liquid line and so that there is an excess of undissolved crystals in the solution. The area of contact between the vapor space and the solution must be as large as possible and the vapor space in the container should be as small as possible.

Eight relative humidity chambers were constructed for three temperatures. Table 3 outlines the salts used and their corresponding relative humidities at the specific temperatures employed. A hygrometer was utilized to check the validity of the literature in describing the relative humidity associated with salts used in this test. The rate of equilibration after opening the container was also checked with the hygrometer and found to be approximately 20 minutes. No less than four half-gram samples of product were placed in each chamber after weighing. These samples were left to equilibrate for two weeks and then weighed again. A final weighing was made a week later to insure that the product had indeed come to equilibrium with the relative humidity.

Table 3. Salts and their associated Relative Humidities

Salt	52^oF	76^oF	100^oF
$(NH_4)_2SO_4$	81.0	80.0	79.1
NaCl	75.7	75.4	75.1
$NaNO_2$	67.4	64.5	61.7
NaBr	62.3	58.0	53.7
K_2CO_3	44.3	43.8	43.4
$MgCl_2 \cdot 6\ H_2O$	33.7	32.8	31.8
$KC_2H_3O_2$	23.6	22.9	21.4
LiCl	11.1	11.1	11.1

Water Vapor Transmission rates (WVTR) and package permeation constant

By modifying ASTM method E96-66, the water vapor transmission rate (WVTR) of the package was determined (ASTM, 1972). Eight packages containing desiccant pellets were weighed and placed in a constant relative humidity chamber. Five additional packages which did not contain pellets were also stored in each chamber to serve as controls. A special set of plexiglass frames were designed to keep the individual unit dose packages separated and open to the 'atmosphere' inside of the chamber. The construction of these frames is shown in Figure 1. The packages were weighed at intervals over a 310 hour storage time. The weight gain was then determined at each temperature utilizing two relative humidity conditions. The following equation yields the moisture gain (Mg) by the desiccant at time t given initial (i) values:

$$Mg = (PP - B)_t - (PP - B)_i \tag{16}$$

Where PP is the weight of the packaged product and B is the weight of the blank or control.

Fill weight of the container

The weight of product in the container was determined by subtracting the average pouch weight from the individual weights of the intact packages. The average of these differences was then calculated. The moisture content at the time of packaging was

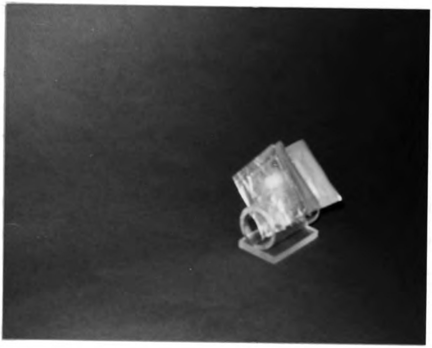

Figure 1. Storage frame photograph

assumed to be equal to the initial moisture content since little time had elapsed between determination of the IMC and packaging.

Headspace volume of the package

It is difficult to determine the headspace of flexible packages because of their three dimensional changes due to pressure and volume. A method was devised, however, where packages containing the product were opened with a small slit. Fine grain sand was poured into the package without deforming or bulging the sides. The sand was then poured out and measured to determine the headspace of the package. Ten replicates for each product were done. As will be seen in the results section, the amount of moisture contained in the headpsace is minimal and does not greatly influence the calculation based on simulation.

Test conditions of actual experimental testing

Four relative humidities were selected to describe a broad range of relative humidity values. Saturated salt solutions were prepared in beakers, and the beakers placed in one gallon containers equipped with tight fitting lids. These containers were placed in three constant temperature environments. One temperature represented ambient conditions in a controlled environment laboratory and two in walk-in cabinets. Ten unit dose packages of each drug product and five blanks were placed in the relative humidity container. These samples were left to equilibrate for varying amounts of time before being weighed and moved to a different temperature-relative humidity combination. Approximately three to four days were spent at each condition. At the end of each period the unit dose containers were weighed and the net weight gain was determined. The samples were rotated through the complete combination of four relative humidities and three temperatures. At each condition the relative humidity and the temperature were held constant. The conditions, time and weight gains are listed in Tables 14 and 15.

Determination of experimental moisture content

The calculation of experimental moisture content can be done by first obtaining the dry weight of the product at time equal zero. This is accomplished through use of the following formula:

$$Do = Wo / [1+(mi/100)] \qquad (17)$$

Where Do is the dry weight of the product at time t=0 in grams. W_o is the initial weight of the product in the unit dose package at t=0 and mi is the initial moisture content of the product calculated on a dry weight basis (g moisture / 100 grams dry product).

The moisture content for a given weighing can be calculated from the following equation:

$$Mc\ (time=t) = [\ (Wt - Do)/Do\ ] \times 100 \qquad (18)$$

Where Wt is the weight of the product in the unit dose package at time

= t in grams. Do is the dry weight of the product as calculated above and the Mc (time=t) is the moisture content at the weighing time t.

CALCULATIONS

Permeability constant of the package

The equations which determine the calculation by simulation utilize the permeability constant of the package. This constant is assumed to be independent of humidity, but dependent upon temperature. Determination of the package permeability constant is done by assuming that the water vapor pressure in the unit dose packages containing the desiccant is essentially zero during the course of the study. By dividing the slope of the linear portion of the permeation rate curve by the partial pressure difference, the permeation constant can be expressed in terms of grams/hour x mm Hg for a specific package system.

Slope and intercept of the EMI

The linear portion of the equilibrium moisture isotherm can be fit to a straight line having the equation $M = a + bHi$ by linear regression.

Moisture content prediction by the calculation based on simulation

A program utilizing the equations described and the experimental data determined was written for the Tandy TRS-80 Model III

Microcomputer. Values for all necessary parameters were entered into the computer and a suitable time step (Dt) was established. A copy of the actual program is presented in Figure 10 located in the Appendix.

RESULTS AND DISCUSSION

Initial moisture content

The data for the initial moisture content determinations are presented in Tables 4 and 5. The optimum drying conditions were established in preliminary experiments where samples were withdrawn at predetermined intervals and moisture content of the product was determined. A drying time of two hours was found to provide acceptable data, as can be seen from the values listed in the tables. The standard deviations are relatively small which allows for confidence in these data. It is very crucial to the entire experiment that the initial moisture content data is accurate, since the equilibirium moisture isotherms are dependent on these values, as is the simulation model itself.

Table 4. Initial moisture content - Aminophyllin

Initial Weight(g)	Initial Dish (g)	Final Weight(g)	Final Dish (g)	Moisture Content (g H_2O/100 g dry product)
2.0628	.9480	1.9995	.9476	5.98
2.0346	.9552	1.9744	.9548	6.04
2.0382	.9563	1.9738	.9560	6.30
2.0428	.9552	1.9798	.9546	6.09
2.0259	.9494	1.9615	.9488	6.30
2.0169	.9455	1.9517	.9450	6.43

Average Initial Moisture Content: 6.19 g H_2O / 100 g dry product
Standard deviation: ±.18 g H_2O / 100 g dry product

Table 5. Initial moisture content - Mycifradin

Initial Weight(g)	Initial Dish (g)	Final Weight(g)	Final Dish (g)	Moisture Content ($g\ H_2O/100\ g$ dry product)
3.1026	.9759	2.9986	.9756	5.13
3.1360	.9800	3.0225	.9799	5.55
3.0866	.9643	2.9715	.9544	5.74
3.1224	.9733	3.0209	.9733	4.96
3.0739	.9583	2.9780	.9581	4.76
3.1306	.9630	3.0219	.9629	5.27

Average Initial Moisture Content: 5.23 g H_2O / 100 g dry product
Standard deviation: $\pm$.37 g H_2O / 100 g dry product

Table 6. Karl Fischer Titration Results (Average of 5 runs)

Aminophyllin	6.66 g H_2O /100 g dry wt. product
Mycifradin	5.86 g H_2O /100 g dry wt. product

Initial moisture values determined by the Karl Fischer Titration are presented in Table 6. By comparing the initial moisture content values for the respective drug products determined by titration with those values arrived at gravimetrically, it can be seen that there is a good agreement.

