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PREDICTING THE MOISTURE UPTAKE OF TABLETS PACKAGED IN SEMIPERMEABLE BLISTER PACKAGES AND STORED UNDER STATIC CONDITIONS OF TEMPERATURE AND HUMIDITY

presented by

JOHN STEVENSON FULCOLY

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PREDICTING THE MOISTURE UPTAKE OF TABLETS PACKAGED IN SEMIPERMEABLE BLISTER PACKAGES AND STORED UNDER STATIC CONDITIONS OF TEMPERATURE AND HUMIDITY

By

John Stevenson Fulcoly

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ABSTRACT

PREDICTING THE MOISTURE UPTAKE OF TABLETS PACKAGED IN SEMIPERMEABLE BLISTER PACKAGES AND STORED UNDER STATIC CONDITIONS OF TEMPERATURE AND HUMIDITY

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A simulation modeling technique is presented that predicts the moisture gain of a packaged product. The moisture isotherm of the product and the water vapor permeability of the package are measured and incorporated into the model with values representing the environmental severity.

The study provides improvements over previous reports in that 1) it presents a detailed description of methods to accurately measure the package WVTR, tablet moisture isotherm, and moisture uptake of packaged product; 2) further, a new technique of using a mathematical fit to describe the moisture isotherm is presented; 3) and a computer program was used requiring a minimum of data entry that enables the differences between isotherm expressions to be evaluated.

The simulated results agree well with experimentally measured moisture gain of tablets packaged in three different materials. A discussion is included that presents several applications of the simulation technique that lead to a timely cost effective package development program.

DEDICATION

This thesis is dedicated to my family, especially to my parents, Mr. and Mrs. Joseph E. Fulcoly, Jr.. Their love and support gave me the strength and spirit to complete this project. Their values have served as an example for me to follow, and have contributed to the success of this achievement as well as to other areas of my personal growth.

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INTRODUCTION

A package designed to contain a pharmaceutical product must insure the product's safety and efficacy from time of manufacture until time of use by the consumer. The responsibility for developing an appropriate package rests with the packaging development team, who in an appropriate time, must evaluate the protective properties of the package while considering economic, manufacturing, and marketing concerns. This ~~thesis~~ will present a cost and time efficient method for evaluating the protective capability of a unit-dose blister package.

A blister package may be required to provide protection from light, oxygen, moisture, and in some cases physical abuse. The most common feature desired in a unit-dose blister, intended to contain a tablet or capsule, is moisture protection. Protection from moisture is important since it is often the determinant of product stability and performance (Hollenbeck, 1982). Water may act as a reactant in drug degradation, or serve as a solvent providing a medium for degradation reactions to proceed in (Carstensen, 1980). The adsorption of moisture by a tablet may also influence such physical properties as hardness and friability, cause swelling, affect dissolution rate, and promote color change.

Techniques used for evaluating the stability of a product stored in a unit-dose package include long-term ambient storage tests, accelerated "stress" tests, and more recently, shelf-life simulation modeling. Present FDA regulations require three year ambient data to support a three year expiration date. To wait three years is not only a financial burden, but may lead to poor product success due to a late launch allowing a competing product to capture some of the market.

To facilitate earlier product submissions, the FDA will accept accelerated test data in support of shorter expiration dates. This allows a company to get a product on the market with a short expiry, and as more data become available, the expiration date may be increased. The test conditions of three months storage at 40^{o}C, and 80% RH are accepted to support two year dating. Therefore many companies design packages that will survive these accelerated conditions. A problem with this approach is that by designing a package that provides adequate protection at the accelerated conditions, the resulting package may offer more than adequate protection at ambient conditions. Gyeszly (1977) has discussed the problems associated with comparing accelerated data to ambient performance. The "overpackaging" that can result from this technique leads to unnecessary material costs. Additionally, to change the package, one must repeat the entire process to satisfy regulatory requirements. Accordingly, a procedure that can identify the performance of a package prior to initiating stability studies will result in considerable time and cost savings.

Predicting shelf-life involves combining expressions for product sensitivity, package effectiveness, and environmental severity into a mathematical model. When dealing with a moisture sensitive tablet, the key parameters include tablet hygroscopicity, package water vapor transmission rate (WVTR), temperature, and relative humidity. The model is capable of predicting the moisture content of the product at any time. Therefore, by knowing the maximum allowable moisture content, the shelf-life can be determined.

Once an appropriate model has been developed it can be used as a tool for preliminary screening of packages. For example, by measuring the (WVTR) of several packages and applying the results to the predictive model, one can ascertain which package will perform most satisfactorily in the long run. Alternately, knowing the critical moisture content and the desired shelf-life, the model can be used to determine the required package permeability. A valuable application of the model is the ability to predict the performance of the same package-product system at more than one condition, enabling one to make direct correlations between accelerated data and ambient performance. This kind of insight can lead to financial savings by selecting the most efficient packages for stability testing and avoiding the need to test additional package systems that later will be proved unsatisfactory.

The predictive capability of the modeling technique makes it suitable for early appraisals of the cost-effectiveness of potential packages. For example, is the additional shelf-life provided by a vinyl-aclar blister over a saran-coated vinyl blister worth the approximately forty percent added material cost? Also it could be that a less expensive, lower barrier material package is suitable for the dry arid conditions of the Middle East, whereas a more protective barrier is required for a hot humid region such as South America. It is the desire to answer questions such as these in a timely and cost efficient manner that provides the impetus for the investigation into shelf-life prediction models.

A technique is described in this thesis for predicting the moisture gain of tablets packaged in semipermeable blisters and stored under static conditions of temperature and humidity. As will be described in the Background section of this thesis, most of the literature to date on predicting moisture gain of packaged products has been directed primarily to foods with a limited number of investigations involving drug formulations. The methods developed in this thesis have been used to predict the moisture gained by tablets stored in three different packages under static conditions. The results show excellent agreement between the predicted and experimentally measured moisture contents. The method is time and cost efficient, since easily measured package and product properties are used in the predictive model. The technique enables one to optimize package requirements, and thereby prevent overpackaging at an early point in the package development program.

BACKGROUND

Investigations into predicting shelf-life began in the mid-forties when Oswin (1946) developed a model to predict the adsorption of moisture by a food to a defined critical limit. Similarly, Felt et al. (1946) predicted the storage-life of cereals based on moisture gained to a critical value related to texture. The Felt model included expressions for package permeation, product formulation and the prevailing storage relative humidity. Paine (1963) extended this work to predict the shelf-life of cigarettes. A model formulated by Salwin and Slawson (1959) predicted equilibrium moisture contents of components of dried food mixes stored in impermeable containers. This work was expanded by Iglesias et al. (1979) to enable a similar prediction for dried food mixes packaged in permeable containers.

Throughout the late sixties and early seventies, extensive research was carried out at the Massachusetts Institute of Technology (MIT) on the subject of using models to predict shelf-life. While previous studies had emphasized predicting moisture gained to a critical content related to physical properties such as crispness and flowability, the MIT studies began to examine the prediction of chemical deterioration caused by moisture and gas permeation.

Simon (1969) developed a computer program to predict storage stability of fruit based on the amount of gas in the headspace. Mizrahi (1970) predicted the extent of browning in dehydrated cabbage as a function of moisture uptake. Quast and Karel (1972) predicted the extent of oxidation in packaged potato chips due to oxygen and moisture permeation. Karel and Labuza (1969) developed shelf-life prediction models for dehydrated foods in conjunction with the development of packages for the NASA Space Program.

Labuza (1972) reviewed mathematical models available for package optimization of foods for storage. The status of models for predicting quality loss of packaged foods was updated by Saguy and Karel (1980). Only in the last few years has the prediction approach been applied to pharmaceutical products. Nakabayashi et al. (1980a,b,c,d,e) predicted both physical and chemical changes of tablets packaged in semipermeable blister packages. Included in this work were predictions of tablet hardness, chemical assay, color, disintegration, and dissolution rate as they relate to moisture change. Kentala et al. (1982) used a computer simulation to predict the moisture gained by tablets repackaged at the hospital pharmacy level.

Jagnanden (1980) predicted the extent of drug degradation of packaged aspirin using an inverse phase gas chromatographic technique.

A model intended to predict moisture change of a packaged tablet must describe two phenomena, transport of water through the packaging material, and adsorption of water by the drug product. The permeation of water vapor through a polymeric film can be described by Fick's First Law of Diffusion and Henry's Law of Solubility, and depends on the permeant concentration gradient that exists across the film. Most of the early prediction models used relatively simple expressions for describing the transport of moisture through the package and onto the food. Felt et al. (1945) described moisture permeation through a film by equation (1).

$$W = R \times A \times T \times (pi - po) \qquad (1)$$

where: W = the weight of water transferred (grams)

R = the permeance of the barrier material (grams/cm2-day-mmHG)

A = permeable area of the package (cm2)

T = time (days)

pi = vapor pressure of higher humidity atmosphere (mm Hg)

po = vapor pressure of lower humidity atmosphere (mm Hg)

More recently Peppas (1980a) applied a more detailed mathematical analysis to the transport properties of polymer films. He described the transport of moisture through a hydrophobic film by equation (2)

$$Nw = Pw\ (Cwi - Cwe) \tag{2}$$

where: Nw = total mole flux of water (moles/cm^2·s)

Pw = film permeability to water (grams-mil/100 in^2·day·cm Hg)

Cwi = concentration of water inside the package (moles/cm^3)

Cwe = concentration of water outside the package (moles/cm^3)

For this investigation equation (3) was used to describe the transfer of water through semipermeable blister packages.

$$dQ/dt = Pp \times Ps/100 \times (He - Hi) \tag{3}$$

where: Q = the quantity of water transferred (grams)

t = time (days)

Pp = the package permeability constant (grams/pkg-day-Atm)

Ps = the saturated vapor pressure at the test conditions (Atm)

He = the external relative humidity (%)

Hi = the internal relative humidity (%)

The vapor pressure inside the package will be determined by the equilibrium moisture sorption isotherm of the packaged product. The moisture isotherm is a plot of the moisture content of the product versus relative humidity. In early models, and some of the more recent studies described by Geyesly (1977) and Kentala (1982), the isotherm was described by an equation for a straight line function as illustrated by equation (4).

$$m = b \times RH + c \tag{4}$$

where: m = moisture content (grams water/100 grams solids)

b = the slope of the line (m/%RH)

RH = relative humidity

c = the y intercept

Both Labuza et al. (1972) and Peppas (1980a) have reported that the straight line interpretation is limited in scope, and is best suited for low values of RH. Peppas and Khanna (1980b) compared five isotherms for effective range of application. They reported that of the five isotherms studied, (BET, Langmuir, Halsey, Oswin, and Freundlich), the Halsey isotherm described the water sorption by foods over the widest humidity range (11% to 90%). The Halsey isotherm is shown in equation (5).

$$\ln aw = -ax(m)^{-r} \tag{5}$$

where: aw = water activity

m = grams water

a,r = constants

This investigation uses three mathematical fits to the data to represent the moisture isotherm. The first equation used was the straight line equation described earlier. The region of the isotherm between 35 and 80% RH was used to calculate the line equation and subsequently, accurately describes the isotherm only in that range of humidities. At high humidities the straight line equation yields lower than actual moisture content, and at low humidities higher than actual moisture contents are calculated.

The subsequent expressions used to describe the moisture sorption of the tablet were found by fitting the experimental data to second and third order polynomial. This approach was found to describe the adsorption of moisture by the tablets over the humidity range of 11 to 90% RH. The second order polynomial is shown as Equation (6), and the third order polynomial is described by Equation (7).

$$m = A + Baw + Caw^2 \tag{6}$$

$$m = A + Baw + Caw^2 + Daw^3 \tag{7}$$

where: m = moisture content (grams per 100 grams solids)

aw = water activity

A,B,C,D = constants found by data fitting

The incorporation of the permeation and sorption equations into a predictive model is described in the Experimental section, and the solution of the sorption equations is discussed in the Results section.

MATERIALS

Tablets

Tablets used in this study were supplied by G.D. Searle Inc., Chicago, IL. The composition of the tablets is propietary. The tablets were round with a diameter of 9.0 mm, and an average weight of 200 mg.

Packages

Foil-backed blister packages constructed of three different materials were investigated. The materials of construction are listed in Table 1. The dimensions of the capsule shaped blisters are shown in Figure 1. Blister strips, and foil lidding, were supplied by Paco Packaging, Lakewood, NJ.

