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SHELF LIFE PREDICTION OF A PACKAGED MOISTURE
SENSITIVE SOLID DRUG PRODUCT OVER A
RANGE OF TEMPERATURE AND RELATIVE HUMIDITY VALUES

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Jack R Giacin
Major professor

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SHELF LIFE PREDICTION OF A PACKAGED MOISTURE SENSITIVE SOLID DRUG PRODUCT OVER A RANGE OF TEMPERATURE AND RELATIVE HUMIDITY VALUES

By

Monica Kirloskar

A THESIS

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ABSTRACT

SHELF LIFE PREDICTION OF A PACKAGED MOISTURE SENSITIVE SOLID DRUG PRODUCT OVER A RANGE OF TEMPERATURE AND RELATIVE HUMIDITY VALUES.

By

Monica Kirloskar

The change in moisture content of moisture sensitive solid dosage forms was determined under various temperature and relative humidity conditions for the purpose of predicting shelf life. Effects of temperature on the coefficients of the best fit model selected by statistical analysis was determined, and moisture content for the product as a function of temperature and relative humidity was calculated. Shelf life of the product, based on the physiochemical properties of the drug and the moisture permeability of the package was then simulated by a computer program. Experimental studies showed that the prediction of the change in moisture content of packaged tablets over time by the simulation model is accurate, within a practical range of temperature and relative humidity. The developed semi-empirical model is considered to have applications in industry, since it provides product shelf life information for a range of temperature and relative humidity conditions, with limited data points.

to my parents

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INTRODUCTION

The temperature and relative humidity at storage are two primary environmental factors influencing the shelf life of a packaged, moisture sensitive drug product. It is critical therefore, to account for associated environmental fluctuations when predicting the shelf life for a packaged product, where physical or chemical deterioration of the product is related to its equilibrium moisture content. In the case of drug products, serious medical hazards may follow from loss of intended potency or unappropriate therapeutic effect associated with deterioration.

Shelf life in pharmaceuticals may be affected by environmental conditions, as well as by inadequately tested or incompatible containers, faulty seals, or permeability of the container. In each case, the pharmaceutical may allow the ingress of unwanted moisture, or the egress of active ingredients.

Water, as the main component of food and biological materials plays a predominant role in determining their shape, structure, as well as their physical and chemical properties. It is also a major control component in mass transfer, chemical reactions, and the activity of microorganisms. Thus, both gain or loss of moisture can influence the quality of a pharmaceutical product. Drug quality is mainly attributed to chemical identity, and to reaction rates as a function of time and environmental conditions. Water may influence the chemical reactivity in different ways. For example, it may act as a reactant, such as in the case of sucrose hydrolysis (Leung, 1986). Further, as a solvent, water may exert a dilution effect on the substrates, thereby decreasing reaction rates. Typically, changes in hardness or color, rate of disintegration of active ingredients and solubility are the consequences of gain or loss of moisture by the product (Nakabayashi et al.,1980 a,b,c, 1981 a,b,c). Effects on texture and viscosity have also been observed and reported in the free water region, where binding forces are weak and a large change in percentage moisture gives only a small change in the associated water activity. However, much of the moisture may be mechanically trapped in the product (Bourne, 1986).

Broadly, there are two methods of shelf life evaluation. They are Actual Storage Testing and Estimation Techniques by Accelerated Test or Simulation Models. Actual Storage Testing by a long term stability study involves storing a packaged dry product under typical storage conditions of temperature and relative humidity. Samples are examined at regular time intervals and the degradation factor is recorded. Although these studies are expensive and require long time periods, they are required by the Federal Food and Drug Administration as part of a New Drug Application (NDA) (USP XXII "Stability Considerations in Dispensing Practice", "Current Good Manufacturing Practice for Finished Pharmaceuticals" 21 CFR). Accelerated test techniques predict product stability by conditioning the packaged product for a predetermined time at extreme storage conditions (i.e. temperature, relative humidity). This data is correlated to the data at ambient storage conditions to obtain a shelf life value. Mistaken assumptions and inherent errors in this procedure are the disadvantages to this type of estimation. Simulation modeling techniques involve combining expressions for product sensitivity, package effectiveness and environmental severity into a mathematical model, as shown in the diagram outlining the general simulation model approach for predicting shelf life (figure 1). This is then applied to predict the maximum allowable moisture content in the product, as a function of time when subjected to a specific storage environment (i.e. temperature and relative humidity).

The moisture content of a packaged product at any time (t) under constant external conditions of temperature and relative humidity, depends upon the equilibrium moisture content of the product and the permeability of the package.

$$Mt = f(Mec, \bar{P}) \qquad (1)$$

where Mt is the moisture content of a packaged product at any time (t), Mec is the equilibrium moisture content of the product [Mec = f(RH)ec], and $\bar{P}$ is the permeability constant of the package. Presuming that the shelf life of the product depends solely on the physical and chemical factors which are related to moisture content, it can be estimated. The other assumptions for