Equilibrium moisture isotherms

Tables 7 and 8 give the numerical data for the equilibrium moisture content of Mycifradin and Aminophyllin under the conditions

Table 7. Equilibrium Moisture Isotherm - Aminophyllin

Temperature = 77 ^{o}F

Relative Humidity (%)	Moisture Content (g H_2 0 / 100 g dry product) Adsorption
12.0	4.25
24.4	4.71
32.8	4.91
43.8	5.52
53.9	6.87
64.0	7.54
75.4	8.63
80.0	10.97

All moisture content values are the average of four samples.

Table 8. Equilibrium Moisture Isotherm - Mycifradin

Temperature = 77 ^{o}F

Relative Humidity (%)	Moisture Content (g H_2 0 / 100 g dry product)	
	Adsorption	Desorption
12.0	6.08	7.45
24.4	7.96	12.76
32.8	9.84	13.67
43.8	12.11	14.34
53.9	14.39	15.06
64.0	18.80	18.80
75.4	28.48	27.43
80.0	30.66	32.07

All moisture content values are the average of four samples.

of the test. The isotherms are shown in Figure 2 and 3, where moisture content (g H_2O/100 g dry wt. product) is plotted as a function of relative humidity. Earlier studies indicated no significant difference between isotherms at 52^o, 77^o, and 100^oF. As shown, the equilibrium moisture isotherm data yielded expected results. The adsorption curves were linear from 10 % relative humidity to about 65 % relative humidity and then showed and exponential increase in slope. The slope for the linear portion of the curve was obtained by liner regression analysis and the correlation coefficients were .95 and .99 respectively. This shows that the slope, which is used in the simulation model, will give an acceptable relationship between the relative humidity and the moisture content of the drug products.

Package WVTR and permeability constant

WVTR data was obtained at three temperatures and at least two humidities. The resultant data is presented in Tables 9 and 10. Table 9 gives the net weight gain of the packaged desiccant at each time period of weighing. Table 10 gives the final calculated results of the permeability constants for the packages. Graphic representations of this data are shown in Figures 4, 5 and 6.