Salts

Saturated salt solutions were prepared to maintain constant relative humidities inside dessicators. Binary salt solutions were selected that would provide a range of relative humidities (RH) from 11 to 90 percent as reported by Greenspan (1976). The salts, and the humidities they maintain at 40^{o}C are listed in Table 2.

Table 1. Flexible materials.

Material	Manufacturer
Polyvinylchloride, 7.5 mil, MCFD 1025	Tenneco, Inc.
Polyvinylchloride/Polyvinlidene (saran) coating, 8.0 mil	Allusuisse
Polyvinylchloride/Polyethylene/ Aclar, 10 mil	Gravure Flex
SBS Paper/Foil/Vinyl coating, 1 mil	American Can

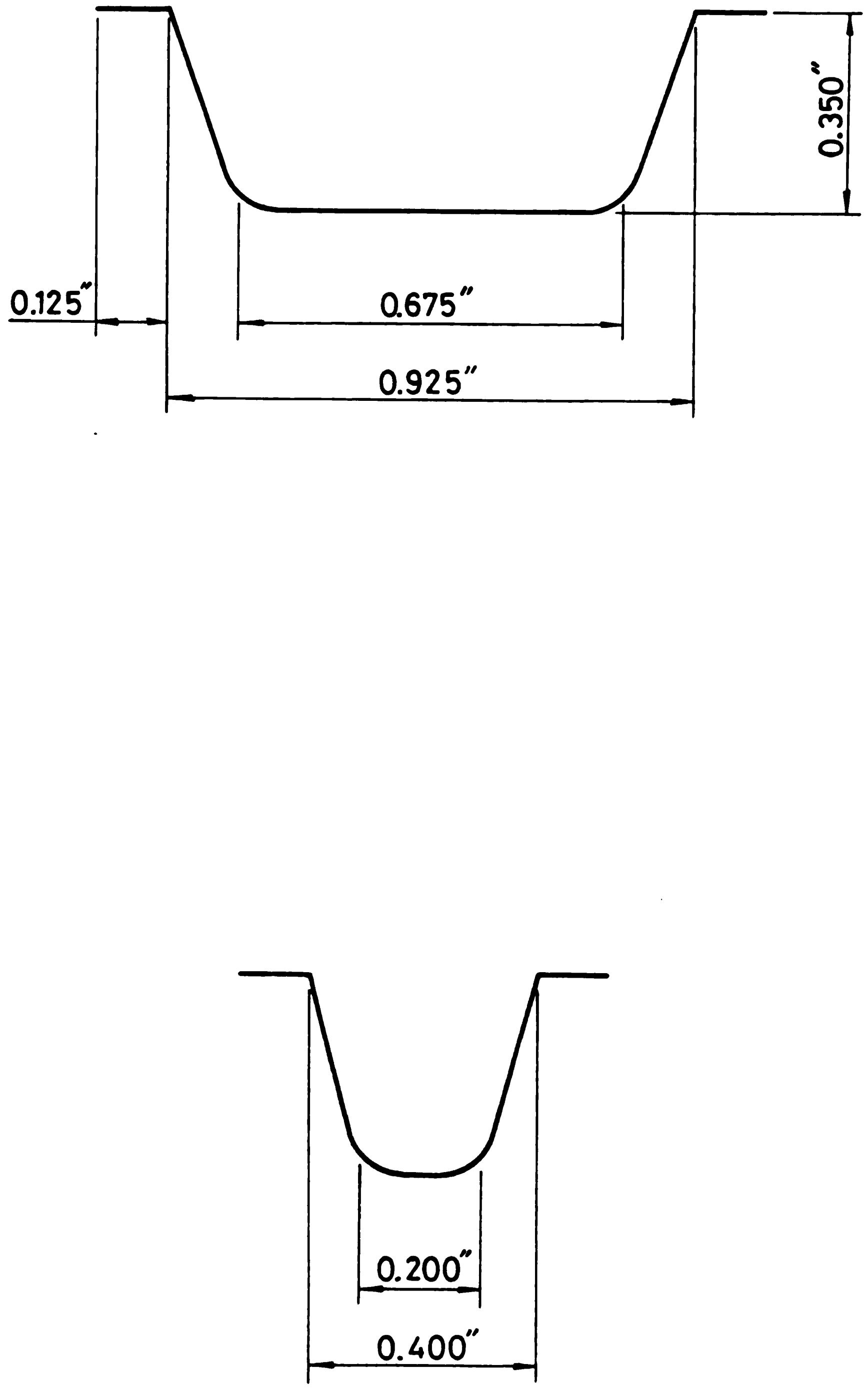


Figure 1. Blister package dimension.

Table 2. Relative humidity of salt solutions at 40^{o}C.

RH[1]	Salt
11.21	Lithium Chloride Granules
33.60	Magnesium Chloride, 4 Hydrate Crystals
48.42	Magnesium Nitrate, 6 Hydrate Crystals
71.00	Sodium Chloride Crystals
89.03	Potassium Nitrate Crystals

[1]Based on values reported by Greenspan (1979).

Water

Water used in preparing the salt solutions was distilled and deionized.

Dessicant

Grade 944 indicating pellets, part number 944-08-X1746, supplied by Hunt Sales Company, Phoenix, MD, were used in the package water vapor transmission determination.

Glass Beads

Solid glass beads (6 mm), supplied by Scientific Products, McGraw Park, IL were used as control fill in the package water vapor transmission determination.

Glassware

KIMEX crystallizing dishes, 6.5 cm x 12.5 cm, manufactured by Kimble, Chicago, IL, were used to contain the salt solutions. Tablets used for determining the moisture isotherm were contained in 7 ml capacity weighing bottles with ground glass stoppers, also manufactured by Kimble.

EQUIPMENT

Balance

A Mettler (Hightstown, NJ) model H51 analytical balance, sensitive to the nearest 0.01 milligram, was used for all weighings in the study.

Desiccators

Space-Saver desiccators manufactured by Bel-Art Products (Pequannock, NJ) were used in the study. These were plastic desiccators measuring 10.75 inches in diameter, and 12.25 inches high, with neoprene O-ring seals.

Environmental Cabinet

A Lunaire (Williamsport, PA) model CL0632-4 environmental cabinet set at $40^{o}C$, and 80% RH was used in the study.

Heat Sealer

A Paco (Lakewood, NJ) model 153 heat sealer set at $275^{o}F$, and 2 sec dwell was used to seal the paper-foil lid stock to the blisters.

Leak Tester

An ARO (Buffalo, NY) model F099-1110-1 leak tester was used to test for seal integrity. Samples were exposed to a 15 inch vacuum for 30 seconds.

EXPERIMENTAL

Initial Moisture Content

The initial moisture content of the tablets was determined by Karl Fisher Titration. Tablets (15) were crushed, transferred into 3 weighing spoons, and placed into titration beakers. Each sample was titrated to the end point with Karl Fisher reagent. The average percent moisture was reported on a (w/w) basis.

Salt Solutions

Salt solutions were prepared by heating approximately 100 ml of water to 50^{o}C in a crystallizing dish. Salt was slowly added while stirring with a glass rod until no more would dissolve. The solutions were set in desiccators which were placed in the environmental cabinet. The solutions were monitored for one week to assure saturation. Where necessary salt or water was added so that a layer of salt (.25 inch) was always visible under a layer of water (.50 inch).

Moisture Sorption Isotherm

The moisture sorption isotherm was determined by plotting equilibrium moisture content (EMC) versus relative humidity. Tablet EMC's were determined by storing the tablets inside the desiccators, and observing weight change due to moisture gain or loss. Tablets were weighed to the nearest 0.01 mg in tared weighing bottles. Five bottles were placed in each desiccator and five set in the cabinet outside of the desiccators, all with the lids off. At selected times the desiccators were opened, and the lids quickly replaced on each bottle. The bottles were allowed to cool to room temperature, and weighed. This procedure was repeated until no significant weight change was observed. EMC's were calculated at each time point using Equation (8).

$$\text{Percent Moisture (g } H_2O/100\text{g Solids)} = (M1 + M2)/Dw \times 100 \quad (8)$$

where M1 = Initial moisture content (grams)

M2 = Moisture content gained or lost (grams)

DW = Dry weight

<u>Package Water Vapor Transmission Rate</u>

Package water vapor transmission rates (WVTR) were determined by a method similar to that specified in the US Pharmacopeia XX, 1980. Ten blisters were filled with desiccant tablets, and five with glass beads. Five empty blisters were tested for seal integrity. The filled packages were weighed to the nearest 0.01 mg and stored in the Lunaire cabinet set at 40^{o}C, 80% RH. At certain time intervals, the blisters were removed from the cabinet, cooled to room temperature, and weighed. Net weight gains were determined for the desiccant filled blisters by subtracting the average control package weight change from the observed gain of each blister. The average net gain of the ten samples was plotted versus time, and the slope of the steady state portion of the resulting plot was used as the package WVTR.

Moisture Content of Packaged Tablets

The moisture increase of packaged tablets was determined similarly to the package WVTR. Ten blisters were filled with tablets that had been weighed to the nearest 0.01 mg, and five blisters were filled with glass beads. The strips were sealed, and the five empty blisters were tested for seal integrity. The packages were weighed to the nearest 0.01 mg and stored in the environmental cabinet. At selected times, packages were removed, allowed to cool for 15 minutes and weighed to the nearest 0.01 mg. The net weight gain by the tablets was determined by subtracting the average control package gain from the observed test package gain. The percent moisture was determined at each point by using Equation (8).

MATHEMATICAL MODEL

The moisture content of packaged tablets, stored under constant external conditions, will depend upon the permeability of the package and the sorption characteristics of the tablet. Therefore to calculate the moisture content of the tablets, a model must be developed to describe the transport of moisture into the package, and the adsorption of moisture by the tablet. The model must also be able to account for changes in both moisture transport and adsorption over time.

The total moisture in a package at any time (Mt) will equal the moisture in the headspace (Mh) and the moisture in the product (Mp).

$$Mt = Mh + Mp \qquad (9)$$

In the case of a blister package with a volume of one cubic centimeter, the amount of water in the headspace is insignificant in relation to the quantity in the tablet. Accordingly, Equation (9) can be changed.

$$Mt = Mp \qquad (10)$$

The change in moisture inside the package can be described by Equation (11).

$$dMt/dt = M \tag{11}$$

where (M) is the amount of water entering the package in (t) time. The amount of water entering the package will be dependent on the permeability of the package, which is described by:

$$dM/dt = Pp \times Ps \times (aw\ ext - aw\ int) \tag{12}$$

where: Pp = package permeability constant (grams water/pkg-day-Atm)

Ps = saturated vapor pressure at the test conditions (Atm)

aw ext = the external water activity

aw int = the internal water activity

The relationship between the equilibrium moisture content of the tablet and water activity is described by the following:

$$aw = f(EMC) \tag{13}$$

Note that f(EMC) will be the equation chosen to describe the moisture sorption isotherm. Equation (12) can now be written as follows:

$$dM/dt = Pp \times Ps \times (aw\ ext - f(EMC)) \tag{14}$$

or

$$dM = Pp \times Ps \times (aw\ ext - f(EMC))\ dt \tag{15}$$

This can also be written as:

$$dM/\ \ aw\ ext - f(EMC) = (Pp \times Ps)\ dt \qquad (16)$$

Since it is assumed that $Mp >> Mh$, and $Mt = Mp$, then the total moisture in the package will equal the EMC times the weight of the dry product (W).

$$M = EMC \times W \qquad (17)$$

Therefore

$$d(EMC \times W)/\ (aw\ ext - f(EMC)) = (Pp \times Ps)\ dt \qquad (18)$$

Rearranging Equation (18) and integrating will give:

$$w \int_{Mo}^{Mi} d(EMC)\ /\ (aw\ ext - f(EMC)) = (PpxPs) \int_{o}^{t} dt \qquad (19)$$

where Mo = moisture content at time = 0

Mi = moisture content at time = t

solving for time,

$$t = W/Pp \times Ps \int_{Mo}^{Mi} d\ (EMC)/(aw\ ext - f\ (EMC)) \qquad (20)$$

Substituting the appropriate equation for the sorption isotherm into Equation (20) and integrating gives the moisture content of the product as a function of storage time for a situation of constant storage conditions of temperature and humidity where there is an interaction between the product and the internal package environment.