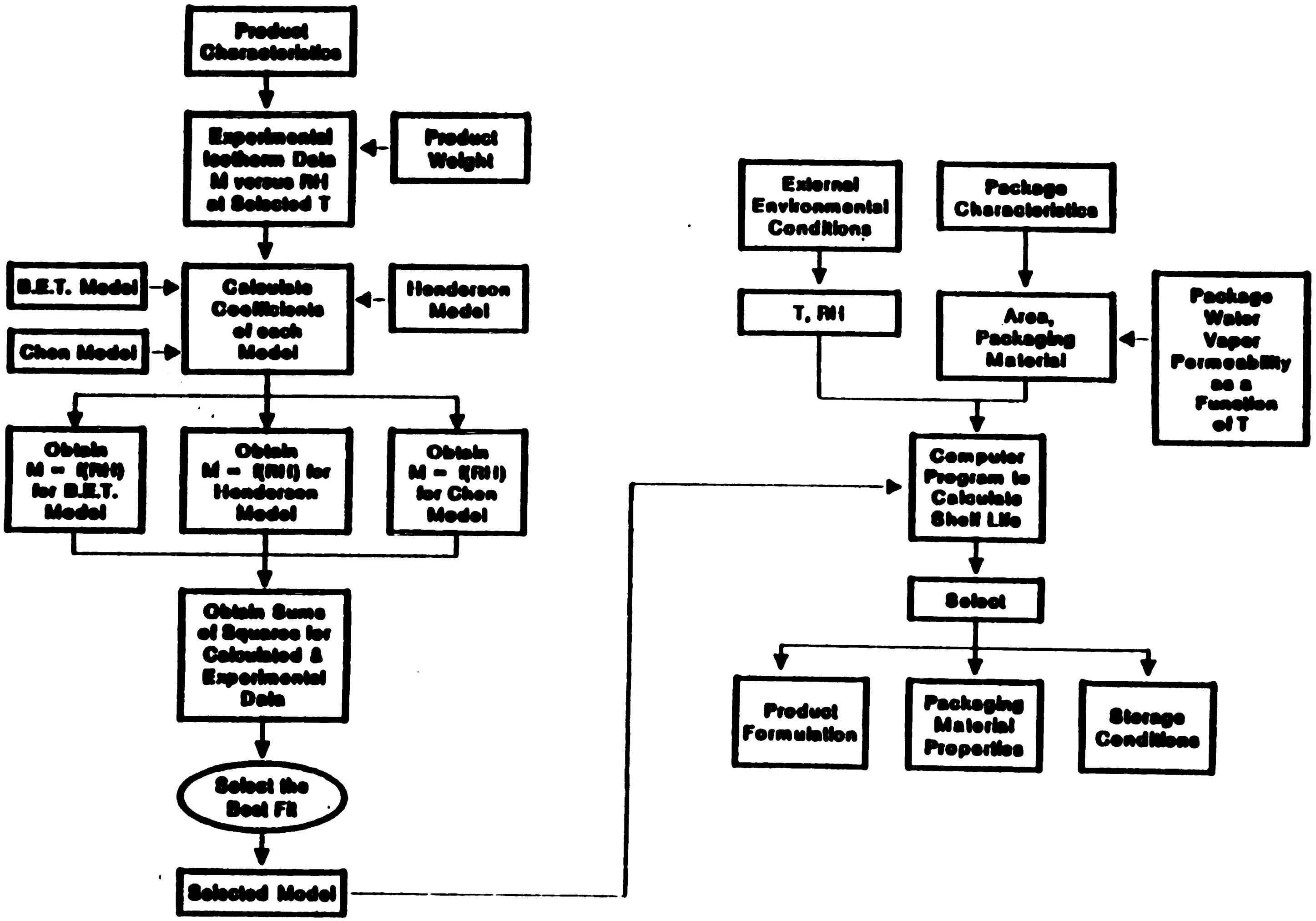

Figure 1 Diagram Outlining the Simulation Model for Predicting Shelf Life

predicting the shelf life by simulation include: (i) the moisture content of the packaged product will come to equilibrium quickly with the internal relative humidity within the package; (ii) the relative humidity inside the package is determined by the permeability of the package; and (iii) the relationship between the moisture content of the product and relative humidity within the package can be represented by an isotherm equilibrium curve.

The problem of shelf life prediction for a pharmaceutical product becomes crucial to packaging, when distribution channels and extended storage possibilities are considered. The shelf life of a packaged moisture sensitive drug product can be predicted by describing two phenomenon pertaining to the package-product system. First, transport of water vapor through the package, and secondly the uptake of water by the drug product. The permeability constant ($\overline{P}$) for water vapor through a polymeric structure is composed of a mobility term, described by the diffusion coefficient (D) and a solubility term described by the solubility constant (S). Both D and S, and therefore $\overline{P}$, are a function of temperature, and their dependency can be described by an Arrhenius type relationship. The sorption of water vapor by the drug product can be described by the equilibrium moisture isotherm. The concept of equilibrium moisture content (EMC) is important in the study of moisture change of packaged moisture sensitive products and is an integral component of the simulation models developed for estimation of shelf life. The EMC is defined as the moisture content of a product after it has been exposed to a particular environment. The water activity of the product at various moisture contents and temperatures will determine whether this product will gain or lose moisture when exposed to a surrounding environment.

Wang (1985) has described a model for predicting the moisture uptake of a packaged moisture sensitive product stored at constant temperature and relative humidity conditions. The model as described by Wang did not however, consider the effect of temperature on the package permeability, and on the sorption characteristics of the product. Therefore, for application of this model, experimental data is necessary at the specific temperature or temperatures of interest. Such data includes the product equilibrium sorption isotherm and the permeability of the package at the temperature or temperatures that the product is desired to be stored at.

Lee (1987) developed a more general simulation model which considered the change in product moisture content as a function of storage time, over a range of temperature and relative humidity values. The model combines the moisture sorption characteristics of the product and the permeability of the package system as a function of temperature. The Brunauer, Emmett and Teller (B.E.T.) equation (1938) was applied to describe the experimental sorption isotherm of the product. A cubic polynomial expression was used to fit the constants of the B.E.T. equation, to allow temperature interpolation. The resultant isotherm data was then fitted by a polynomial expression and substituted into the shelf life estimation model.

The agreement between experimental and calculated shelf life stability data obtained from the model, was considered to be within acceptable limits. These findings showed that the relationship between product shelf life and storage environment can be modeled within a practical range of temperature and relative humidity values, based on permeability data of the package and the equilibrium sorption isotherm of the product, obtained at three temperatures.

In the present study, three representative equations or models were selected to describe the experimental sorption isotherms. Two pharmaceutical products, orange flavored multivitamin tablets and ibuprofen tablets were evaluated. A statistical procedure was developed to select the best fit model from the data, for the experimental isotherms. Constants of the best fit equations were determined at selected temperature values, and fitted into the original equations. From these expressions, sorption isotherms at temperature (T) were calculated by interpolation. These values were then applied to a general simulation model to predict the shelf life within a practical range of temperature and relative humidity values, without having to obtain isotherm data for the product at the particular condition.