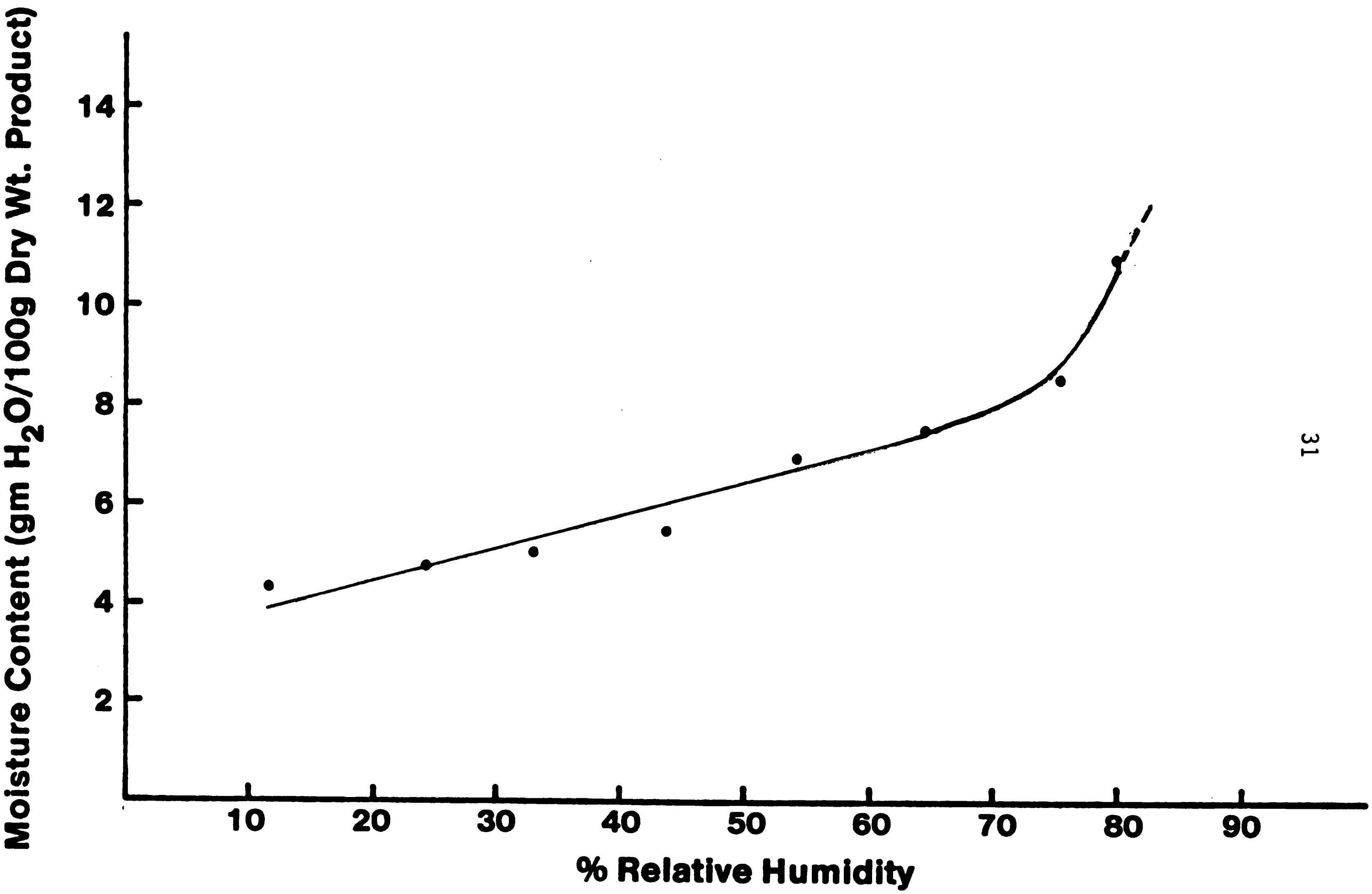

Figure 2. Equilibrium moisture isotherm - Aminophyllin

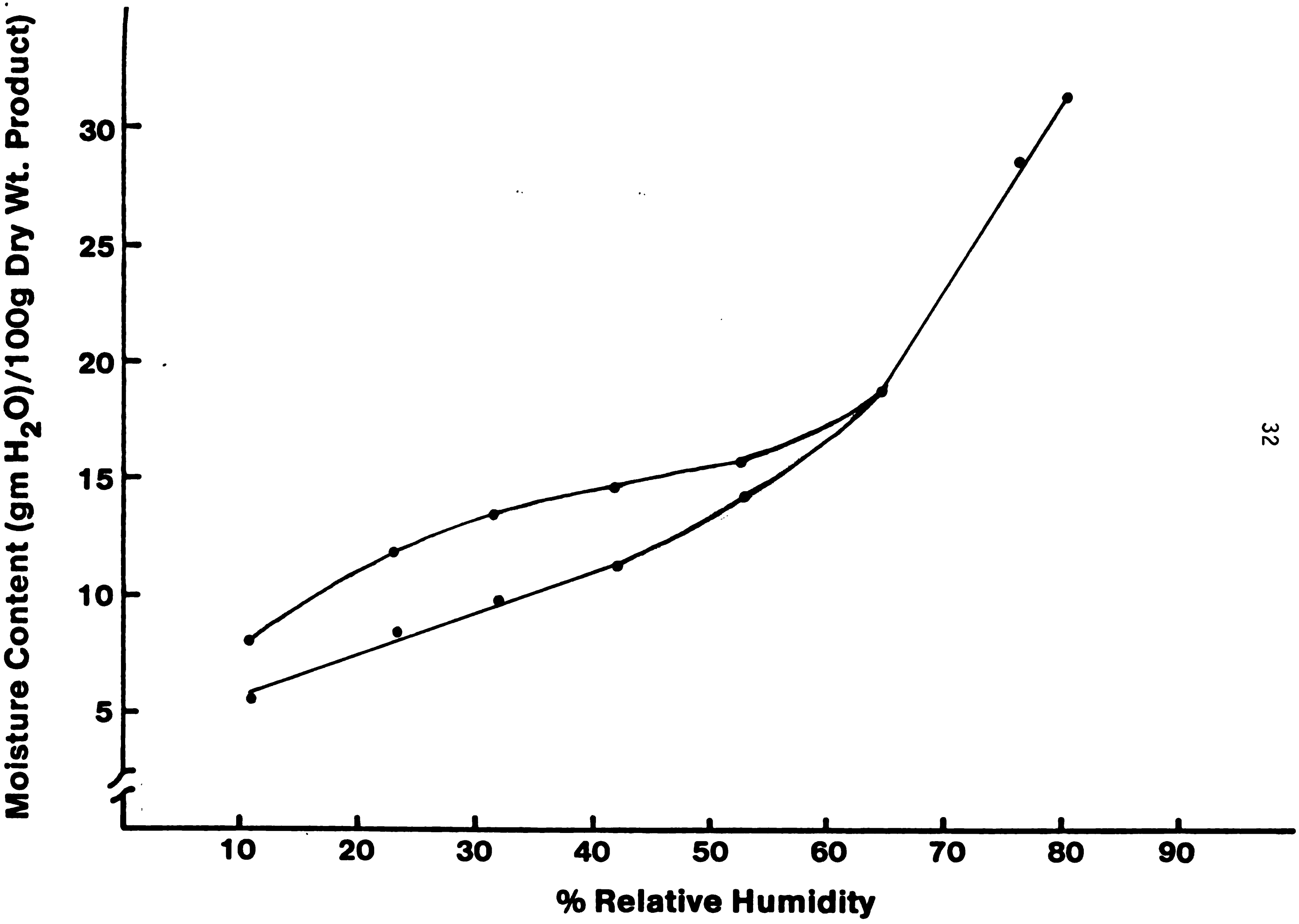

Figure 3. Equilibrium moisture isotherm - Mycifradin

Table 9. WVTR - Net weight gain of packaged desiccants (g)

Temperature = 52 ^{O}F

Time(hours)	Relative Humidity 44.3%	Relative Humidity 62.3%
0	0	0
48	.0003	.0000
144	.0005	.0001
240	.0012	.0007
336	.0016	.0014
504	.0033	.0036
720	.0044	.0052

Temperature = 76 ^{O}F

Time(hours)	Relative Humidity 43.8%	Relative Humidity 58.0%
0	0	0
48	.0008	.0006
120	.0019	.0020
144	.0023	.0021
192	.0028	.0026
288	.0044	.0052
312	.0050	.0058

Temperature = 100 ^{O}F

Time(hours)	Relative Humidity 43.5%	Relative Humidity 53.7%	Relative Humidity 75.1%
0	0	0	0
48	.0006	.0007	.0009
120	.0121	.0153	.0196
144	.0139	.0165	.0224
192	.0152	.0181	.0240
288	.0168	.0202	.0273
312	.0175	.0212	.0288

Table 10. WVTR and Package permeability constants

Temperature (^oF)	Relative Humidity (%)	WVTR (g/hr/package)	Package Permeability Constant (g/hr x mmHg /pkg)
52	44.3	8.34×10^{-6}	1.36×10^{-6}
	62.3	8.64×10^{-6}	1.30×10^{-6}
			Average = 1.33×10^{-6}
76	43.8	1.60×10^{-5}	1.59×10^{-6}
	58.0	2.07×10^{-5}	1.56×10^{-6}
			Average = 1.57×10^{-6}
100	43.5	7.22×10^{-5}	3.38×10^{-6}
	53.7	8.38×10^{-5}	3.17×10^{-6}
	75.1	1.19×10^{-4}	3.22×10^{-6}
			Average = 3.26×10^{-6}