RESULTS AND DISCUSSION

The moisture sorption properties of the tablets were characterized by storing tablets for three months in desiccators containing saturated salt solutions. At selected times during the storage period, the tablets were weighed to determine any change in weight due to moisture transfer. The moisture content at each time interval was then calculated as described in the Experimental section (see Equation 8). The calculated moisture contents are presented in Tables 3 to 8. Specifically, each table reports the moisture content for individual tablets over the entire storage time at one humidity condition. Also reported are the average tablet moisture content and the standard deviation at each sampling point. The results demonstrate that the tablets reach equilibrium in two weeks. This is shown graphically in Figure 2, where the average moisture content is plotted as a function of storage time for the respective humidity conditions employed.

Comparing the results of tablets stored at the same conditions allows the variability of the test method to be examined. At all conditions the results were found to be very consistent. Statistical analysis by the student's t-test showed that with a 95% confidence interval, the

Table 3. Percent moisture[1] of tablets stored at 40°C, 11% RH.

Sample	Days						
	15	23	30	50	65	78	116
1	2.301	2.399	2.214	2.394	2.296	2.665	2.527
2	2.342	2.391	2.180	2.402	2.332	2.667	2.516
3	2.348	2.436	2.272	2.405	2.354	2.712	2.666
4	2.155	2.217	2.139	2.221	2.119	2.399	2.613
5	2.268	2.366	2.161	2.314	2.376	2.570	2.590
Average	2.283	2.374	2.193	2.347	2.295	2.602	2.58
Std. Dev.	0.079	0.069	0.052	0.080	0.103	0.125	0.062

[1]Reported as grams water per 100 grams solids.

Table 4. Percent moisture[1] of tablets stored at 40°C, 33% RH.

Sample	Days						
	15	23	30	50	65	78	116
1	3.868	3.802	3.715	3.654	3.449	3.873	4.216
2	3.836	3.862	3.608	3.719	3.576	3.905	3.862
3	3.613	3.613	3.761	3.587	4.442	4.094	4.575
4	3.710	3.751	3.610	3.589	3.636	3.961	3.767
5	3.769	3.822	3.889	3.691	3.811	4.150	4.316
Average	3.759	3.770	3.717	3.648	3.783	3.994	4.147
Std. Dev.	0.102	0.096	0.117	0.060	0.391	0.121	0.332

[1]Reported as grams water per 100 grams solids.

Table 5. Percent moisture[1] of tablets stored at $40^{o}C$, 48% RH.

Sample	Days						
	15	23	30	50	65	78	116
1	5.096	5.181	5.086	5.061	4.767	5.296	5.445
2	5.453	5.443	5.406	5.311	5.149	5.463	5.296
3	5.149	5.228	5.274	5.205	5.137	5.540	5.353
4	5.175	5.275	5.070	5.196	4.996	5.201	5.370
5	5.083	5.161	5.066	4.993	4.967	5.140	5.250
Average	5.191	5.258	5.180	5.153	5.003	5.326	5.343
Std. Dev.	0.151	0.112	0.153	0.126	0.155	0.168	0.074

[1]Reported as grams water per 100 grams solids.

Table 6. Percent moisture[1] of tablets stored at 40°C, 71% RH.

Sample	Days						
	15	23	30	50	65	78	116
1	8.431	8.416	8.334	8.304	8.033	8.375	8.349
2	8.557	8.547	--	8.436	8.240	8.582	8.511
3	8.559	8.554	--	8.317	8.224	8.498	8.523
4	8.486	8.535	8.360	8.295	8.409	8.491	8.595
5	8.447	8.390	8.338	8.286	8.261	8.370	8.588
Average	8.496	8.488	8.344	8.328	8.233	8.463	8.513
Std. Dev.	0.060	0.078	0.014	0.062	0.134	0.090	0.099

[1]Reported as grams water per 100 grams solids.

Table 7. Percent moisture[1] of tablets stored at 40°C, 80% RH.

Sample	Days						
	10	15	23	37	50	65	116
1	8.639	8.822	8.639	9.583	8.665	8.978	9.708
2	8.700	8.838	8.764	9.721	8.763	8.923	9.684
3	8.516	8.098	8.583	9.618	8.659	8.919	9.480
4	8.565	8.782	8.666	9.643	8.701	9.034	9.643
5	8.562	8.841	8.738	9.762	8.766	9.131	9.734
Average	8.596	8.676	8.678	9.665	8.709	8.997	9.642
Std. Dev.	0.073	0.324	0.074	0.074	0.049	0.088	0.118

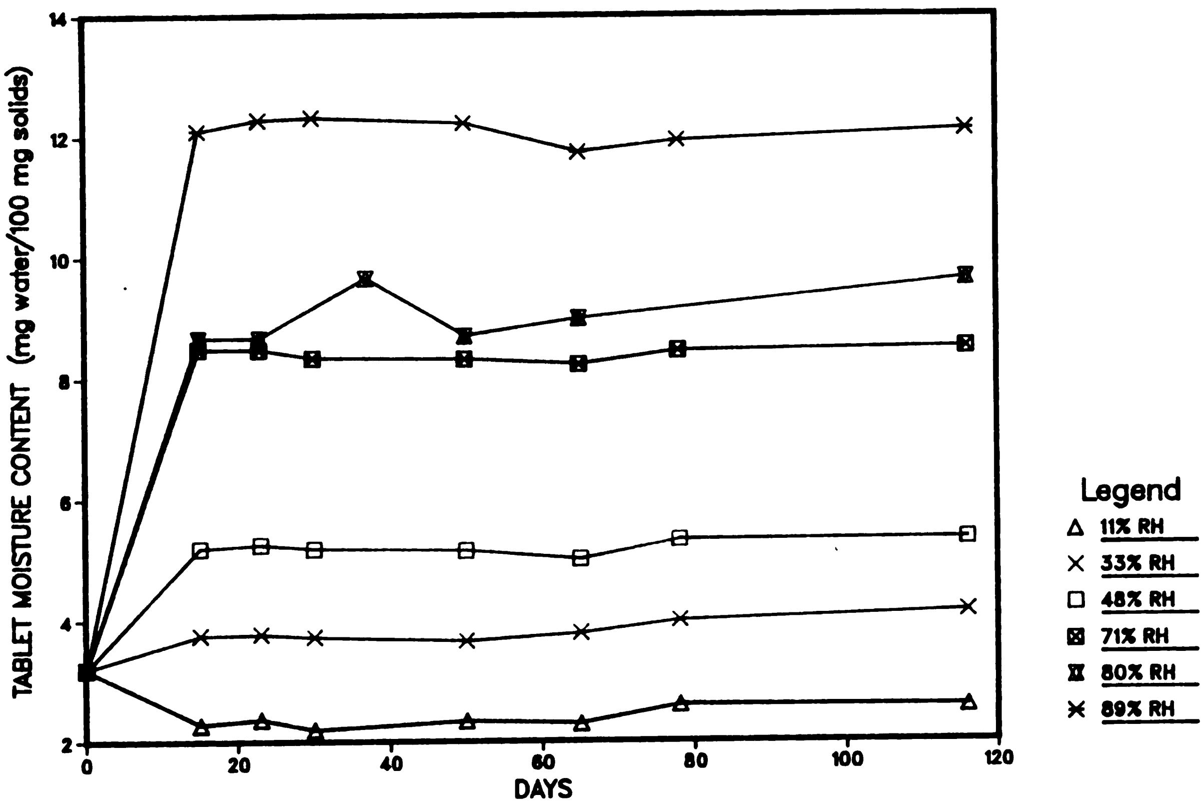
[1] Reported as grams water per 100 grams solids.

Table 8. Percent moisture[1] of tablets stored at 40°C, 89% RH.

Sample	Days						
	15	23	30	50	65	78	116
1	12.100	12.185	12.315	12.215	11.700	11.930	12.135
2	12.121	12.385	12.406	12.279	11.820	12.031	12.126
3	12.013	12.320	12.285	12.199	11.666	11.847	12.103
4	12.049	12.240	12.281	12.219	11.812	11.945	12.090
Average	12.071	12.282	12.322	12.228	11.749	11.939	12.114
Std. Dev.	0.049	0.879	0.058	0.035	0.078	0.075	0.021

[1] Reported as grams water per 100 grams solids.

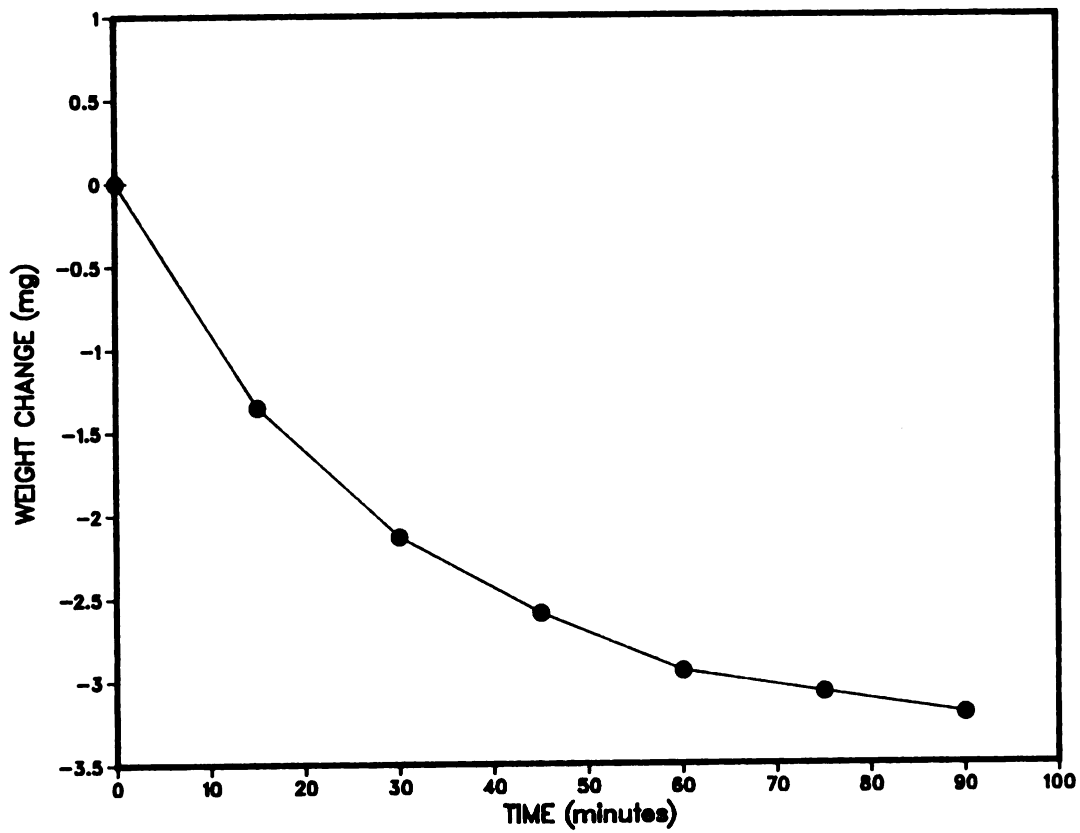
FIGURE 2. MOISTURE CONTENTS OF TABLETS AT 40°C AND VARYING RELATIVE HUMIDITIES



slope of the respective sorption profile curves are approximately zero, indicating that the tablets had reached equilibrium and the moisture content values, represented actual equilibrium conditions. As shown, tablets in general were observed to vary in weight by only fractions of a milligram. The highest variation observed between individual values of the average (2.5 mg) occurred at 80% RH and is likely due to cabinet variability. Chart recordings verified that the humidity inside the cabinet, normally 80%, fluctuated in the range of t ± 5%. It should be noted that at this high humidity range, fluctuations will have a greater effect on moisture content than fluctuations at lower humidity conditions. Further, small differences in moisture content may be due to the assumption that the initial moisture content of all tablets was identical.

The use of glass weighing bottles provided greater accuracy than many previous simulation studies which measured moisture change by storing tablets on open weighing trays. Originally a similar approach was used for this study but was found to give inaccurate results. When tablets were placed on open dishes, within 20 minutes enough moisture was lost to lower the moisture content by as much as 1.0% of the original weight value. The rate of moisture loss that occurred under these circumstances is shown in Figure 3, where the weight change of the

FIGURE 3. MOISTURE LOSS OF TABLETS AT AMBIENT CONDITIONS (taken from storage conditions 40°C 80% RH)



tablets is plotted as a function of time stored after initial weighing.