The objectives of this study include: (i) development of a procedure for selection of the best fit model or equation to describe the equilibrium sorption isotherm of a moisture sensitive pharmaceutical product. Selection will be based on statistical analysis of experimental and calculated data of product moisture content as a function of relative humidity; (ii) evaluating the effect of temperature on the coefficients of the equation selected to describe the equilibrium sorption isotherm of the product. This will allow for the calculation of the moisture content of the product as a function of relative humidity and temperature, over a selected range; (iii) develop a computer program which combines the expression for the isotherm as a function of temperature and the expression for the water vapor permeability of the package as a function of temperature with the equation for predicting the moisture uptake of the product as a function of time and storage environment, to give the shelf life simulation model. A further objective is to study the possibility of determining the minimum number of experimental data points necessary to fully describe the temperature and relative humidity dependency of the moisture sorption isotherm, and its application to shelf life prediction of packaged moisture sensitive drug products.

LITRATURE REVIEW

Water Activity

In pharmaceutical products a specific dose or concentration of a therapeutically active compound is to be present in a product. Thus, chemical stability is considered from the rate of degradation of the active drug, and not from the viewpoint of rate of formation of degradation products (Parrott, 1970). The availibility of free water can be a significant factor in the effectiveness of food processing and preservation and the potential for biochemical reactions and subsequent stability of the product. Water in foods exerts a vapor pressure, the magnitude of which depends upon the amount free to vaporize. Water activity (Aw) is the quotient of the water vapor pressure of the substance divided by the vapor pressure of pure water at the same temperature. Maximum storage stability of many dehydrated substances occurs at moisture contents close to the B.E.T. monolayer values (Brunauer et al., 1938) corresponding to Aw = 0.2 to 0.4 (Salwin, 1959). Salwin also suggested that the water molecules covering the active sites of the dry solids form a protective film against oxygen.

Most of the unit operations used in food processing have as a goal: (i) the removal of water to stabilize the material, as in drying and concentration, (ii) the transformation of water into a nonactive component, as in freezing; or (iii) the immobilization of water in gels, structured foods and low and intermediate moisture foods. The main and essential way in which the immobilization of water is measured is through the consideration of Aw, and its relationship to moisture content. Based on the thermodynamic concept of water chemical potential in solutions, Aw has served as an index of how successful we are at controlling water behavior in food or drug systems. Aw is also the parameter that controls the driving force in water removal operations, and is therefore essential for design purposes (Maguer, 1986).

Water may also change the mobility of the reactants by affecting the viscosity of food systems. Water may form hydrogen bonds or complexes with the reacting components. For example, lipid oxidation rate may be affected by hydration of trace metal catalysts or hydrogen bonding of hydroperoxides with water. The structure of a solid matrix may also change substantially with changes in moisture content, thus indirectly influencing reaction rates. In addition, water influences protein conformation, and the transition of amorphous-crystalline states of sugar and starch (Leung, 1986). To obtain desirable textures it is usually necessary to have a high moisture content, which means the Aw is high enough to support microbial growth. When dried to an Aw level that will not support microbial growth, the texture usually becomes too hard, dry, tough or crumbly (Bourne, 1986).

Shelf Life Simulation Models

Mathematical models have been used in both, the food and pharmaceutical sciences to describe the effect of temperature on the rate of a reaction , including high abuse temperatures. The continuous change in the distribution system may result in a more rapid rate of product deterioration, if subjected to high abuse temperatures. Also, the water activity of dry foods can increase with temperature increase (Labuza and Riboh, 1982). If the temperature accelerating factor is given, then extrapolation to lower temperatures could be used to predict shelf life of the product. This accelerating factor or the Arrhenius Q10 factor is the ratio of shelf life at two temperatures 10 degrees apart. When Q10 is not known, most reactions can be applied to fit a zero order or a first order mathematical equation such as,

$$\frac{-dA}{dt} = k(A)^{n} \qquad (2)$$

where A is the quality factor measured in some units of amount, n is the reaction order, k is the rate constant obtained from the slope of the plot of appropriate reaction extent (A) versus time (t) (Labuza, 1982). However, upon freezing, food product reactants are concentrated in the unfrozen liquid, creating a higher rate of quality loss at certain temperatures, which is not accounted for by the Q10 value, and will cause prediction errors (Fennema, 1985).

Chemical reactions can also cause a loss of vitamins such as vitamin C, where oxygen is limiting (Singh et al., 1974). Since vitamin C is quite unstable at pH values above 5.0, its degradation is generally considered as a loss in product quality. Labuza (1982) also showed that for frozen vegetables, when 15-20% of the vitamin C is lost, they also become unacceptable from a sensory standpoint. This is due to similar reaction Q10 values for sensory characteristics and nutrient.

Mizrahi and Karel (1977 a,b) studied shelf life simulation models extensively at the Massachusetts Institute of Technology by using computer aided mathematical solutions to predict chemical deterioration caused by moisture and oxygen interaction with food products. Karel and Labuza (1969) developed shelf life prediction models for dehydrated space foods. Studies were conducted on lipid oxidation in potato chips (Quast et al.,1972, a,b,c). Degradation of ascorbic acid in tomato juice was studied independently by two groups, Wanninger (1972) and Rimer and Karel (1978). Davis (1970) worked on the evaluation and selection of flexible film for food packaging.

Shelf life prediction has also been investigated under specific packaging conditions. Studies on their quality change due to gain or loss of moisture have been published. Labuza et al. (1972) used mathematical models to optimize flexible film packaging of food for storage. Nakabayashi et al.(1980 a) studied the stability of lactose-cornstarch tablets by mathematical modeling for quantification of physio-chemical changes of tablets due to moisture absorption through multilayer overwrapped types of packages, taking into consideration the construction of actual packages and the variations of ambient temperature and relative humidity during prolonged storage. Pires (1988) studied the effect of repetitive opening and closing of bulk packages. Oswin (1945) studied the influence of water vapor transmission rate (WVTR) on shelf life of packaged cigarettes.