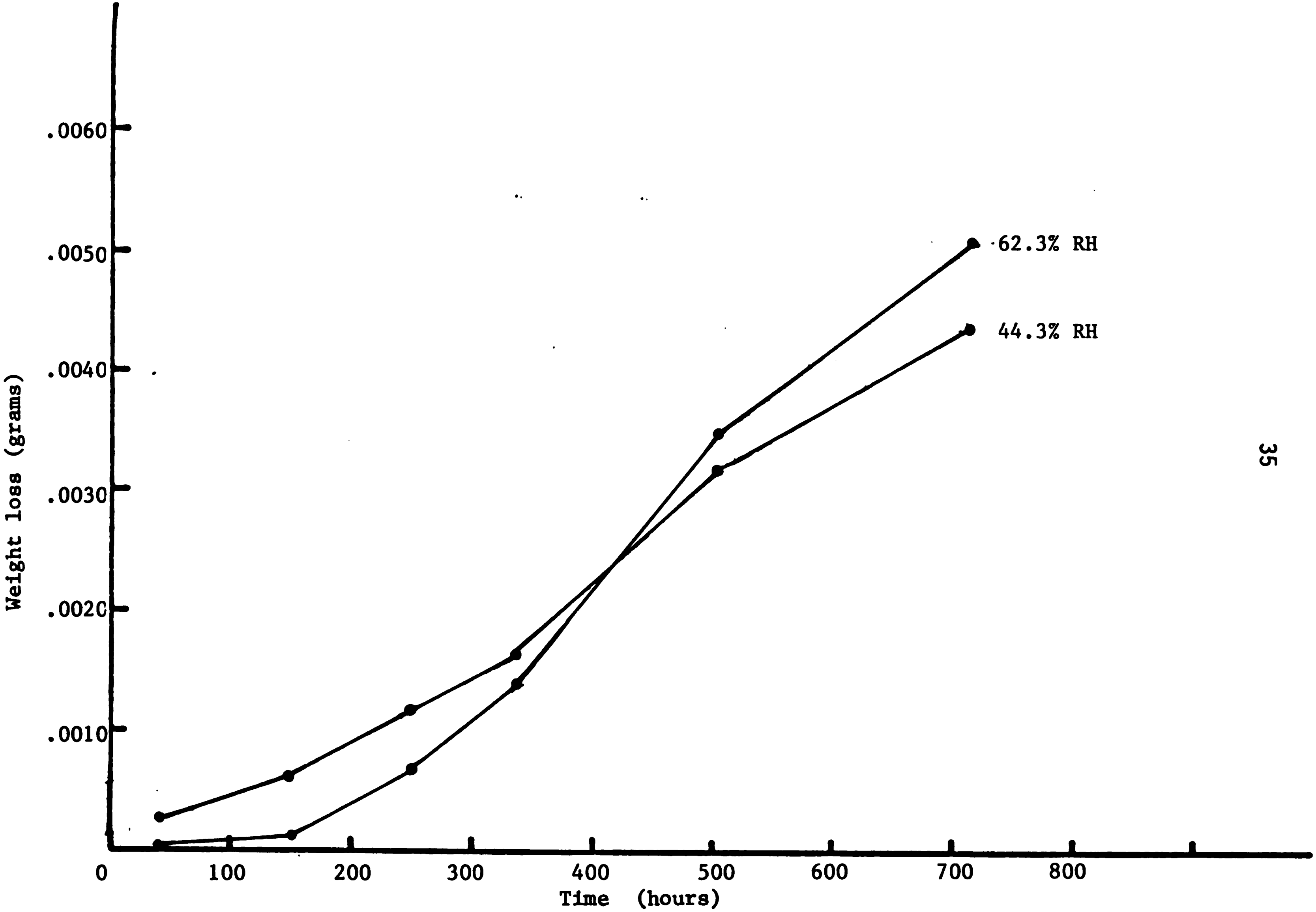

Figure 4. WVTR curves for 52 ^{O}F

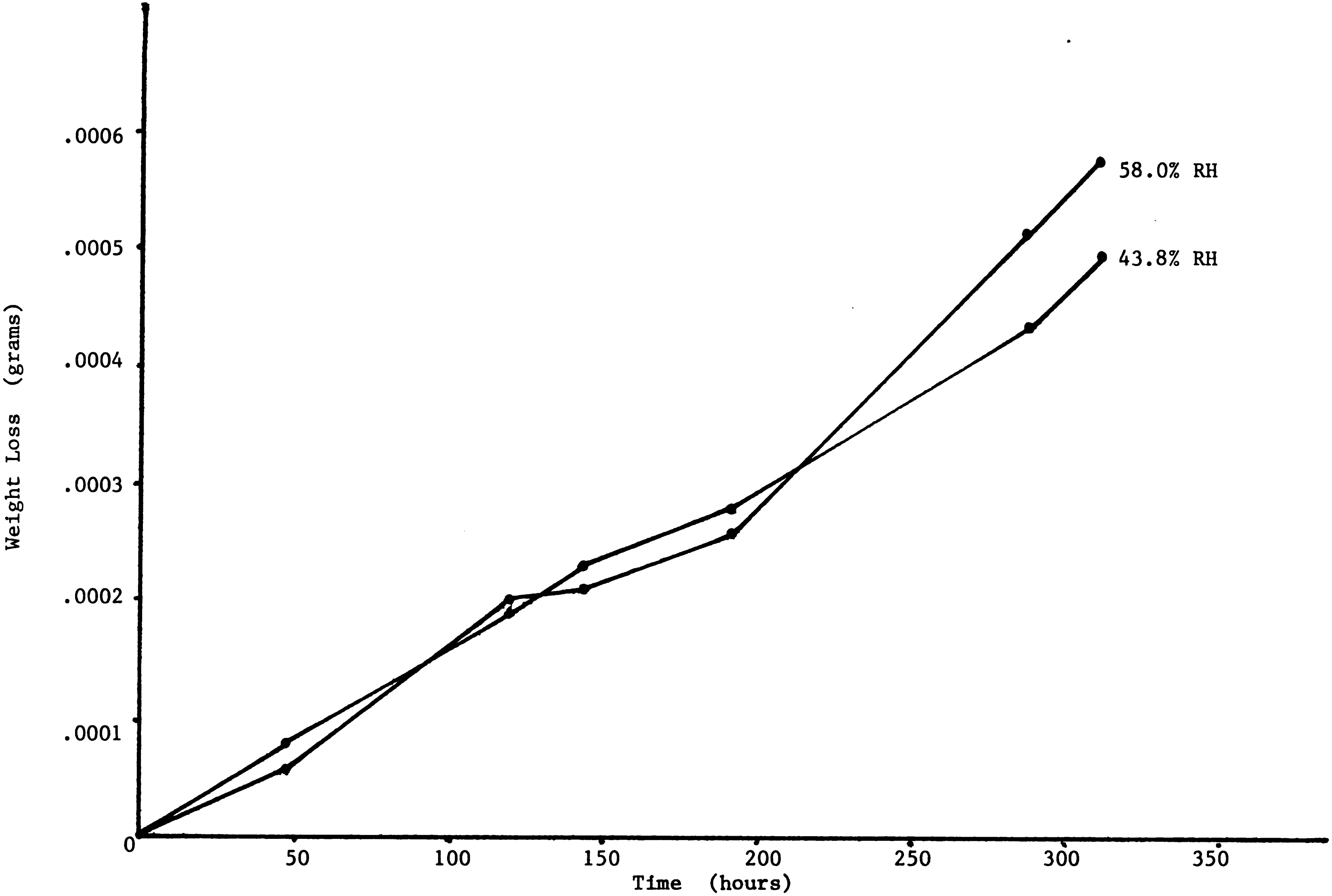

Figure 5. WVTR curves for 76 °F

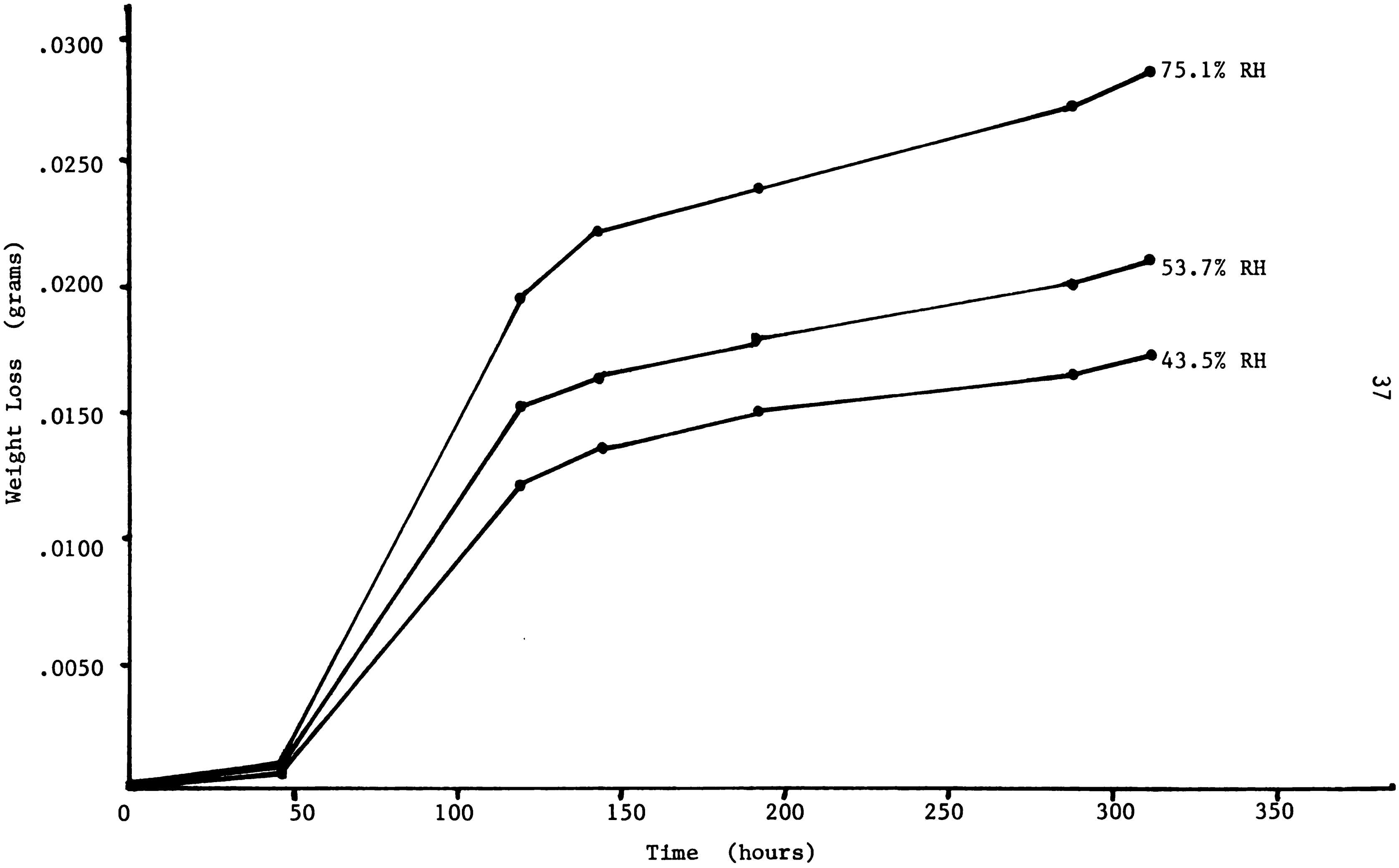

Figure 6. WVTR curves for 100 ^{o}F

The accuracy of this data is also demonstrated from the Arrhenius calculation, where a plot of 1/temperature (^{o}K) vs. the log of the permeability constant is made. Numerical data for this relationship is given in Table 11. The correlation coefficient is .93 which shows that the permeation data indeed follows known kinetic theory.

It is also important to note that, under conditions of the test, no significant differences were found between permeability constants obtained at differing relative humidities at the same temperature. Because of the hydrophilic nature of cellophane in the saran coated cellophane top of the unit dose package, it was thought that the packages would not behave in a linear manner with respect to water vapor transmission. Under this scenario the cellophane would attract moisture to such an extent as to increase the permeation through the upper film. This was found not to be the case, as the data shows that the permeation constant is indeed constant within the relative humidity range tested.

Fill weight and headspace measurement

The fill weight and the headspace measurement were both done as described in the experimental methods sections. Data obtained by these methods are given in Table 12.

Table 11. Arrhenius data

Temperature ^{o}F	^{o}K	1/temperature ^{o}K	Permeability Constant (g /hour x mmHg)
52	284	.00352	1.33×10^{-6}
77	297.4	.00336	1.575×10^{-6}
100	310.8	.00322	3.26×10^{-6}

Equation of the linear regression fit: $y = -1452 - 1268 x$
Correlation coefficient: .93

Table 12. Fill weight and headspace measurement

	Aminophyllin	Mycifradin
Average package fill weight (g)	.2146	.5022
Average package headspace (cm^3)	2.6	2.2

Note: These values are the average of ten samples.

Correlation of the calculation based on simulation with actual experimental testing

Table 13 illustrates the actual and predicted values for Aminophyllin. Table 14 does the same for Mycifradin. The 12 intervals with their corresponding temperature and relative humidity conditions are presented on the left. The actual experimental run is then compared with the moisture content value predicted from the simulation model. Figures 7 and 8 illustrate these values.