The equilibrium moisture content was plotted versus relative humidity to show the moisture sorption isotherm of the tablets at $40^{o}C$ (Figure 4). The average moisture content, standard deviation and 95% confidence interval for each condition are reported in Table 9. It should be noted that at each humidity condition, all calculated moisture contents were treated as one population to obtain the average EMC's reported.

Examining the moisture isotherm by itself allows one to draw some conclusions on the type of packaging that will be needed to protect a product. Knowing the initial moisture content of a product, one can observe that storage conditions at which the product will begin to gain or lose moisture. The tablets tested in this study had an initial moisture content of 3.1% and from Figure 4 it can be seen that the relative humidity associated with this moisture content was approximately 25%, at the temperature of test. Thus at a humidity of 60%, which is likely to be encountered in actual storage, the tablets will equilibrate to a moisture content of 6.0% (Figure 4). Further, it can be expected that the tablets will equilibrate to a higher moisture content at a lower temperature. Therefore if a 6.0% moisture content is unacceptable, a high barrier package must be used, whereas if a moisture content of

FIGURE 4. MOISTURE SORPTION ISOTHERM OF TABLETS AT 40°C

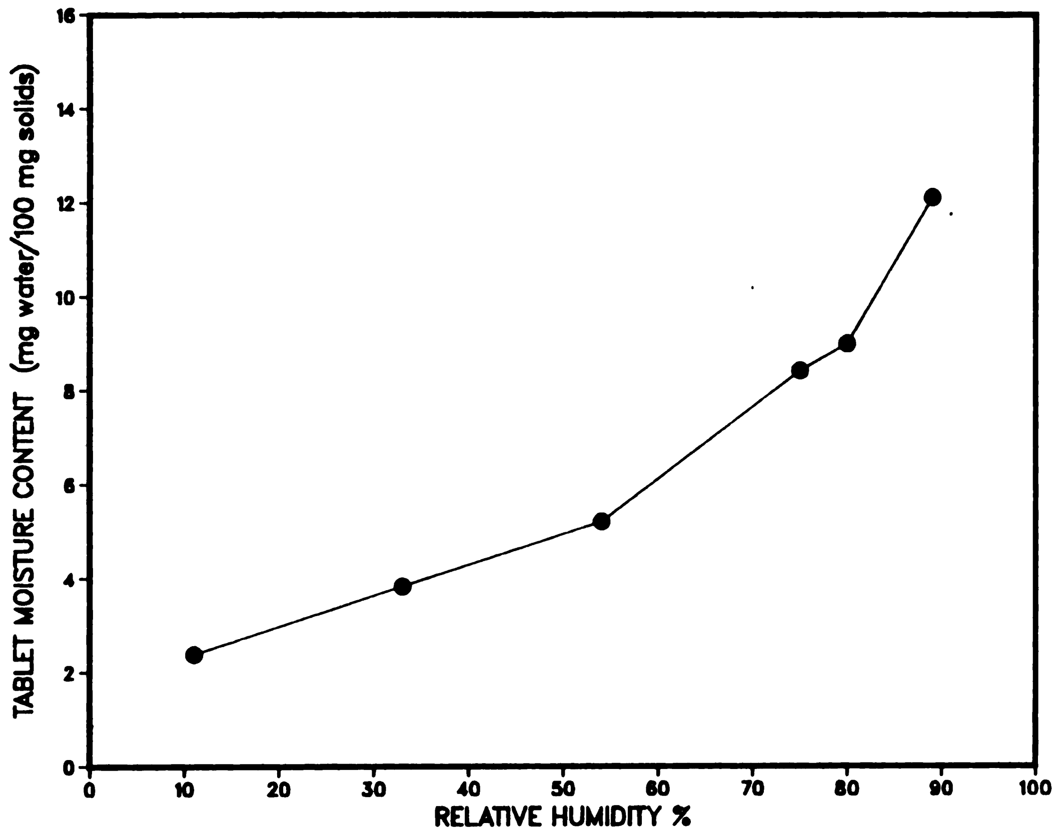


Table 9. Equilibrium moisture contents of tablets at 40°C.

Relative humidity	EMC[1]	Std. Dev.	95% C.L.	n[2]
11.21	2.383	0.164	0.056	35
33.60	3.831	0.253	0.046	35
48.42	5.208	0.166	0.263	35
71.00	8.413	0.130	0.046	35
80.00	8.995	0.458	0.159	35
89.03	12.101	0.200	0.078	28

[1]Reported as grams water per 100 grams solids.

[2]Number of observations.

12.0% is the critical value, a lower barrier would be required since the tablet would not be expected to reach that value unless exposed to 90% RH.

Package water vapor transmission rates (WVTR) are listed in Table 10. Blisters were filled with desiccant and glass beads as described in the Experimental section and the gain in weight was measured at selected time intervals. The average gain in moisture of each package as a function of time is shown in Figure 5. A least-squares analysis was used to determine the best fitting line to the data. The slope of each line is equal to the package WVTR and represents the amount of water entering the package in one day under the test conditions. Dividing the WVTR by the water vapor partial pressure gives the permeability constant of each package. These values are reported in Table 10 and are used in the predictive model.

The WVTR results clearly show the superior moisture protection of the vinyl-aclar blisters. The WVTR of the vinyl-aclar blisters (0.21 mg/day), was 50% of the transmission rate of the saran-coated blisters (0.48 mg/day), and less than one-tenth that of the PVC blisters 3.5 mg/day.

Tablets were packaged in the three blisters and stored at 40^{o}C, 80% RH to generate storage stability data with which to compare predicted values. Moisture contents of tablets packaged in each blister structure and stored at

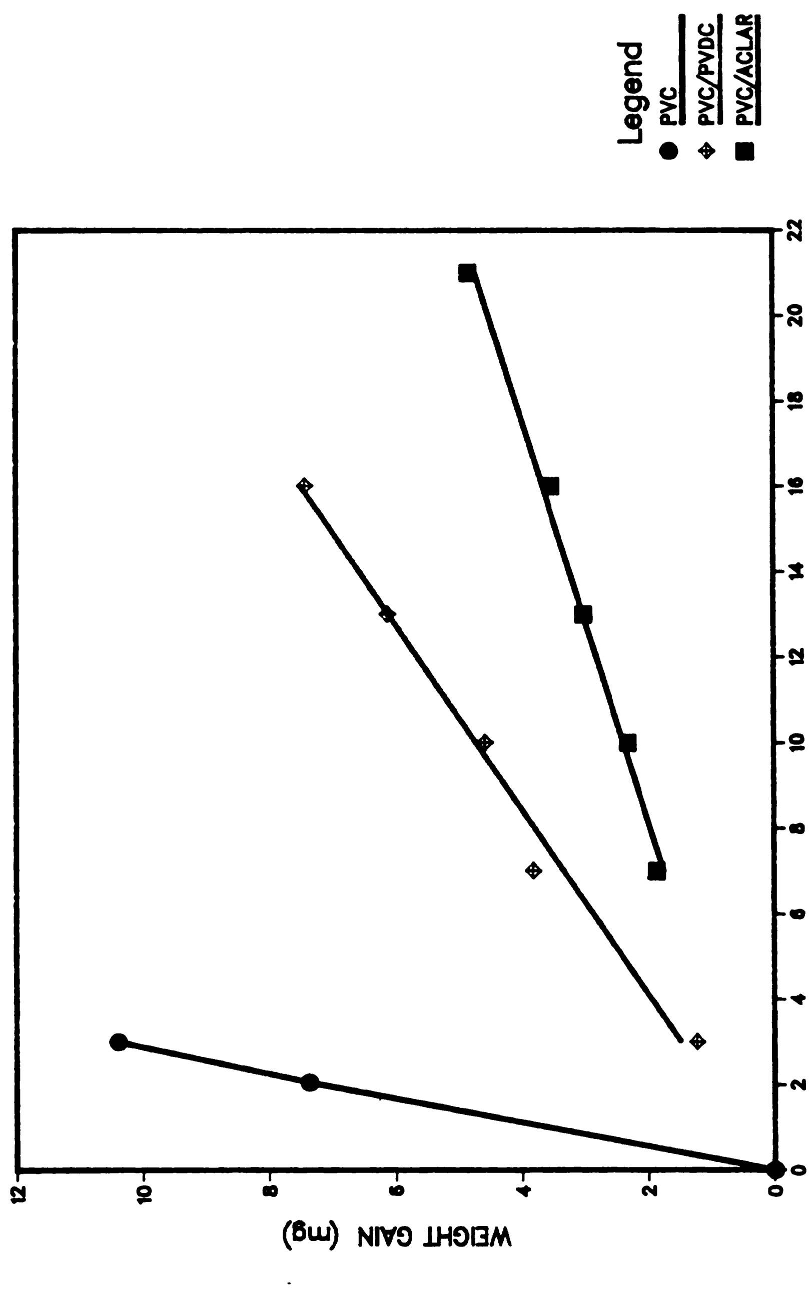
Table 10. Moisture permeability of blister packages.

Material	WVTR[1]	Permeability Constant[2]
Polyvinylchloride (PVC)	3.50	7.9 x 10 (-5)
Saran Coated PVC	0.48	1.1 x 10 (-5)
Vinyl-Aclar Laminate	0.21	4.8 x 10 (-6)

[1] Expressed as milligrams water per day-package.

[2] Expressed as grams water per package-day-Atm.

FIGURE 5. Weight Gain of Blisters at 40°C 80%RH Due to Moisture Transmission



40°C, 80% RH are reported in Table 11 and presented graphically in Figure 6. The moisture contents were calculated as described in the Experimental section.

The package WVTR and moisture sorption data provide some insight as to the expected moisture uptake of the packaged tablets. The package WVTR's indicate that the tablets in the PVC blisters should gain moisture more rapidly than the higher barrier packages. Further, as the vapor pressure differential between the inside of the package and outside decreases, the rate of moisture gain will slow. These points are reinforced by the experimental results. The moisture gain vs storage time plots presented in Figure 6 show that the tablets in PVC blisters gained moisture most rapidly and equilibrated to a moisture content of 8.0%. This value is slightly lower than expected from the sorption isotherm. Unfortunately the cabinet malfunctioned and it could not be determined if the tablets in the other packages would equilibrate to the same moisture content.

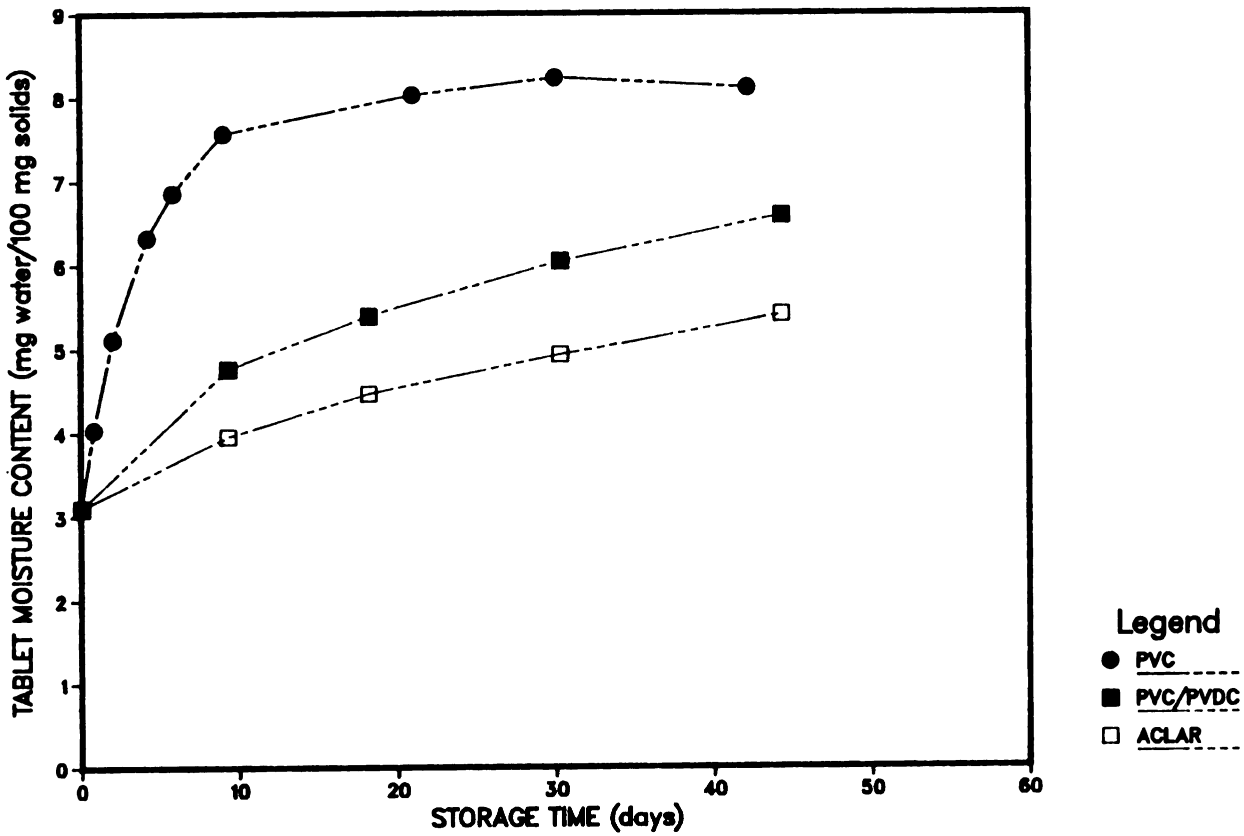
As discussed earlier, the experimental isotherm was fitted by three techniques and the resulting equations were incorporated into the predictive model. A minitab statistical program was used to obtain the equations that described the data by a linear fit, a second order and a third order polynomial expression. The following equations were calculated to describe the sorption isotherm:

Table 11. Moisture content[1] of packaged tablets stored at 40^oC and 80% RH.