Felt et al. (1945) compared the shelf life data for packaged cereal to actual field studies, and by calculation showed good agreement between calculated and observed results. Veillard et al. (1979) studied moisture transfer prediction for blister packages. Moisture permeation was studied by Reamer et al. (1977, 1978), by comparing the permeation characteristics of commercially available unit dose repackaging systems. From their studies a pharmacist could evaluate the moisture permeation of any unit dose repackaging system. Similar studies based on computer aided simulation were also done by Kentala et al. (1982).

Concepts of mass transfer to study shelf life were introduced by Heiss (1958), who developed a mathematical model which considered the moisture absorption properties of food, the water vapor permeability of the packaging material and the surrounding atmospheric conditions. Salwin and Slawson (1959) also developed a procedure to predict moisture transfer in combinations of dehydrated foods, from the knowledge of sorption isotherm of the individual components. Iglesias et al. (1979) extended Salwin and Slawson's work and predicted the moisture transfer in a mixture of packaged dehydrated foods.

A mathematical relationship between water vapor sorption by the product and package permeability was developed by Wang (1985), which allows calculation of relative humidity within the package at time(t). From the moisture equilibrium curve, the moisture content of the product can be calculated at any time (t) from the following expression.

$$t = \frac{g}{\bar{P}(T).Ps} \cdot \int_{Mo}^{Mt} \frac{dM}{[Aw(e)-Aw(M,T)]} \tag{3}$$

where t is the expected time, g is the dry product weight, $\bar{P}(T)$ is the permeability constant of the package, M is the instant moisture content differential, Mo is the initial moisture content, Mt is the moisture content at time t, Aw(e) is the water activity external to the package, Aw(M,T) is the internal water activity given as a function of temperature and moisture content of the product, T is the temperature, and Ps is the saturation pressure of water at temperature T. Experimental data has demonstrated that within a practical range of temperature and relative humidity values, the change in moisture content over time can be accurately predicted by solution of equation 3.

Absorption of moisture by the drug product can be described by the equilibrium moisture isotherm. It is described as the moisture content of the product after it has been exposed to a specific environment. The equilibrium moisture content (EMC) of a hygroscopic product is reached after the moisture content of the product has come to equilibrium with the moisture of the surrounding atmosphere. Plotting EMC versus equilibrium water activity (or % ERH) describes the water sorption or desorption characteristics of the product. This is the moisture sorption isotherm. The general configuration or shape of this curve depends on the properties of the product. Typically it results in a sigmoidal shaped curve, such as that described by the B.E.T. equation (Brunauer et al., 1938), which is probably the most popular food isotherm equation. A mathematical expression of the moisture sorption isotherm is necessary, and is incorporated into the model for shelf life simulation of a packaged moisture sensitive product.

Chirife and Iglesias (1978) compiled and mathematically described various equations for fitting water sorption isotherms of food. The equations evaluated were theoretical, semi-empirical, or were obtained by curve fitting of the experimental data. Several of the equations reported were equivalent or similar in aspect, although their origins are different. Some of these equations have been widely used, while others have had little or no success.

Several commonly used isotherm models are described below:

(i) The B. E. T. equation (Brunauer et al., 1938)

The B.E.T. equation is :

$$\frac{Aw}{(1-Aw)M} = \frac{1}{Mm\ C} + \frac{Aw(C-1)}{Mm\ C} \qquad (4)$$

where Mm is the monolayer moisture content, and C is the constant related to the net heat of sorption. The B.E.T. equation usually holds only between water activities from about 0.05 to 0.45, but this gives enough data so that the parameters Mm and C can be calculated (Labuza, 1968). The B.E.T. monolayer calculation is an effective method for estimating the amount of water bound to specific polar sites in dehydrated food systems (McLaren and Rowen, 1952 ; Duckworth and Smith, 1963). Although in the original B.E.T. expression (Labuza, 1968) the C term is related to the net heat of sorption for the first layer, Iglesias and Chirife (1976a), after examining a number of food systems, disregarded the use of the B.E.T. equation to estimate the heat of water sorption in foods. Iglesias et al. (1977a) discussed the statistical procedure to be used for the evaluation of parameters Mm and C from the well known linear form of the B.E.T. equation (equation 4) and from a rearranged one proposed by Caurie et al. (1976), which is:

$$\frac{1}{(1-Aw)M} = \frac{1}{Mm\ C} + \frac{1}{Mm}\ \frac{(1-Aw)}{Aw} \qquad (5)$$

Iglesias et al. (1977a) showed that conventional (or unweighted) least squares should not be used in equation 5, in order to derive the parameters Mm and C.

(ii) The Bradley equation

In Bradley's equation,

$$\ln (1/Aw) = K_2 K_1^{M} \qquad (6)$$

K_2 is a function of the sorptive polar groups, and K_1 is a function of the dipole moment of the sorbed vapor. Hoover and Mellon (1950) found that their data for the sorption of water in proteins, were fitted well by the

Bradley equation in the range of water activity 0.05 to 0.95. Equation 6 may be transformed into,

$$\ln \ln (1/Aw) = \ln K_2 + M \ln K_1 \quad (7)$$

which is a convenient form for testing, since a linear relationship should be obtained when plotting $\ln \ln(1/Aw)$ versus M.

(iii) The Caurie equation (Caurie, 1970)

The equation proposed by Caurie,

$$\ln C = \ln A - r\,Aw \quad (8)$$

was based purely on mathematical calculation. For the Caurie equation, r and A are constants and C is the water concentration. According to Caurie (1970), equation 6 is valid from zero water activity up to 0.85 water activity for most foods. Negatively sloping straight lines were obtained by plotting literature sorption data of certain foods (Caurie, 1970).