There is good agreement of the actual with predicted values for the Mycifradin samples. The Aminophyllin samples, however, have much less agreement. Upon reflection, it was determined that the adsorption equilibrium moisture isotherm was actually a hybrid of adsorption and desorption phenomena for the Aminophyllin group. The initial moisture content of Aminophyllin is at 6% and this corresponds to a relative humidity of around 40%. Therefore, when the EMI was generated, the samples that went into relative humidities lower than 40% were desorbing, while those higher than 40% were adsorbing. This same phenomena did not occur with Mycifradin as its initial moisture content corresponds to about 9% relative humidity and so all environments for the EMI determination would be adsorptive. These differences undoubtedly affected the results.

As can be seen from the graph, the predicted values seem not as responsive as the actual system. The amplitude of change is greater in the experimental run when compared with the predicted values. The percent error, however, is well within expected limits considering the variability of the material, weighing accuracy and environmental changes. The largest percent error in the Aminophyllin run was 15.3%, while the largest percent error associated with the Mycifradin run was only 8.7% and many predictions were well below this value.

The validity of the calculation based on simulation model is demonstrated by both the Aminophyllin and Mycifradin runs.

Table 13. Actual and predicted Aminophyllin moisture content

	Temp. (^{o}F)	RH(%)	Time(hrs)	Moisture Content (g H_2O / 100 g dry product)		Percent Error
				Actual	Predicted	
1	52	11.1	121.5	6.91	6.22	10.0
2	52	44.3	210.5	6.69	6.21	7.2
3	52	62.3	383.5	6.54	6.28	4.0
4	52	75.7	477.5	6.48	6.34	2.2
5	77	11.1	521.0	6.50	6.28	3.4
6	77	43.8	567.0	7.40	6.27	15.3
7	77	58.0	624.0	6.88	6.29	8.6
8	77	75.4	671.5	6.88	6.35	7.7
9	100	11.1	719.0	6.48	6.17	4.8
10	100	43.8	768.0	6.56	6.16	6.1
11	100	53.7	816.5	6.83	6.20	9.2
12	100	75.1	862.5	7.30	6.34	14.1

Table 14. Actual and predicted Mycifradin moisture content

	Temp. (^{o}F)	RH(%)	Time(hrs)	Moisture Content (g H_2O / 100 g dry product)		Percent Error
				Actual	Predicted	
1	52	11.1	121.5	6.87	6.57	4.4
2	52	44.3	210.5	6.64	6.62	0.3
3	52	62.3	383.5	6.61	6.79	2.7
4	52	75.7	477.5	6.70	6.90	3.0
5	77	11.1	521.0	6.89	6.89	0.0
6	77	43.8	567.0	6.99	6.96	0.4
7	77	58.0	624.0	7.11	7.08	0.4
8	77	75.4	671.5	7.14	7.23	1.3
9	100	11.1	719.0	7.38	7.17	2.8
10	100	43.8	768.0	7.86	7.39	6.0
11	100	53.7	816.5	8.32	7.69	7.6
12	100	75.1	862.5	8.92	8.14	8.7