Storage time days	PVC	Package System PVC/PVDC	PVC/Aclar
0.0	3.10	3.10	3.10
0.8	4.04	--	--
2.0	5.12	--	--
4.2	6.33	--	--
5.8	6.86	--	--
9.0	7.57	4.76	3.95
18.0	--	5.39	4.46
21.0	8.03	--	--
30.3	8.23	6.04	4.92
44.0	8.11	6.58	5.40

[1]Reported as grams water per 100 grams solids.

FIGURE 6. MOISTURE CONTENT OF PACKAGED TABLETS STORED AT 40° C, 80% RH



$$mc = 0.09 + 0.113\ RH \quad 21)$$

$$mc = 2.33 + 0.0046\ RH + 0.0011\ RH^2 \quad 22)$$

$$mc = 1.14 + 0.127\ RH - 0.0018\ RH^2 + 0.00002\ RH^3 \quad 23)$$

The above equations describe the isotherm in terms of moisture content as a function of relative humidity. In application of the predictive model, the isotherm is expressed in terms of relative humidity as a function of moisture contents that is in the form RH = f (EMC). Accordingly, the isotherm was expressed by the following:

$$RH = 0.0043 + 8.7336\ EMC \quad 24)$$

$$RH = -22.523 + 16.587\ EMC - 0.608\ (EMC)^2 \quad 25)$$

$$RH = -31.252 + 20.389\ EMC - 1.107\ (EMC)^2 + 0.02\ (EMC)^3 \quad 26)$$

It should be noted that the linear equation was calculated using only the data points between 30 and 80% RH, while all the data points were used to calculate the second and third order polynomes. A Minitab statistical package was used and correlation coefficients were found to be 97.9%, 97.3%, and 97.2%, respectively. The point 0.0 was not used in the line calculations. Subsequently the respective equations should be used only for interpolation and not extrapolation beyond the data set. As shown in Figure 7, the isotherm expressions do not accurately predict moisture levels below 11% RH. The isotherm expressions are however acceptable in this study since the model is used to predict moisture uptake at higher ranges of humidities (i.e. >25% RH). It should be noted that the moisture isotherm was also fitted by the following exponential function (see Appendix A).

$$\text{Log } y = mx + b \qquad 27)$$

This expression was found to accurately describe the isotherm and should be considered when selecting an expression of the isotherm to incorporate into the simulation model. It was however, not used in the actual simulation modeling, only the linear and polynomial expressions were considered.

The calculated moisture contents obtained using equations 21 to 23 are reported in Table 12. These results indicate that the linear model best describes the isotherm in the humidity range of 45 to 70%. The second and third order polynomials accurately describe the isotherm over the entire humidity range of interest. The isotherms calculated by each equation are shown in Figure 7 where they are compared to the experimentally determined isotherm. It should be noted that higher moisture contents at 80% RH were calculated using the equations than

FIGURE 7. MOISTURE SORPTION ISOTHERM DESCRIBED BY THREE MATHEMATICAL EQUATIONS

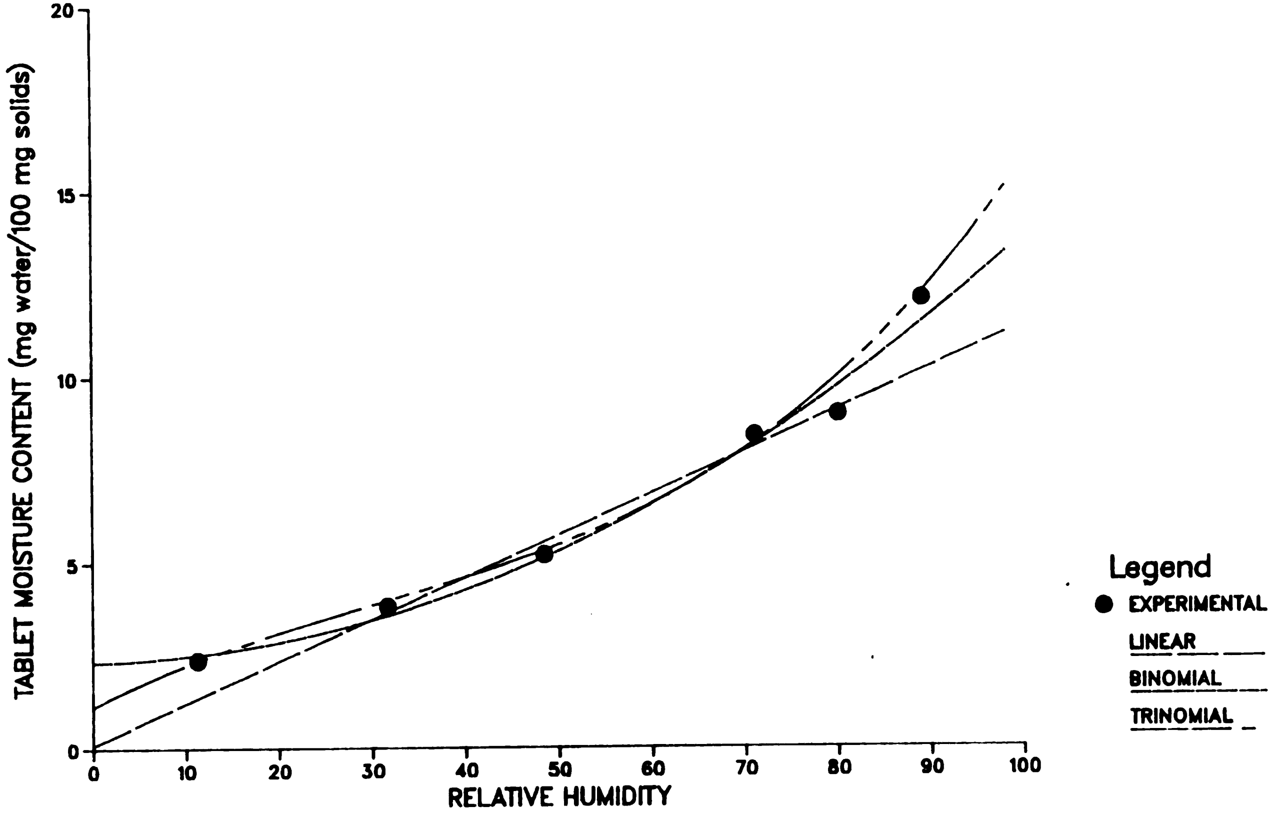


Table 12. Equilibrium moisture content[1] of tablets at different relative humidities at 40°C.

RH (%)	Experimental	Isotherm Model		
		Linear	Binomial	Trinomial
11.21	2.38	2.28	2.48	2.44
33.60	3.80	3.80	3.60	3.87
48.42	5.20	5.61	5.10	5.29
71.00	8.40	8.14	8.36	8.41
80.00	8.99	9.13	9.74	10.00
89.03	12.10	10.12	11.65	12.25

[1]Reported as grams water per 100 grams solids.

determined experimentally. Accordingly, moisture contents predicted using these isotherm equations will be higher than the experimentally measured value.

Equation (20) was used to predict the moisture gain of packaged tablets using the three isotherm models previously described. A computer program (Appendix B) written by Dr. Julian Lee and Mr. Mark Wang of Michigan State University School of Packaging was utilized for solving equation 20. The data that must be entered are the test temperature and humidity, the saturated vapor pressure at the test temperature, the package permeability constant, the initial moisture content of the tablet, and the equation for the moisture isotherm.

The moisture uptake of tablets stored in each package was calculated using the program shown in Appendix B. Each isotherm equation was used in the model to determine if there was a significant difference in results. Therefore there are three sets of results for each package. The predicted moisture contents are reported in Tables 13-15 for the PVC, saran-coated PVC, and vinyl-aclar blisters respectively. Each table includes the experimentally measured moisture contents and the predicted values using the three expressions for the isotherm. The results are shown graphically in Figure 8-10. As shown, good agreement between the predicted values and the experimental data was obtained, with the predicted values being within 10% of

Table 13. Experimental and calculated moisture content[1,2] of tablets packaged in PVC blisters.

Days	Experimental	Linear	Binomial	Trinomial
0.0	3.1	3.1	3.1	3.1
0.8	4.04	4.00	4.00	4.00
1.8	--	5.00	5.00	5.00
2.0	5.12	--	--	--
4.1	--	6.50	--	--
4.2	6.33	--	--	--
4.3	--	--	6.50	6.50
5.1	--	7.00	--	--
5.5	--	--	7.00	7.00
5.8	6.86	--	--	--
8.3	--	8.00	--	--
9.0	7.57	--	--	--
9.3	--	--	8.00	8.00
17.0	--	9.00	--	--
17.8	--	--	9.00	9.00
21.0	8.03	--	--	--
30.0	8.23	--	--	--
32.0	--	--	--	9.50
34.0	--	--	9.50	--
44.0	8.11	--	--	--

[1]Reported as grams water per 100 grams solids.

[2]Storage conditions of 40°C, 80% RH.

Table 14. Experimental and calculated moisture content[1,2] of tablets packaged in saran-coated PVC blisters.

Days	Experimental	Linear	Binomial	Trinomial
0.0	3.10	3.10	3.10	3.10
8.7	--	--	4.50	4.50
9.0	4.76	4.50	--	--
17.7	--	5.50	--	--
18.0	5.39	--	5.50	5.50
23.1	--	6.00	--	--
23.8	--	--	6.00	6.00
30.3	6.04	--	--	--
44.0	6.58	--	--	--
46.4	--	7.50	--	--
50.7	--	--	7.50	--
51.4	--	--	--	7.50
79.2	--	8.50	--	--
88.2	--	--	8.50	--
95.2	--	--	--	8.50
122.1	--	9.00	--	--
250.9	--	--	9.50	--
282.3	--	--	--	9.50

[1]Reported as grams water per 100 grams solids.

[2]Storage conditions of 40°C, 80% RH.

Table 15. Experimental and calculated moisture content[1,2] of tablets packaged in vinyl-aclar blisters.

Days	Experimental	Linear	Binomial	Trinomial
0.0	3.10	3.10	3.10	3.10
9.0	3.95	--	--	--
11.5	--	--	4.00	4.00
12.0	--	4.00	--	--
18.0	4.46	--	--	--
20.0	--	--	4.50	4.50
20.5	--	4.50	--	--
29.7	--	--	5.00	5.00
30.0	--	5.00	--	--
30.3	4.92	--	--	--
40.7	--	5.50	--	--
41.1	--	--	5.50	5.50
44.0	5.40	--	--	--
84.6	--	7.00	--	--
90.5	--	--	7.00	--
91.7	--	--	--	7.00
181.6	--	8.50	--	--
202.2	--	--	8.50	--
204.7	--	--	--	8.50

[1]Reported as grams water per 100 grams solids.

[2]Storage conditions of 40°C, 80% RH.