(iv) The Chen equation (Chen, 1971)

The Chen model (Chen, 1971) is based on the steady state of drying equation and is limited to situations where diffusion is the principal mode of mass transport. The equation developed is,

$$Aw = \exp\,[k + a \exp(bM)] \quad (9)$$

where k, a and b are temperature dependent constants. In applying this equation to a number of materials, Chen and Clayton (1971) found that the values for the constant k were very close to unity. Therefore, Chen's equation may be simplified to a two parameter equation,

$$Aw = \exp[a \exp(bM)] \qquad (10)$$

which can be further simplified to

$$\ln(-\ln Aw) = \ln a - bM \qquad (11)$$

which is similar to the Bradley equation (equation 7). Equation 11 can be further simplified as

$$\ln(-\ln Aw) = k - aM \qquad (12)$$

(v) The Harkins - Jura equation

This equation is expressed mainly for regions in which adsorbed molecules form a condensed film, as,

$$\ln Aw = B - A/M^2 \qquad (13)$$

where A and B are constants. Plotting ln Aw versus $1/M^2$ gives a straight line. Labuza (1968) suggested that this equation does not hold for water activity above 0.4.

(vi) The Halsey equation

Halsey (1948) developed the following equation to provide an expression for condensation of multilayers at a relatively large distance from the surface,

$$Aw = \exp(-a/RTM^r) \qquad (14)$$

where a and r are constants. It was observed by Iglesias et al. (1976a) that the use of the RT term does not eliminate the temperature dependence of constants a and r. Consequently, this equation was further simplified to the form,

$$Aw = \exp(-a/M^{r}) \qquad (15)$$

where a and r are constants (Iglesias and Chirife, 1976b). This equation described the sorption behavior fairly well, between the range of water activity 0.1 to 0.8.

(vii) The Halsey's modified equation

In order to describe the temperature dependency of the isotherm, Iglesias and Chirife (1976c), modified Halsey's equation as,

$$Aw = \exp[-\exp(bT + c)\ M^{-r}) \qquad (16)$$

where b, c and r are constants.

(viii) The Henderson equation (Henderson, 1952)

This is one of the most widely used models relating water activity and the amount of water sorbed, as,

$$1 - Aw = \exp - (kM^{n}) \qquad (17)$$

where k and n are constants. This can be rewritten as,

$$\ln[-\ln(1-Aw)] = n \ln M + \ln k \qquad (18)$$

such that a plot of ln [-ln (1-Aw)] versus ln M should give a straight line.

MODEL DEVELOPMENT

Shelf Life Model

A diagram outlining the proposed simulation model approach is shown in figure 1. The expression that describes the time needed for a product packaged in a moisture-semipermeable material to change its equilibrium moisture content from an initial to a final value, when the environmental humidity condition changes, is given by equation 19.

$$t = \frac{W}{\overline{P}(T).Ps} \cdot \int_{Mo}^{Mt} \frac{dM}{[Aw(e) - Aw(M,T)]} \tag{19}$$

where t = time

W = dry weight of product (g)

$\overline{P}(T)$ = permeability constant of the package at temperature T (g water/day. mm Hg. pkg)

Ps = saturated vapor pressure of water at temperature T (mm Hg)

dM = instant moisture content differential

Mo = initial moisture content

Mt = moisture content at time t

Aw(e) = water activity external to the package

Aw(M,T) = internal water activity given as a function of temperature and moisture content of the product

T = temperature

The internal water activity, Aw(M,T), can be obtained from the sorption equilibrium isotherm, that relates moisture content and water activity at a given temperature as follows.

Sorption Isotherm

From an initial examination of a series of moisture sorption equations for fitting isotherm data, three models were selected. These were,

Chen equation :

$$M = \frac{k - \ln(-\ln Aw)}{a} \tag{20}$$

Henderson equation :

$$M = \exp\{(1/n)[\ln(-\ln(1-Aw)) - \ln K]\} \tag{21}$$

B.E.T. equation :

$$M = \frac{B \cdot J \cdot (RH)}{(Cs-RH)\,[1 + (B-1)\,(RH/Cs)]} \qquad (22)$$

These equations represent a synopsis of the characteristic geometric configurations or shapes which describe equilibrium sorption isotherms and have been transformed to convenient linearized forms. The linearized equations are as follows:

Chen equation :

$$\ln(-\ln Aw) = k - aM \qquad (23)$$

Henderson equation :

$$\ln[-\ln(1-Aw)] = n \ln M + \ln K \qquad (24)$$

B.E.T. equation :

$$\frac{RH}{(Cs-RH)\,(M)} = \frac{1}{BJ} + \frac{(B-1)}{BJ}\,\frac{(RH)}{Cs} \qquad (25)$$

Selecting the best fit model

For the pharmaceutical tablet considered, the best fit of the experimental equilibrium sorption data to the linearized form of equations 23-25 was determined by linear regression analysis. The correlation coefficient estimated the degree of fit among the three equations or models. The estimate for the parameters in the equations was calculated graphically using slope and intercept values from equations 23-25. By substituting these parameter values back into the isotherm equation, calculated sorption data was obtained. A comparison of the experimental and calculated isotherm data, given by a value of sums of squares, discriminated the best fit model.