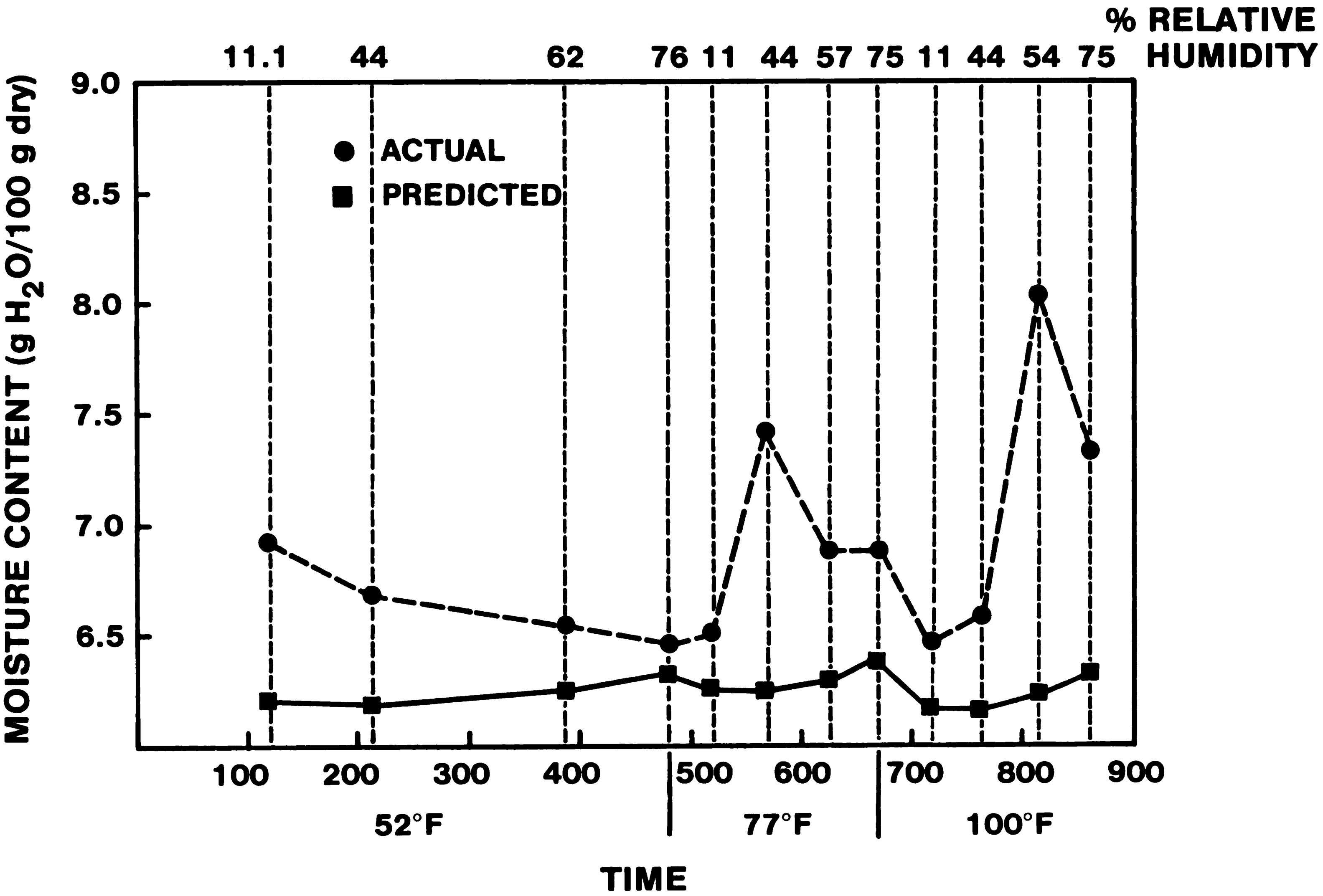

Figure 7. Actual and predicted moisture content - Aminophyllin

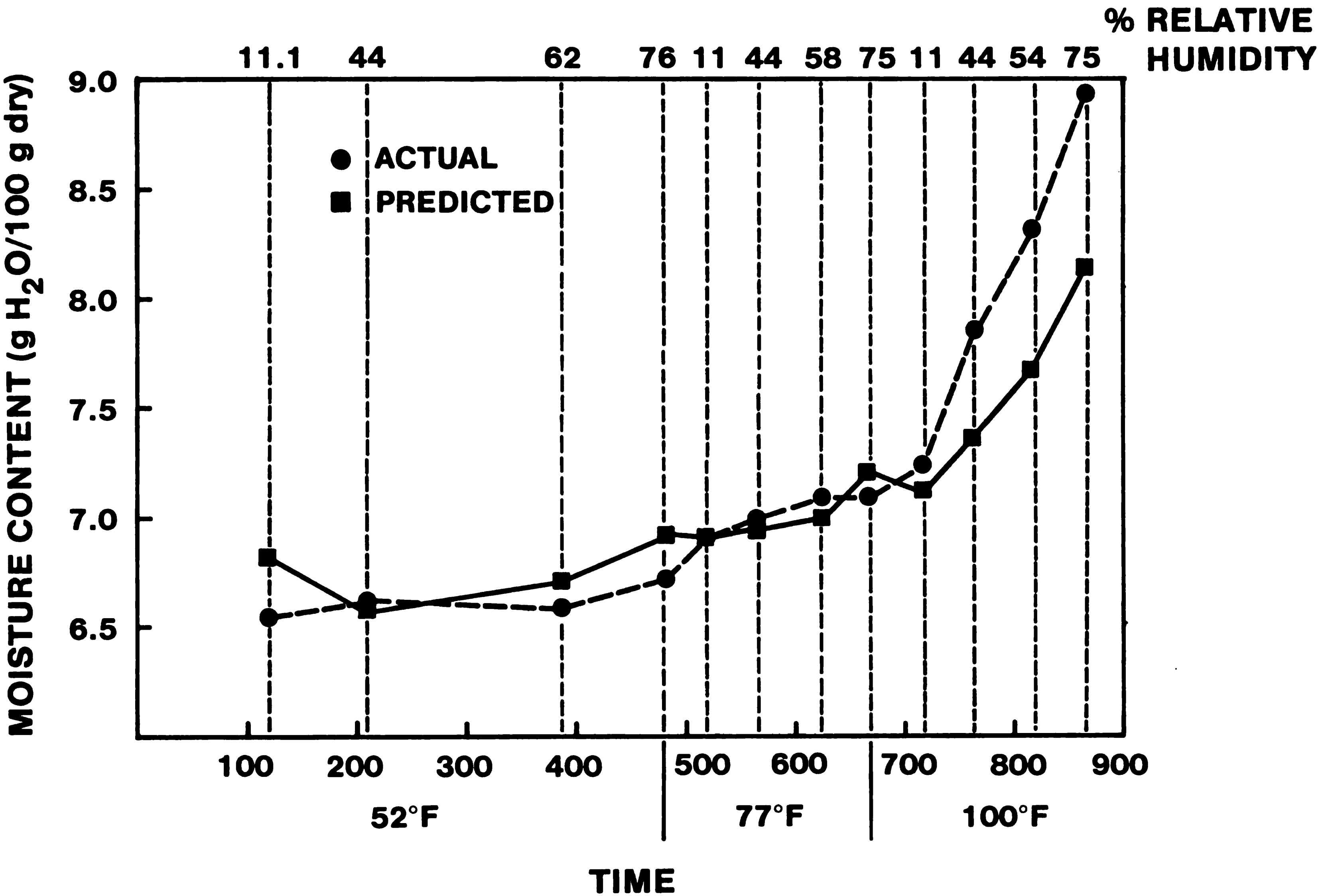

Figure 8. Actual and predicted moisture content - Mycifradin

EXPERIMENTAL ERROR

The experimental errors involved in this study can be divided into i) errors associated with initial moisture content, equilibirium moisture isotherm, package permeability, packaging material and fabrication, storage conditions, ii) errors associated with sampling and iii) errors inherent in the assumptions made in developing the model.

As has been noted earlier, the determination of the initial moisture content is key to the proper functioning of the model and to the establishment of an accurate equilibrium moisture isotherm. Care was taken in the weighing and drying of samples when the gravimetric analyses were employed. However, adsorption of moisture by the dried tablets between the oven and the balance is a possibility which can introduce error. The evolution of volatile vapors from the drug products during drying could also cause the initial moisture content to be calculated as higher than the true value. The Karl Fischer titration method has an associated error of +/- .05 milliliter of reagent and is considered to be very accurate if adequate precautions are taken to dry the reaction beaker and stirring bar.

The equilibrium moisture isotherm data is subject to the same associated errors as will be covered later under storage conditions. In addition to this, the assumption is made that a straight line is an appropriate relationship for the EMI between 11% and 65% relative humidity.

The package permeability data is dependent upon the packaging material, fabrication and storage conditions. The packaging material may have minute, invisible pinholes which promote permeant 'flow' instead of actual mass transport or true permeation. The material thickness is also not uniform. As with most materials used in the packaging industry, a variance of between 10 and 20% is not uncommon. In addition, the lamination may not be uniform in either the layers of polymer, foils or primers.

The fabrication, in this case the seal and the perforation, may not be uniform for all of the samples. The temperature of the heat sealing grips may fluctuate before the thermostat reactivates the heating elements.