FIGURE 8. EXPERIMENTAL VS. PREDICTED MOISTURE CONTENT OF TABLETS IN PVC BLISTERS AT 40°C, 80% RH

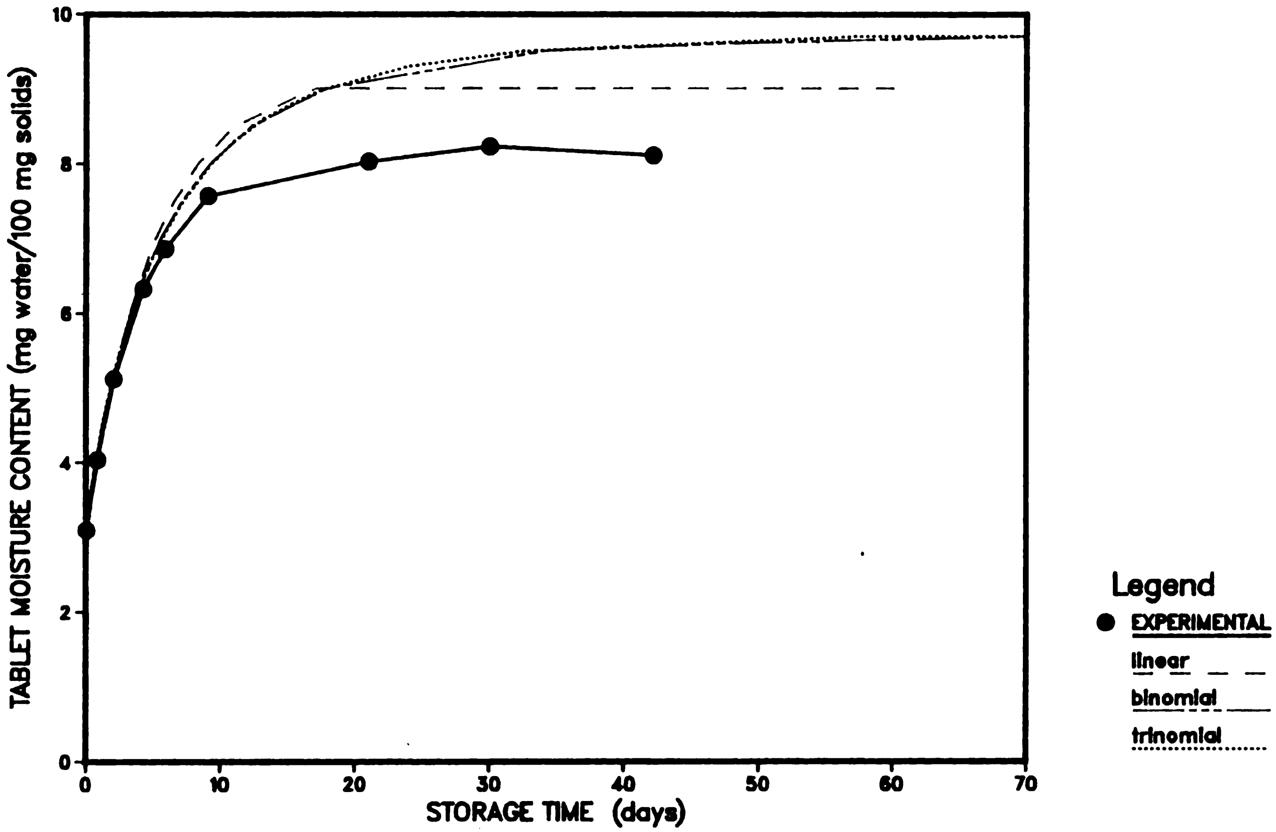


FIGURE 9. EXPERIMENTAL VS. PREDICTED MOISTUER CONTENT OF TABLETS IN PVC/PVDC BLISTERS AT 40°C, 80% RH

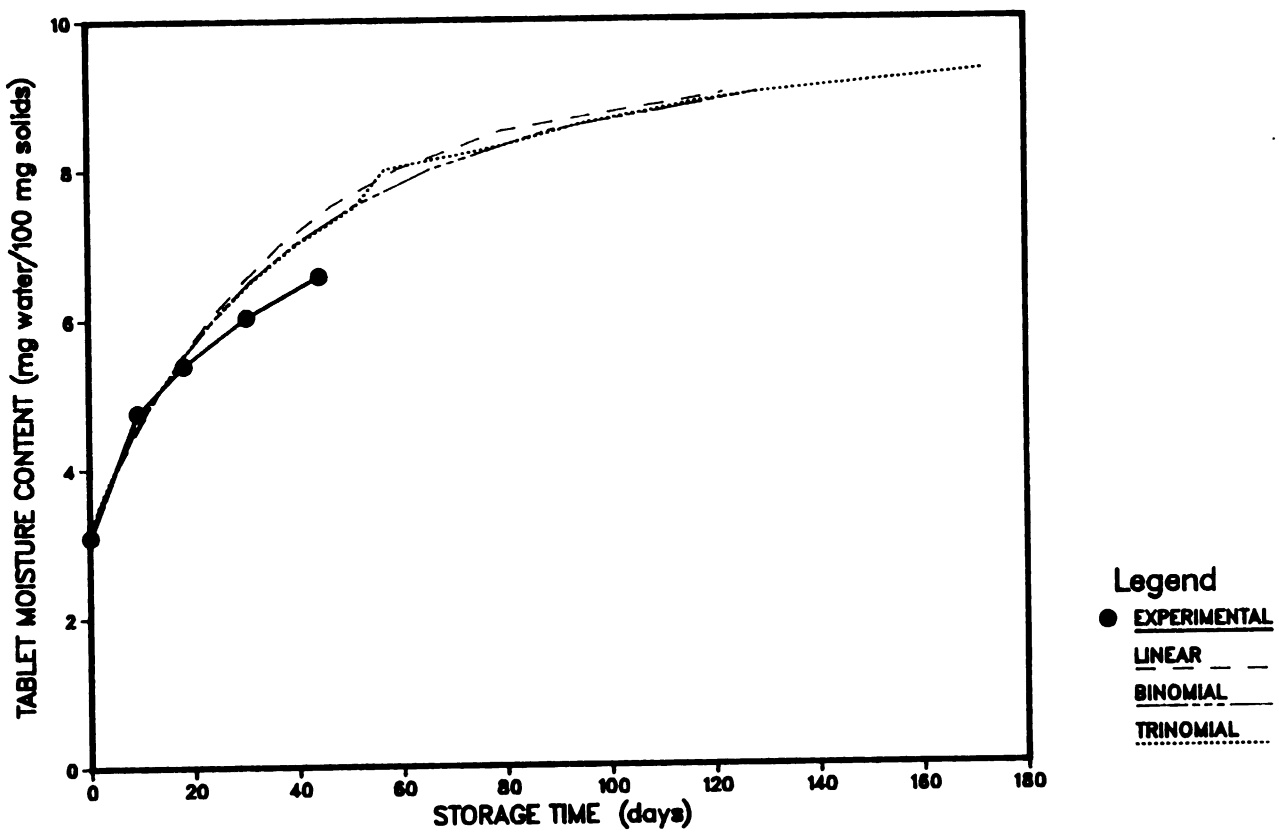
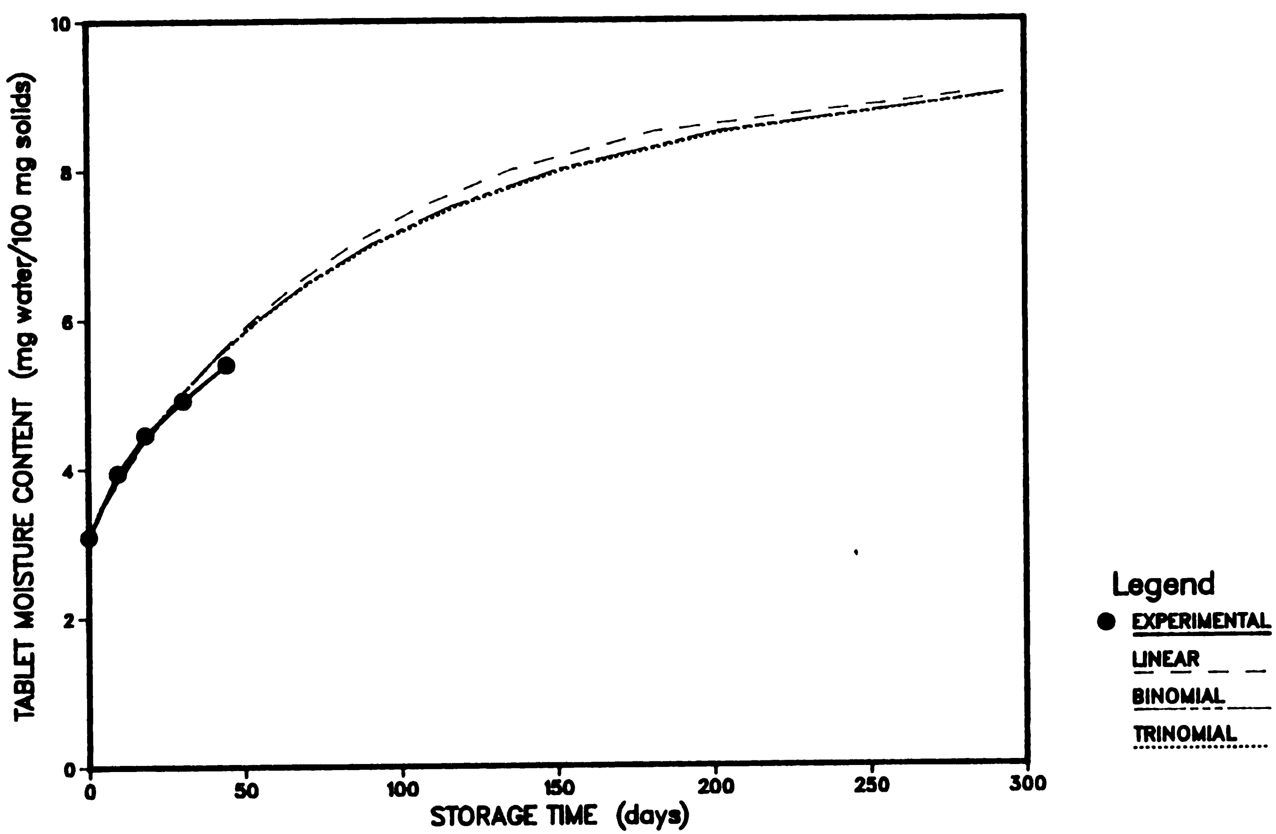


FIGURE 10. EXPERIMENTAL VS. PREDICTED MOISTURE CONTENT OF TABLETS IN PVC/ACLAR BLISTERS AT 40° C, 80% RH



the experimental data. As discussed previously, a small difference in RH will have a large impact on moisture content at the test conditions of 80% RH.

For the three package systems, the differences between the calculated moisture content values based on the respective isotherm expressions are insignificant. This can be explained by the fact that the isotherms calculated by the linear and by the curve fitting method are very close and in fact overlap in the region from 50 to 75% relative humidity (Figure 7). Accordingly, for this product all three isotherm expressions accurately predict changes of moisture in this region. It would be expected from Figure 7 that if the area of interest was 90% RH a greater difference in predicted values would result and the values predicted by the second and third order polynomials would be more accurate. Further, if the product was different and did not have a linear isotherm, again the second and third order expressions would provide a more accurate prediction.

Using the three isotherm equations, higher values of moisture content at 80% RH were calculated than found experimentally (Figure 7). These values are reported in Table 12 and range from 9.2% for the linear model to 10.00% for the third order expression, as compared to the experimental value of 8.99%. This explains the difference between the linear based predictions and the polynomial based predictions. The isotherm results (Figure 7) indicate that at 80% RH the tablets should equilibrate to a moisture of 8.99%. However, the tablets packaged in the PVC blisters equilibrated to only 8.1% moisture and therefore the predictions appear high (Figure 8). The cabinet malfunctioned before the tablets in the aclar and saran-coated blisters reached equilibrium and therefore it could not be determined at what equilibrium moisture content the tablets equilibrated in these packages. If it is assumed that the 8.99% moisture would have been reached, then the predictions are accurate to within 12%. The current data indicates that the predictions are within 4% of the experimental values.

APPLICATIONS

The simulation technique presented has been shown to be effective in predicting the moisture gain of a packaged product. Based on the time and resource efficiencies of the predictive technique and the inability of accelerated stress tests to accurately estimate product quality under ambient conditions it is the recommendation of this author that the simulation modeling technique be used routinely in the early stages of package development for moisture sensitive products. Several key areas where the simulation modeling technique can be applied are discussed below.