Effect of temperature on sorption isotherm

The effect of temperature on the moisture sorption isotherm of a moisture sensitive product was evaluated by quantifying the effect of temperature on the coefficients of equations 23 - 25. To obtain an expression for the internal water activity, first the equation which accurately describes the equilibrium sorption isotherm of the product is selected. This can be illustrated by a three parameter equation like,

$$M = f\,[Aw,\ b,\ c,\ d] \qquad \text{(i)}$$

where Aw is the water activity and b, c and d are parameters. The sorption isotherms of the product at three temperatures T1, T2 and T3 (T1 < T2 < T3) were determined. The moisture content of the product at the respective temperatures is then given by,

$$Mi = f\ [Aw,\ bi,\ ci,\ di]\ ,\ i = 1,2,3 \qquad \text{(ii)}$$

Values of the parameters bi, ci, di are correlated as a function of temperature, using Newtons divided difference interpolating formula (discussed in the following section). Expressions for the constants b, c, d are written as a function of temperature as,

$$M(T) = f\ [Aw,\ b(T),\ c(T),\ d(T)] \qquad \text{(iii)}$$

From equation (iii) the moisture content of the product can be calculated at any temperature between T1 and T3. Applying the Newton-Raphson method (explained below), the internal water activity in equilibrium with the product can be expressed as,

$$A(M,T) = f\ [M,\ B(T),\ C(T),\ D(T)], \qquad \text{(iv)}$$

where B, C and D are constants.

Now equation (iv) can be substituted into equation 19 to determine the moisture content change of the packaged product over time. The permeability constant of the package $\bar{P}(T)$ is obtained by measuring the package water vapor permeability at the three temperatures T1, T2 and T3, and using an Arrhenius type of equation to correlate P as a function of temperature.

At constant temperature, and from sorption equilibrium data, the internal water activity of the product was taken to be equal to the water activity of the environment surrounding the product. From isotherm expressions, such as equations 20 - 22, water activity could be related to the moisture content of the product.

From equation (iv), and using equations 23 - 25, the moisture content of the product can then be calculated as a function of relative humidity, at any temperature between T1 and T3. A series of values of M(T) and relative humidity (water activity) can then be calculated.

Newton's divided-difference interpolation:

Newton's divided-difference interpolating formula is a strategy for obtaining an improved estimate by introducing some curvature into the line connecting the points. With 3 data points available this can be accomplished with a second-order or quadratic polynomial of the form,

$$f(x) = b_0 + b_1(x-x_0) + b_2(x-x_0)(x-x_1) \qquad \text{(v)}$$

i.e., $f(x) = a_0 + a_1x + a_2x^2$

where $a_0 = b_0 - b_1x_0 + b_2x_0x_1$

$a_1 = b_1 - b_2x_0 - b_2x_1$

$a_2 = b_2$

with $x = x_0$ in (v), we can determine the values of the coefficients.

$$b_0 = f(x_0) \qquad \text{(vi)}$$

Substituting (vi) in (v) evaluated at $x = x_1$

$$b_1 = \frac{f(x_1) - f(x_0)}{x_1 - x_0} \qquad \text{(vii)}$$

Finally equations (vi) and (vii) can be substituted into equation (v) which can be evaluated at $x = x_2$ and solved for

$$b_2 = \frac{\dfrac{f(x_2) - f(x_1)}{x_2 - x_1} - \dfrac{f(x_1) - f(x_0)}{x_1 - x_0}}{x_2 - x_0} \qquad \text{(viii)}$$

where, b_1 represents the slope of the line connecting points x_0 and x_1. Thus, the first two terms of the equation (v) are equivalent to linear interpolation from x_0 to x_1. The last term, $b_2(x-x_0)(x-x_1)$, introduces the second-order curvature into the formula. It can be shown that equation (v) manifests a structure similar to the Taylor series expansion (Chapra S.C., Canale R.P., 1985).

Newton-Raphson method for solving equations:

In this method guess the first approximation to the root of the equation $f(x) = 0$. Use the first approximation to get a second, the second to get a third, and so on. To go from the n^{th} approximation x_n to the next approximation x_{n+1}, the following formula is used.

$$x_{n+1} = x_n - \frac{f(x_n)}{f^1(x_n)} \qquad (ix)$$

where $f^1(x_n)$ is the derivative of f at x_n. We use the tangent to approximate the graph of $y = f(x)$ near the point $p(x_n,y_n)$, where $y_n = f(x_n)$ is small, and we let x_{n+1} be the value of x where that tangent line crosses the x-axis. We assume that the slope $f^1(x_n)$ of the tangent is not zero. The equation of the tangent is

$$y - y_n = f^1(x_n)(x-x_n) \qquad (x)$$

We put $y_n = f(x_n)$ and $y = 0$ into equation (x) and solve for x:

$$x - x_n = \frac{-f(x_n)}{f^1(x_n)} \qquad \text{(xi)}$$

or as in equation (ix)

$$x = \frac{x_n - f(x_n)}{f^1(x_n)}$$

(Thomas and Finney, 1981). Equation 19 is then solved for the root of the equation obtained from Newton-Raphson method. Knowing the constant values in the equation, the function is solved in the interval between the initial moisture content and the critical moisture content, and subintervals obtained by the approximation from equation (ix).

Temperature dependence of the package permeability

The $\overline{P}(T)$ term was obtained at three temperatures, T1, T2, and T3, and the data fitted to an Arrhenius type expression to correlate $\overline{P}$ as a function of temperature.

Computer Simulation Model

To solve equation (19), a trapezoidal numerical integration procedure was used. The value of time (t) obtained, indicated the time required for the initial moisture content (Mo) of the product to change, at the temperature To and the initial humidity RHo, to a final value Mt at Tt and RHt. A flow-chart for the computer program is shown in Appendix 1. The program written in BASIC for this purpose is an extension to Lee's study (Lee, 1987) and is presented in Appendix 2.

MATERIALS AND METHODS

For this study, 200 mg Motrin IB Ibuprofen, analgesic tablets were used, as the moisture sensitive product. All the tablets used were from a single lot. The active ingredient in each tablet is Ibuprofen USP 200 mg. The other ingredients in this formulation being carnauba wax, corn starch, hydroxypropylmethyl cellulose, propylene glycol, silicon dioxide, pregelatinized starch, stearic acid and titanium dioxide.

Determination of Initial Moisture Content

The initial moisture content (IMC) was determined by the Karl Fischer titrimetric method. The procedure was adapted from the general moisture content determination process of The Upjohn Company, Kalamazoo, Michigan. A precision "Aquatrator", Manual model, (Precision Scientific Company, Chicago, Illinois) was used for the Karl Fischer conductometric moisture determination apparatus.