The storage conditions consisted both of the saturated salt relative humidity chambers and the constant temperature laboratory and cabinets. The saturated salt solutions, although universally accepted, are liable to certain errors. Chemical impurity of the salts, lack of adequate non-dissolved salts, and dried salts above the solution all have great impact on the relative humidity that is created (Hygrodynamics, 1963). Of special significance is the temperature. For this study, the temperature was controlled by the laboratory and cabinet. These devises had normal fluctuation of two degrees. According to the literature, if there is a difference of two degrees between the solution and the temperature of the vapor space above the solution, this can result in a five percent error in relative humidity. Finally, literature relating specific salts to specific relative humidities often vary as much as 1.5% (Hygrodynamics, 1963).

Certain errors were associated with the methods used for sampling. In order to weigh the product in the equilibrium moisture isotherm analysis or the final product-in-package run, the samples had to be removed from the constant humidity chambers. This introduced an error into the chamber and a certain length of time elapsed before the chambers reestablished equilibrium.

Finally, assumptions made, which allow the model to be developed, may be a possible source of error. One assumption is that the rate of permeation of moisture into the drug product is more rapid than permeation through the packaging material. Although reasonable, this was not tested during the experiment.

SUMMARY AND SUGGESTIONS FOR FURTHER WORK

This study shows the validity of the simulation modeling technique for adequately predicting the moisture content of two solid unit dose drug products under fluctuating storage conditions. By first obtaining data concerning the permeation characteristics of the package, the equilibrium moisture isotherm of the product and the initial moisture content of the product, it is possible to model the behavior of the packaged product over a number of intervals of varying temperature and relative humidity. Although specific to these drug products, this technique has implications for other pharmaceutical products such as liquid unit dose packages, multiple dose packages, overwrapped unit dose containers as well as to other products such as food, cosmetic or seed systems.

Further research could examine distribution applications of the model such as primary package placement within a shipper or pallet load (with respect to moisture pick up) or accuracy of the model in predicting the moisture content of actual shipments using warehouse, distribution system and climatic data. Product degradation due to oxidation could also be studied. An experiment could be designed that would compare the adsorption of water by powdered vs. tableted drug products to discover the surface area dependency of the model.

In conclusion, the calculation based on simulation method is a scientific approach to solving the problem of moisture content prediction without using costly storage stability or unreliable accelerated test techniques.

APPENDIX

APPENDIX

```
10 '     Program Kliment10
15 '
20 '        VARIABLES USED IN THIS PROGRAM
30 'N$=Name of the product     A0=Initial Y intercept
31 'B0=Initial slope           IMC=Initial moisture content
32 'T1=Beginning of the interval T2=time at end of interval
33 'DT=delta T - length of the time step
34 'P=Package Permeability Constant
35 'T=Temperature in degrees Kelvin
36 'PS=Water vapor Pressure       HE=external relative humidity
37 'HI=internal relative humidity
38 'V=Staging variable
39 'MC=moisture content
40 '
90 CLS:INPUT "INPUT THE NAME OF THE PRODUCT";N$
92 PRINT:INPUT"INPUT THE INITIAL WEIGHT OF THE PRODUCT (in grams)";W
94 PRINT:INPUT THE HEADSPACE VOLUME FOR THE PACKAGE IN cubic
   centimeters";V
100 INPUT "FOR THE INITIAL TEMPERATURE, PLEASE INPUT THE Y INTERCEPT
    OF THE EMI CURVE";A0
110 INPUT "FOR THE INITIAL TEMPERATURE, PLEASE INPUT THE SLOPE
    OF THE EMI CURVE";B0
120 INPUT "INPUT THE INITIAL MOISTURE CONTENT"; IMC
130 HI=(IMC-A0)/B0
140 CLS
150 PRINT "INPUT THE TIME IN HOURS AT THE BEGINNING OF THIS INTERVAL"
155 PRINT "NOTE:  THIS SHOULD NOT BE EQUAL TO THE TIME AT THE END OF
    THE LAST INTERVAL"
158 INPUT T1
160 PRINT "INPUT THE TIME IN HOURS AT THE END OF THIS INTERVAL"
161 PRINT"
    TO END THE PROGRAM INPUT 0":INPUT T2
162 IF T2 = 0 THEN END
165 INPUT" INPUT THE DT -length of the time step";DT
170 CLS:PRINT "FOR THIS INTERVAL OF CONSTANT RH AND TEMPERATURE
    PLEASE GIVE THE FOLLOWING DATA:"
180 PRINT:INPUT "PACKAGE PERMEABILITY CONSTANT (in g/hr mmHg)";P
190 INPUT"TEMPERATURE IN DEGREES KELVIN";T
200 INPUT"CORRESPONDING WATER VAPOR PRESSURE"'PS
210 PRINT:INPUT"THE EXTERNAL RELATIVE HUMIDITY":HE
220 PRINT"PRINT"FOR THIS TEMPERATURE, INPUT THE FOLLOWING EMI DATA:"
```

```
230 INPUT"INPUT THE Y INTERCEPT";A
240 INPUT"INPUT THE SLOPE";B
270 LPRINT"   "N$
280 LPRINT"TEMPERATURE deg K = " T "    EXTERNAL RH = "HE
285 LPRINT"TIME ELAPSED hrs.  INTERNAL RH PRODUCT MOISTURE CONTENT"
290 PRINT"TIME ELAPSED hrs.  INTERNAL RH PRODUCT MOISTURE CONTENT"
300 FOR I = T1 TO T2 STEP DT
310     DQ=(HE-HI)*DT*P*PS/100
320     V=(W*B/100)+((18*V*PS)/(R*T*100))
330     HI+HI+(DQ/V)
340     MC=A+B*HI
350     LPRINT"           "I"            "HI"                "MC
355     PRINT"           "I"            "HI"                "MC
360 NEXT I
370 LPRINT;LPRINT
380 GOTO 140
```

LIST OF REFERENCES

LIST OF REFERENCES

Aguilera, J.M., Chirife, J., Flink, J., and Karel,M. 1975. Computer simulation of non-enzymatic browning during potato dehydration. Lebensm. Wiss. U. Technol. 8:128.

American Society of Hospital Pharmacists 1977. Guidelines for repackaging oral solids and liquids in single unit and unit dose packages. Am. J. Hosp. Pharm. 34:1355.

American Society of Hospital Pharmacists 1979. ASHP guidelines for repackaging oral solids and liquids in single unit and unit dose packages. Am. J. Hosp. Pharm 36:223-4.

American Society of Testing and Materials. Part 20. Standard test method for water vapor transmission of materials in sheet form. (1972).

Bentley, D. 1970. Statistical Techniques in predicting thermal stability. J. Pharm. Sci. 4:464-8.

Boquet, R., Chirife, J., and Inglesias, H. A. 1978. Equations for fitting water sorption isotherms of foods: Part II. J. Food Technol. 13:319.

Bowles, G. 1972. Expiration dating needed to ensure medication's potency, safety, stability for use. Mod. Hosp. 119:130.

Carstensen, J. T., Johnson, J. B., Valentine, W., Vance J. J. 1964. Extrapolation of appearance of tablets and powders from accelerated storage tests. J. Pharm. Sci. 53:1050-54.

Charie, H. J., East, E., and Van der Veen, W. 1963. Effect of moisture on storage properties of dehydrated food products. Proc. 1st Int'l Congress on Food Sci. and Technol. 1:45.

Chirife, J. and Iglesias, H. A. 1978. Equations for fitting water sorption isotherms of foods: Part 1--A review. J. Fd. Technol. 13:159.

Clark and Hudson 1968. Accelerated stability tests: Practical considerations in their conduct and analysis. Manf. Chem. Aer. News 39:25-27.