Shelf-life Estimates

By measuring the moisture sorption isotherm of a product at a particular temperature and calculating the moisture permeability constant of a package at that temperature, the shelf-life of the packaged product can be predicted based on moisture uptake. It should be noted that the critical moisture content of the product must be known to fully utilize this concept. The critical moisture content is defined as the highest acceptable moisture content and will depend on the impact of moisture on texture or chemical activity of the product.

Generating a stability profile using the predictive model as done in Figures 8-10, in which product moisture content is plotted as a function of storage time, allows one to estimate the time required before the packaged tablet will reach the critical moisture content. For example, as shown in Figure 6, if the critical moisture content of the tablet was 5%, it would take tablets packaged in PVC, PVC/PVDC, and Aclar blisters 2, 14 or 42 days respectively to reach the critical moisture content.

Package Comparisons

The predictive model can also be used to calculate the impact on shelf-life of alternate packages. The capability to make estimates of this type allows for certain packaging decisions to be made prior to expensive and labor intensive storage studies. The shelf-life estimate can be used to select only the most suitable package or packages for further evaluation, thus saving time and resources upfront.

The data that is required to make the estimate are the package WVTR's and the product isotherm. As demonstrated by the results of this study, this testing is not very labor intensive and can be done in a timely manner. It should be noted that once the package WVTR's are measured, they may be applied to more than one product, furthering the utility of this method.

Package Requirements

The simulation modeling technique can be used to determine the package requirements for a given product. For example, by entering the moisture adsorption data, storage conditions, required shelf-life, and the critical moisture content into the predictive model, an optimum package WVTR can be ascertained. Referring to Figure 6, if the tablet was required to withstand one month at accelerated conditions and the maximum allowable moisture content was 5%, the model would verify that only packages with WVTR's below 0.48 mg/day would be acceptable.

Package Cost Effectiveness

The simulation modeling technique can be used as an early screen of packages so that the most cost effective package will be placed into stability programs. By using the predictive model to determine the shelf-life provided by several packages and comparing the cost of the packages, one can decide the most cost effective material to work with. Using the example described above, it may be decided that the additional shelf-life provided by a vinyl-aclar blister over the saran-coated blister (28 days) may not justify the added package material cost.

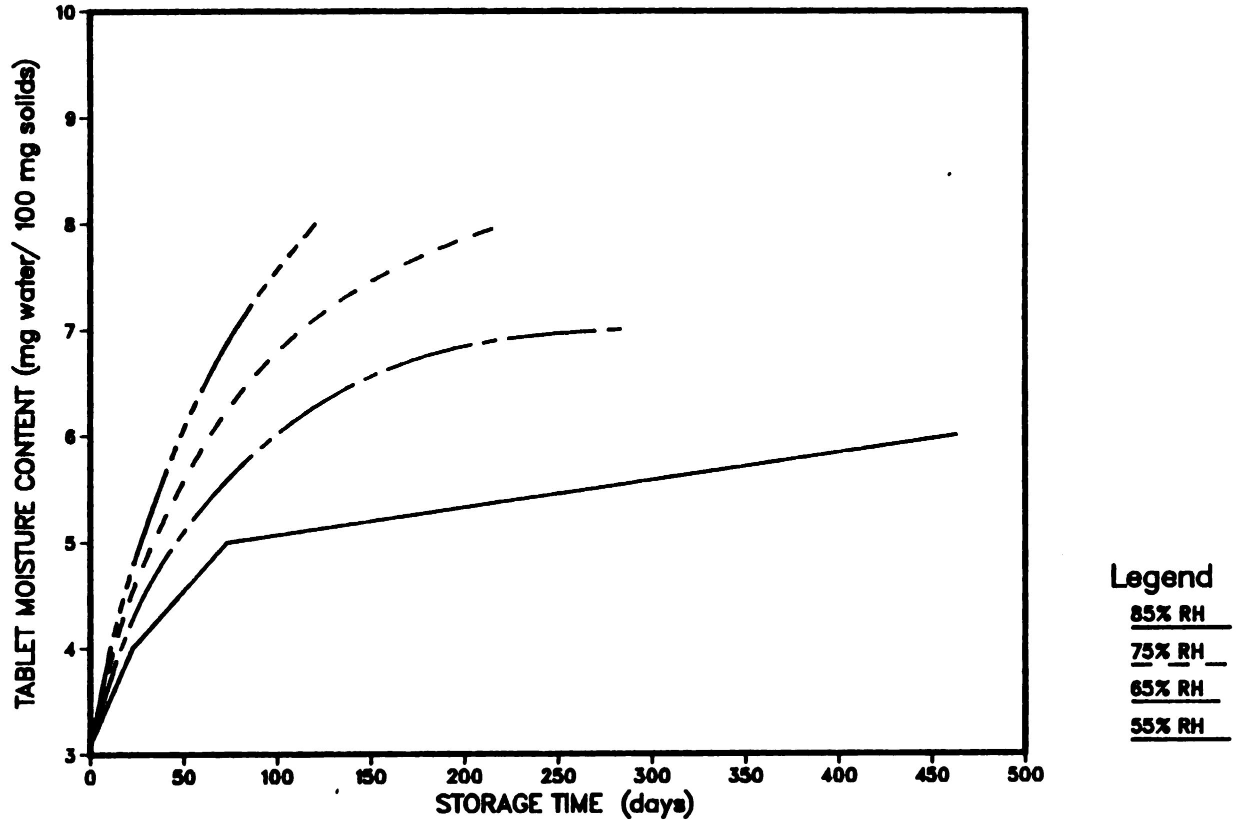
Environmental Impact

The predictive technique can also be used to assess the impact of the storage conditions on shelf-life. This is shown in Figure 11 where the computer aided storage stability profile curves for the tablet packaged in PVC/Aclar blisters are presented for storage environments of 40°C and 85, 75, 65, and 55% RH's. As shown, the impact of the external humidity on moisture uptake is significant. One very useful way to apply this concept is to relate the performance of a package at accelerated conditions to that at ambient conditions. This capability will explain the difference in performance of a product-package system when stored at high humidity conditions and subsequently should reduce the alarm that often occurs when a package is found to fail at accelerated test conditions. For example, as shown in Figure 11, only 48 days were required for the tablets to reach 6% moisture at conditions of 80% RH whereas it would take 463 days to reach the same moisture content at conditions of 55% RH. It should be noted that both these estimates are based on a temperature of 40°C and that lowering the temperature would be expected to further increase the time required to reach a moisture content of 6%.

World-wide Packaging

The same principles as described above also provide the capability to make world-wide packaging decisions. If a company is marketing a product in environments that differ significantly, it may be possible to realize cost

FIGURE 11. PREDICTED EFFECT OF HUMIDITY ON MOISTURE UPTAKE OF TABLETS PACKAGED IN VINYL–ACLAR BLISTERS AT 40° C



reductions by custom designing the packaging for the specific environment. For example, a product to be marketed in both the Middle East and South America would require more protection from moisture for the hot and humid region than it would for the relatively dry arid Middle East region. The simulation model can be used by incorporating the appropriate data to make this type of evaluation.

While this discussion has centered around blister packages, the predictive technique can be applied to other container systems. Examples are plastic bottles, flexible pouches, composite cans, and containers consisting of more than one component such as a bag in a box. With the ever increasing cost of package components it is extremely important to minimize the cost of the package without sacrificing product protection. In addition, aggressive marketing strategies dictate that the package development process be kept to a minimum of time. Further, the resource and analytical constraints of an organization in addition to budgeting for research and development, make it essential for the package development program to be as efficient as possible. All these considerations reinforce the utility of the shelf-life prediction technique as a package development tool.

CONCLUSION

A technique has been presented that uses easily measured product and package properties to predict the final performance of the packaged product. The moisture sorption isotherm of a tablet and the moisture permeability of three blister packages were incorporated into a mathematical model capable of predicting the moisture uptake of the packaged tablet stored at constant conditions of temperature and humidity.

While this technique has been applied in the past to various dehydrated products, this study has incorporated several improvements: 1) it presents a detailed description of methods to accurately measure the package WVTR, tablet moisture isotherm, and moisture uptake of packaged product. The gravimetric methods described offer the advantages of time and resource efficiency and were found to be both accurate and precise; 2) further, a new technique of using a mathematical fit to describe the moisture isotherm was presented; and 3) a computer program that requires a minimum amount of data entry has been developed which allowed evaluation of the respective isotherm models in the predictive equation.

The results demonstrated that the simulation model accurately predicted the moisture gain of tablets packaged in the blister packages by utilizing data generated on the tablets and packages by themselves. As previously discussed, the economies provided by, and the applications of the simulation modeling technique, warrant its incorporation into the package development programs of moisture sensitive products.

APPENDICES

Appendix A. Equilibrium moisture content[1] of tablets at different relative humidities at 40°C.

RH (%)	Experimental	Isotherm Model	
		Linear	Exponential
11.21	2.38	2.28	2.41
33.60	3.80	3.80	3.88
48.42	5.20	5.61	5.13
71.00	8.40	8.14	8.11
80.00	8.99	9.13	9.44
89.03	12.10	10.12	11.70

[1]Reported as grams water per 100 grams solids.

APPENDIX B

```
]?CHR$(9);"130N":LI


LOAD SH#6
LIST

  5  HOME
 10  REM LINE 0 TO 350 ARE USED FOR CURVE FITTING OF SORPTION
     ISOTHERM EXPERIMENTAL DATA
 25  REM THE ORDER OF EQUATION,
 30  REM PAIRS OF (M%, RH%) WILL BE REQUESTED
 40  REM THE OUTPUT IS RH%=FN(M%)
 50  PRINT "THIS PROGRAM IS DESIGNED FOR SHELF LIFE ESTIMATION"
 51  PRINT
 52  PRINT "SORPTION ISOTHERM WILL BE EXPRESSED AS
     RH%=A+BM+CM*M+DM*M*M+-----"
 54  PRINT
 55  PRINT "THE DATA A USER SHOULD PREPARE"
 57  PRINT "FOR INPUT IN USING THIS PROGRAM"
 60  PRINT "ARE:"
 62  PRINT "   1. SORPTION ISOTHERM DATA"
 64  PRINT "      POINTS (M%, RH%)"
 66  PRINT "   2. ORDER OF EQUATION FOR"
 68  PRINT "      THE SORPTION ISOTHERM"
 70  PRINT "   3. TEMP OF TEST ENVIRONMENT CELSIUS"
 72  PRINT "   4. AREA OF PKG IN METER SQUARE"
 74  PRINT "   5. WEIGHT OF PRODUCT IN GRAMS"
 80  PRINT "   6. THICKNESS OF PKG IN MIL"
 82  PRINT "   7. INITIAL MOISTURE CONTENT %"
 85  PRINT "   8. RH% OF STORAGE ENVIRONMENT (S)"
 90  PRINT
 92  PRINT
 94  PRINT "HIT ANY KEY TO START THE PROGRAM"
 96  GET H$: IF H$ = "" THEN 96
100  HOME
110  PRINT "ENTER THE NUMBER OF SORPTION ISOTHERM EXPERIMETNAL DATA
     POINTS"
115  INPUT M
116  PRINT
120  PRINT "ENTER THE ORDER OF EQUATION"
125  INPUT N1
126  N = N1 + 1
127  PRINT
130  DIM X(M),Y(M),X1(N + 1,N +1)
140  FOR I = 1 TO M
150  PRINT "ENTER A PAIR OF M%  AND RH% COORDINATES"
155  INPUT X(I),Y(I)
156  PRINT
160  NEXT I
162  PRINT
163  PRINT
```

```
180  FOR J = 1 TO N
190  FOR I = 1 TO N
195  X1(I,J) = 0
200  FOR K = 1 TO M
210  X1(I,J) =X1(I,J) + X(K)   (I + J - 2)
220  NEXT K
230  NEXT
240  NEXT
255  X1(I,1) = M
260  FOR I = 1 TO N
270  X1(I,N + 1) = 0
280  FOR K = 1 TO M
290  X1(I,N + 1) = X1(I,N + 1) + Y(K) * X(K) ^ (I - 1)
300  NEXT
310  NEXT
320  GOSUB 5000
330  A1 = X1(1,N + 1)
331  B1 = X1(2,N + 1)
332  C1 = X1(3,N + 1)
333  D1 = X1(4,N + 1)
334  E1 = X1(5,N + 1)
335  PRINT "A= "A1
336  PRINT "B= "B1
337  PRINT "C= "C1
338  PRINT "D= "D1
339  PRINT "E= "E1
352  PRINT
355  PRINT
356  PRINT "HIT ANY KEY TO CONTINUE"
360  GET A$: IF A$ = "" THEN 360
370  GOSUB 6000
2000 HOME
2070 PRINT
2080 PRINT "ENTER PERMEABILITY CONSTANT IN          GM*MIL/DAY*METER
          SQURE*MM HH"
2090 INPUT P
2100 PRINT
2110 A8 = 1132570000
2112 PRINT "ENTER THE TEMPERATURE OF TEST ENVIRONMENT IN
          DEGREES CELSIUS"
2114 INPUT TS
2116 PRINT
2118 J8 =  -5269 / (T8 + 273)
2120 J8 =  EXP (J8)
2122 PS = J8 * A8
2124 PRINT "THE SATURATED WATER VAPOR PRESSURE IS "PS" MMHG"
2126 P1 = PS
2130 PRINT
2140 PRINT "ENTER AREA OF PACKAGE IN METER SQUARE"
```