The unit consisted of two exposed platinum wires which is the sensing element of the circuit. If the solution contains moisture (water) a high resistance, due to polarization, impedes the flow of current across this electrode. As the moisture reacts with the Karl Fischer reagent, the resistence of the solution gradually decreases at the electrode (depolarizes) and current flow increases, as indicated by the microammeter. The end point is defined as the chosen value so that each drop of titrant is still sensed when this value is reached.

The Karl Fischer reagent was standardized according to the following procedure: The buret was flushed with Karl Fischer reagent. Approximately 30 ml of absolute methyl alcohol was added to the reaction vessel (beaker) and placed into position on the aquameter. This was titrated to end point with Karl Fischer reagent. Approximately 300 mg of sodium tartrate, neutral, ACS grade was weighed accurately and added to the above solution. The mixture was then titrated to end point. The water equivalent of the Karl Fischer reagent, expressed in mg of water per ml of Karl Fischer reagent, was calculated according to equation 23.

$$(Sw \times 0.1566)/KF = \text{Water equivalent (mg/ml)} \qquad (23)$$

where Sw = weight of sodium tartrate (mg)

0.1566 = water content of sodium tartrate

KF = ml of Karl Fischer reagent used

Two tablets were accurately weighed on weighing paper using a Mettler AE 160 electronic balance, having up to four decimal place accuracy. Again, approximately 30 ml of absolute methyl alcohol was added to the reaction vessel on the aquameter. The tablets were then added to the above solution and titrated to the end point. The moisture content of the tablets, was expressed as weight percent (wt/wt), using the following expression:

$$(KF \times We)/Sw \times 100 = \%\ \text{water} \qquad (24)$$

where KF = ml of Karl Fischer reagent used in titration

We = Water equivalent of Karl Fischer reagent (in mg/ml)

Sw = Sample weight (in mg)

Five replicate analyses, were performed for determination of IMC. The average IMC expressed as grams of water per 100 grams of dry weight of product, was calculated from the percent moisture content obtained from equation 24, for all five replicates.

Moisture Sorption Isotherm

A gravimetric method was used for determining the moisture sorption isotherm at 12, 21, 28 and 33 degrees Celsius. The equilibrium moisture content was expressed as percent moisture on a dry weight basis (gms moisture/100 gms dry product).

Temperature control chambers were regulated at the desired temperatures of 12, 21, 28 and 33 degrees Celsius. The relative humidity was maintained by tightly closed, 5 gallon buckets which held the samples. The relative humidity ranged from 21.4 to 90.5 percent and was obtained by saturated solutions of appropriate salts. Table 1A and 1B displays the relative humidity values corresponding to the salt solutions at the respective temperatures of test. Salt solutions were prepared by adding deionized water to the chemically pure salt in a crystallization dish, with constant stirring until approximately half the salt crystals were dissolved. The relative humidity and temperature were monitored daily by humidity sensors mounted in the lid of the buckets. (Hygrodynamics, "Creating and maintaining humidities by salt solutions", technical bulletin No. 5. Hygrodynamics Newport Scientific, Inc. 8246-E Sandy Court, Jessup, MD 20794-0189).

Table 1A. Saturated salt solutions for relative humidity buckets

Saturated salt solution	Formula
Potassium Acetate	$KC_2H_3O_2$
Magnesium Chloride	$MgCl_2.6H_2O$
Potassium Carbonate	$K_2CO_3.2H_2O$
Magnesium Nitrate	$Mg(NO_3)_2.6H_2O$
Sodium Nitrite	$NaNO_2$
Ammonium Sulphate	$(NH_4)_2SO_4$
Potassium Nitrate	KNO_3

Table 1B. Equilibrium relative humidities for saturated salt solutions at 12, 21, 33, 28 degrees C

Saturated salt solution	% Relative humidity			
(degrees C):	12	21	33	28
$KC_2H_3O_2$	22	21.6	21.4	21.4
$MgCl_2.6H_2O$	32.8	32	29	31.2
$K_2CO_3.2H_2O$	45	45	42	43.5
$Mg(NO_3)_2.6H_2O$	58.5	55.1	52	53.5
$NaNO_2$	65.2	62.5	62	62
$(NH_4)_2SO_4$	80	78.5	77	77.5
KNO_3	90.5	88.5	88	88

Approximately 2 to 3 grams of tablets were accurately weighed into petri dishes and placed into the relative humidity buckets. Three replicates were made at each condition of temperature and relative humidity. At predetermined time intervals, the humidity buckets were opened and lids quickly placed on each petri dish. The samples were weighed and returned to the respective environmental chambers until saturation levels in weight gain were obtained. This indicated that equilibrium had been achieved. The average weight gain from three replicates was used to determine the equilibrium moisture content (EMC) at each relative humidity, calculated using the following expressions:

Let Pi = initial product weight (gms)
Pf = final product weight (gms)
IMC = initial moisture content (gms H_2O/ gm dry weight product)

$$\text{then EMC} = \left[\frac{Pf\,(1+IMC)}{Pi} - 1 \right] \times 100 \qquad (25)$$

Moisture sorption isotherms were obtained by plotting the equilibrium moisture content versus relative humidity for each temperature.

RESULTS AND DISCUSSION

Initial Moisture Content

The initial moisture content of the product was determined by the Karl Fischer titrimetric method. The data obtained was used to calculate the initial moisture content needed to determine the equilibrium moisture content. Since the nature of the Karl Fischer Reagent is such that its titer value may vary during the course of the day due to atmospheric moisture pickup, its titer value was checked frequently. Also fresh Karl Fischer reagent was used for every analysis.

The initial moisture content was found at the start of each sorption isotherm experiment for a new temperature. The average of three replicates was used for calculation of EMC. The values of initial moisture content are listed in Table 2.