Connors, C. A., Amidon, G. L. and Kennon, L. 1979. Chemical stability of pharmaceuticals - a handbook for pharmacists. John Wiley & Sons, New York.

Davies, O. L. and Budgell, D. A. 1980. Accelerated storage tests on pharmaceutical products: effect of error structure of assay and errors in recorded temperature. J. Pharm. Sci. 32:155-159.

Easter, R. A. 1953. Forecasting shelf-life. Mod. Pkg. 2:128.

Felt, C. E., Buechele, A. C., Borchardt, L. F., and Koehn, R. C. 1945. Determining shelf-life of packaged cereals. Cereal Chem. 22:261.

Garrett, E. R. 1956. Prediction of stability in pharmaceutical preparations II. Vitamin stability in liquid multivitamin preparations. J. Pharm. Sci 45:171.

Garrett, E. R. and Carper, R. R. 1955. Prediction of stability in pharmaceutical preparations I. Color stability in a liquid multisulfa preparation. J. Pharm. Sci. 44:515.

Gupta, V. D., Stewart, K. R., Gupta, A. 1980. Stability of oral solid drugs after repackaging in single unit containers. Am. J. Hosp. Pharm. 32:165,169.

Gyeszly, S. W. 1980. Shelf life simulation. Package Engr. June 1980 25:70.

Harrington, J. F. 1973. Packaging seed for storage and shipment. Seed Sci. and Technol. 1973:701.

Hygrodynamics 1963. Technical Bulletin No. 5 Creating and maintaining humidities by salt solutions. Am. Inst. Co. Silver Springs, Maryland.

Karel, M. 1973. Quantitative analysis of food packaging and storage stability problems. Am. Inst. Chem Eng. 69:107.

Karel, M. 1975. Protective packaging of foods. In "Physical Principles of Food Preservation.:" Ed. Karel, M., Fennema, O. R., and Lund, D. B., p. 399. Marcel Decker, New York.

Kirkwood, T. B. L. 1977. Predicting the Stability of Biological Standards and Products. Biometrics. 33:736-742.

Kleinberg, M. L., Stauffer, G. L., and Latiolais, C. J. 1980. Stability of five liquid drug products after unit dose repackaging. Am. J. Hosp. Pharm. 37:680-2.

Kliment, R. 1979. Prediction of moisture content of packaged dry food products by a calculation based on simulation. Mich. ST. U. School of Pkg. thesis.

Labuza, T. P. 1968. Sorption phenomena in foods. Food Technol. 22:263.

Labuza, T. P. 1971. Kinetics of lipid oxidation in foods. CRC Crit. REv. Food Technol. 2:355.

Labuza, T. P. 1972. Nutrient losses during drying and storage of dehydrated foods. CRC Crit. Rev. Food Technol. 3:217.

Labuza, T. P. 1973. Effect of dehydration and storage. Food Technol. 27:21.

Labuza, T. P., Mizrahi, S., and Karel, M. 1972. Mathematical models for optimization of flexible film packaging of foods for storage. Trans. of the ASAE., 150.

Lachman, L., Lieberman, H. A., Kanig, J. L. 1976. The theory and practice of industrial pharmacy. 2nd ed. Lea and Febiger, Philadelphia. pp. 32-77.

Lee, Sumtung, DeKay, H. G. and Banker, G. S. 1965. Effect of water vapor pressure on moisture sorption and the stability of aspirin and ascorbic acid in tablet matrices. J. Pharm. Sci. 54:1153-58.

Lordi, N. G and Scott, M. W. 1965. Stability charts - design and application to accelerated stability testing of pharmaceuticals. J. Pharm. Sci. 54:531-37.

Manathunya, V. 1976. Predictions of shelf life of packaged cereal by an accelerated test technique and a mathematical model. Mich. St. U. School of Pkg. thesis.

Mitchell, J. and Smith, D. M. 1948. Aquametry. Interscience Publishers, New York.

Mizrahi, S. and Karel, M. 1977. Accelerated stability tests of moisture-sensitive products in permeable packages by programming rate of moisture content increase. J. Food Sci. 42:958.

Mizrahi, S. and Karel, M. 1977. Accelerated stability tests of moisture sensitive products in permeable packages at high rates of moisture gain and elevated temperatures. J. Food Sci. 42:1575.

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

Mizrahi, S., Labuza, T. P., and Karel, M. 1970. Feasibility of accelerated test for browning in dehydrated cabbage. J. Food Sci. 35:804.

Nakabayashi, K., Shimamoto, T., Mima, H. 1980. Stability of packaged solid dosage forms I. Shelf life prediction for packaged tablets liable to moisture damage. Chem. Pharm. Bull. 28:1090-1098.

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

Nakabayashi, K., Shimamoto, T., Mima, H. 1980. Stability of packaged solid dosage forms III. Kinetic studies by differential analysis on the deterioration of sugar-coated tablets under the influence of moisture and heat. Chem Pharm. Bull. 28:1107-1111.

Nakabayashi, K., Tsuchida, T., Mima, H. 1981. Stability of packaged solid dosage forms IV. Shelf life prediction of packaged aspirin aluminum tablets under the influence of moisture and heat. Chem Pharm. Bull 29:2027-34.

Nakabayashi, K., Shimamoto, T., Mima, H., Okada, J. 1981. Stability of packaged solid dosage forms V. Predictions of the effect of aging on the disintegration of packaged tablets influenced by moisture and heat. Chem. Pharm. Bull 29: 2051-56.

Nakabayashi, K., Hanatani, S., Shimamoto, T. 1981. Stability of packaged solid dosage forms VI. Shelf life prediction of packaged prednisolone tablets in relation to dissolution properties. Chem. Pharm. Bull. 29:2057-61.

Nold, E. G., Tschampel, M., Stauffer, G. 1977. Stability of drugs repackaged into unit dose containers. Am. J. Hosp. Pharm. 34:1294.

Oswin, C. P. 1945. The kinetics of package life. Jr. Soc. Chem. Ind. Trans. 64:419.

Quast, D. G. and Karel, M. 1972. Computer simulation of storage life of foods undergoing spoilage by two interacting mechanisms. J. Food Sci. 37:679.

Reamer, J. T. and Grady, L. T. 1978. Moisture permeation of newer unit dose repackaging materials. Am. J. Hosp. Pharm. 35:787-793.

Reamer, J. T., Grady, L. T., Shangraw, R. F. and Mehta, A. M. 1977. Moisture permeation of typical unit dose repackaging materials. Am J. Hosp. Pharm. 34:35-52.

Resnick, S. and Chirife, J. 1979. Effect of moisture content and temperature on some aspects of non-enzymatic browning in dehydrated apple. J. Food Sci. 44:601.

Rhomberg, M. 1979. More unit dose products are forecast. Am. J. Hosp. Pharm. 36:1728,30.

Simon, I. B., Labuza, T. P., and Karel, M. 1971. Computer-aided predication of food storage stability: Oxidation deterioration of shrimp product. J. Food Sci. 36:280.

Taborsky-Urdinola, C. J., Gray, V., Grady, L. T. 1981. Effects of packaging and storage on the dissolution of model prednisone tablets. Am. J. Hosp. Pharm. 38:1322-7.

Tardif, R. 1965. Reliability of accelerated storage tests to predict stability of vitamins (A, B_1, C) in tablets. J. Pharm. Sci. 54:281-84.

United States Pharmacopeia 1975. Stability considerations in dispensing practise. 19:708.

Veillard, M., Bentejac, R., Duchene, D., Carstensen, J. T., 1979. Moisture transfer tests in blister package testing. Drug Dev. Ind. Pharm. 5:227-244.

Washburn, E. W. 1926. International Critical Tables. McGraw-Hill Book Co. Inc. New York. 1:67-68.