SUM =

```
2150  INPUT A2
2160  PRINT
2170  PRINT"ENTER DRY WEIGHT OF PRODUCT IN GRAM"
2180  INPUT W
2190  PRINT
2200  PRINT "ENTER THICKNESS OF PACKAGE MATERIAL IN MIL"
2210  INPUT L
2220  PRINT
2230  PRINT "ENTER INITIAL MOISTURE CONTENT IN      GM/100 GM
            DRY PRODUCT"
2240  INPUT MO
2260  PRINT
2270  PRINT
2280  PRINT
2290  A1 =  -A1
2300  B1 =  -B1
2310  C1 =  -C1
2320  D1 =  -D1
2325  E1 -  -E1
2330  PRINT A1,B1,C1,D1,E1
2340  PRINT
2350  PRINT "ENTER THE NUMBER OF STORAGE ENVIRONMENT"
2360  INPUT N2
2370  DIM RH(N2)
2380  FOR K = 1 TO N2
2390  PRINT
2400  PRINT "ENTER THE RH% OF THE STORAGE ENVIRONMENT ONE AT A TIME"
2410  INPUT RH(K)
2420  PRINT
2430  PRINT "ENTER THE NUMBER OF FINAL MOISTURE"
2440  PRINT "CONTENTS UPON WHICH YOU WOULD LIKE TO"
2450  PRINT "HAVE SHELF LIFE PREDICTION"
2460  INPUT N
2470  PRINT
2480  FOR I = 1 TO N
2490  PRINT "ENTER MOISTURE CONTENT IN GM/100 DRY PRODUCT ONE AT
            A TIME"
2500  INPUT M1(K,I)
2510  PRINT
2520  NEXT I
2540  Q = (M1(K,I) - MO) / 10
2550  SUM = 0
2560  FOR J = 0 TO 9
2570  X = ((1 / 2) * Q + MO) = Q * J
2580  Y = RH(K) + A1 + B1 * X + C1 * X * X + D1 * X * X * X + E1 •• *
      X * X * X
2590  Y1 = (1 / Y)
2600  IF Y1 > 0 THEN 2630ELSE541
2610  T(K,I) = 0
2620  GOTO 2670
2630  A4 = (Y1 + Q)
2640  SUM = SUM + A4
```

$$\int_a^b \frac{1}{RH_{sat} - f(y)} \, dy$$

$$y = AX^3 + 3x^2 + Cx + \vartheta$$

```
2660  F(K,I) = ((L * M) / (P * A2 * P1)) * SUM
2670  NEXT I
2680  PRINT
2690  PRINT
2700  PRINT "M%", "TIME(DAY)"
2710  PRINT
2720  FOR I = 1 TO N
2730  PRINT M1(K,I),T(K,I)
2740  NEXT I
2750  PRINT
2760  PRINT "DO YOU WANT TO TRY SOME OTHER M%"? ENTER Y FOR YES,
             N FOR NO."
2770  INPUT Z$
2780  IF Z$ "N" THEN 2810
2790  PRINT
2800  GOTO 2430
2810  NEXT K
2820  PRINT
2830  PRINT "HIT ANY KEY TO PLOT OUT M% VS TIME"
2840  GET A$: IF A$ = "" THEN 2840
2850  GOSUB 7000
2860  PRINT
2870  PRINT
2874  PRINT
2875  PRINT "THIS IS THE END OF THE PROGRAM"
2880  END
5000  REM
5010  FOR K = 1 TO N
5020  P1 = 0
5030  M1 = 0
5040  FOR J = K TO N
5050  IF ABS (X1(J,K)) > 1 THEN 5060ELSE1080
5070  GOTO 5090
5080  D = ABS (X1(J,K)
5090  IF D > M1 THEN 5100ELSE1130
5100  M1 = D
5110  P1 = X1(J,K)
5120  M = J
5130  NEXT
5140  IF  ABS  (P1) > 0 THEN 5150ELSE1300
5150  IF M < > K THEN 5160ELSE1210
5160  FOR J = K TO N + 1
5170  A = X1(K,J)
5180  X1(K,J) = X1(M,J)
5190  X1(M,J) = A
5200  NEXT
5210  FOR J = K TO N + 1
5220  X1(K,J) = X1(K,J) / P1
```

— if want to try some other M%

K ? Relative Humidity, assume only 1.

```
5230  NEXT
5250  FOR J = N + 1 TO K STEP - 1
5260  X1(L,J) = X1(L,J) - X1(L,K) * X1(K,J)
5270  NEXT
5280  NEXT
5290  NEXT
5300  GOTO 5340
5310  PRINT "DEPENDENT OR INCONSISTANT"
5320  PRINT "INPUT DATA ERROR"
5330  RETURN
5340  FOR J = N TO 2 STEP  - 1
5350  FOR I = (J - 1) TO 1 STEP  - 1
5360  X1(I,N + 1) = X1(I,N + 1) - X1(J,N + 1) * X1(1,J)
5370  X1(I,J) = 0
5380  NEXT
5390  NEXT
5400  RETURN
6000  REM
6001  HOME
6005  PRINT "ENTER THE UPPER LIMIT OF M% IN GM/100GM DRY PRODUCT"
6006  INPUT Y2
6007  HGR2 : HCOLOR=3
6010  A = 15:B = 175:C = 275
6020  HPLOT A,5 TO A,B TO C,B
6030  Y1 = 0
6040  RY = Y2 - Y1
6050  ST = RY / 100
6060  SY = (A - B) / RY
6070  X1 = 0:X2 = 100
6080  SX = (C - A) / (X2 - X1)
6090  DEF FN X(Y) = X1(1,N + 1) + X1(2,N + 1) * Y + X1(3,N + 1) * Y *
      Y + X1(4,N + 1) * Y * Y * Y
6100  FOR 1 = Y1 TO Y2 STEP ST
6110  GX = FN X(I)
6120  GX = A + SX * GX
6130  GY = 175 + SY * I
6140  IF GX < 0 OR GX > 279 OR GY < 0 OR GY > 179 THEN 6170
6150  IF GX < 45 THEN 6170ELSE1660
6170  NEXT I
6175  GOSUB 7500
6180  FOR I = 1 TO 5000: NEXT
6190  TEXT
6200  RETURN
7000  HOME
7010  PRINT "ENTER THE UPPER LIMIT OF TIME"
7020  INPUT R
7030  PRINT
7040  PRINT "ENTER THE UPPER LIMIT OF M%"
7050  HGR2 : HCOLOR = 3
7070  A = 15:B = 175:C = 275
7090  X1 = 0:X2 = R
```

```
7100  SX = (C - A) / (X2 - X1)
7110  Y1 = O:Y2 = MMAX
7120  SY = (A - B) / (Y2 - Y1)
7130  FOR K = 1 TO N2
7140  FOR I = 1 TO N
7150  GX(K,I) = A + SX * T(K,I)
7160  GY(K,I) = 175 + SY * M1(K,I)
7170  PRINT GX(K,I),GY(K,I)
7180  NEXT I
7190  NEXT K
7200  M3 = 175 + SY * MO
7210  FOR K = 1 TO N2
7220  FOR I = 1 TO N - 1
7230  IF GX(K,I) < 5 OR GX(K,I + 1) < 5 THEN 7270
7240  IF GX(K,I) > 275 OR GX(K,I + 1) > 275 THEN 7270
7250  IF GY (K,I) < 15 OR GY(K,I + 1) < 15 THEN 7270
7260  HPLOT GX(K,I),GY(K,I), TO GX(K,I + 1),GY(K,I + 1)
7270  NEXT I
7280  HPLOT A,M3 TO GX(K,1),GY(K,1)
7290  NEXT K
7295  GOSUB 8200
7300  FOR I = 1 TO 7000: NEXT
7310  TEXT
7320  HOME
7330  PRINT "PLOT AGAIN? ENTER Y OR N"
7340  INPUT R$
7350  IF R$ = "N" THEN 7370
7360  GOTO 7000
7370  RETURN
7500  REM SHAL DEMO
7510  PRINT CHR$ (4) ; "BLOAD SHAPE ALPHABET,A24576"
7520  POKE 232, PEEK (43634): POKE 233, PEEK (43635)
7530  SCALE= 1
7540  ROT= 1
7570  ST$ = "I"
7580  VT = 22.4
7590  HT = 40
7600  GOSUB 9000
7610  ST$ = "I"
7620  VT = 22.4
7630  HT = 19.8
7640  GOSUB 9000
7650  ST$ = "O"
7660  VT = 23.1
7670  HT = 2
7680  GOSUB 9000
7690  ST$ = "50"
```

```
7700  VT = 23.1
7710  HT = 19
7720  GOSUB 9000
7730  ST$ = "100"
7740  VT = 23.1
7750  HT = 38
7760  GOSUB 9000
7761  ST$ = "RH%"
7762  VT = 23.1
7763  HT = 27
7764  GOSUB 9000
7770  ST$ = "-"
7780  VT = 1
7790  HT = 2.8
7800  GOSUB 9000
7810  ST$ = "-"
7820  VT = 10.7
7830  HT = 2.8
7840  GOSUB 9000
7850  ST$ = "0"
7860  VT = 22.3
7870  HT = 1
7880  GOSUB 9000
7890  ST$ = STR$  (Y2)
7900  VT = 1
7910  HT = 1
7920  GOSUB 9000
7930  Y3 = Y2 / 2
7940  ST$ = STR$ (Y3)
7950  VT = 10.7
7960  HT = 1
7970  GOSUB 9000
7971  ST$ = "M%"
7972  VT = 5
7973  HT = 1
7974  GOSUB 9000
7980  RETURN
8200  REM SHAL DEMO
8210  PRINT CHR$ (4);"BLOAD SHAPE ALPHABET,A24576"
8220  POKE 232, PEEK (43634): POKE 233, PEEK (43635)
8230  SCALE= 1
8240  ROT= 1
8250  ST$ = "I"
8260  VT = 22.4
8270  HT = 40
8280  GOSUB 9000
```

```
8300  VT = 22.4
8310  HT = 19.8
8320  GOSUB 9000
8340  VT = 23.1
8350  HT = 2
8360  GOSUB 9000
8370  R1 = R / 2
8380  ST$ = STR$ (R1)
8390  VT = 23.1
8400  HT = 19
8410  GOSUB 9000
8420  ST$ = STR$ (R)
8430  VT = 23/1
8440  HT = 38
8450  GOSUB 9000
8451  ST$ = "T(DAYS)"
8452  VT = 23.1
8453  HT = 27
8454  GOSUB 9000
8460  ST$ = "-"
8470  VT = 1
8480  HT = 2.8
8490  GOSUB 9000
8500  ST$ = "-"
8510  VT = 10.7
8520  HT = 2.8
8530  GOSUB 9000
8540  ST$ = "0"
8550  VT = 22.3
8560  HT = 1
8570  GOSUB 9000
8580  ST$ = STR$ (MMAX)
8590  VT = 1
8600  HT = 1
8610  GOSUB 9000
8620  MX = MMAX / 2
8630  ST$ = STR$ (MX)
8640  VT = 10.7
8650  HT = 1
8660  GOSUB 9000
8661  ST$ = "M%"
8662  VT = 5
8663  HT = 1
8664  GOSUB 9000
8670  RETURN
```

```
9000  HT = 7 * (HT - 1):VT = 8 * VT - 1
9010  FOR I = 1 TO LEN (ST$)
9020
9030  IF CH = O THE 9050
9040  XDRAW CH AT HT,VT
9050  HT = HT + 7
9060  NEXT I
9070  RETURN
```

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