Table 2. Initial Moisture Content of Ibuprofen Tablets

Analysis #	(temperature set) degrees Celsius		Average moisture content gms water/100 gms dry product
1	12		3.02
2	21		3.02
3	33		3.01
4	28		3.01
		Average:	3.015 +/- 0.016

The average initial moisture content obtained was 3.015 +/- 0.016 gms water/100 gms dry weight of product. According to the United States Pharmacopeia, the specification for moisture content in Ibuprofen tablets is not more than 5% (wt/wt), USP XXI (1985).

Equilibrium Moisture Isotherm

Values for the equilibrium moisture content and the associated relative humidity values for the Ibuprofen tablets determined at temperatures of 12, 21, 33, and 28 degrees Celsius are summarized in Table 3, 4, 5, and 6 respectively. The equilibrium sorption isotherms for the data are plotted in Figures 2, 3, 4, and 5, respectively.

Table 3. Equilibrium Moisture Content (EMC) of Ibuprofen tablets at 12 degrees Celsius

Relative humidity %	Equilibrium moisture content gms water/100 gms dry weight
22	3.62
32.8	4.20
45	4.73
58.5	5.13
65.2	5.81
80	7.56
90.5	8.59

Table 4. Equilibrium Moisture Content (EMC) of Ibuprofen tablets at 21 degrees Celsius

Relative humidity %	Equilibrium moisture content gms water/100 gms dry weight
21.6	3.44
32	3.98
45	4.56
55.1	4.83
62.5	5.42
78.5	7.13
88.5	8.33

Table 5. Equilibrium Moisture Content (EMC) of Ibuprofen tablets at 33 degrees Celsius

Relative humidity %	Equilibrium moisture content gms water/100 gms dry weight
21.4	3.21
29.6	3.60
42	4.22
52	4.60
62	5.18
77	6.88
88	7.96

Table 6. Equilibrium Moisture Content (EMC) of Ibuprofen tablets at 28 degrees Celsius

Relative humidity %	Equilibrium moisture content gms water/100 gms dry weight
21.4	3.27
31.2	3.73
43.5	4.32
53.5	4.62
62	5.25
77.5	6.95
88	8.15

I. Application to simulation model

Here 28 degrees Celsius was used as the temperature to verify the results of the study. According to the theory developed for the simulation model, the values for the constants of the isotherm equations were obtained by linearizing the expressions for the three isotherm equations selected. The linearized plots of isotherm data for the three models, at the four temperatures, are

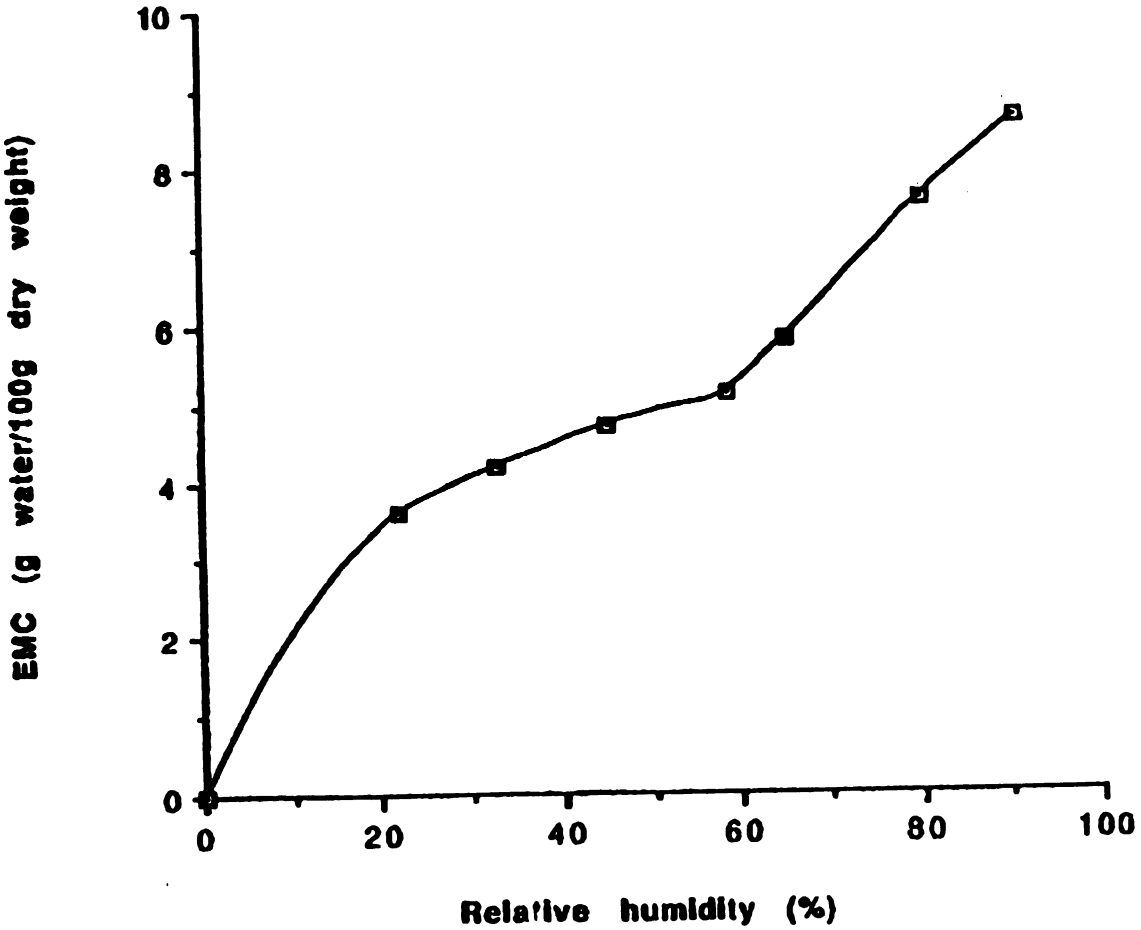

Figure 2 Experimental Moisture Sorption Isotherm of Ibuprofen tablets 12 degrees C

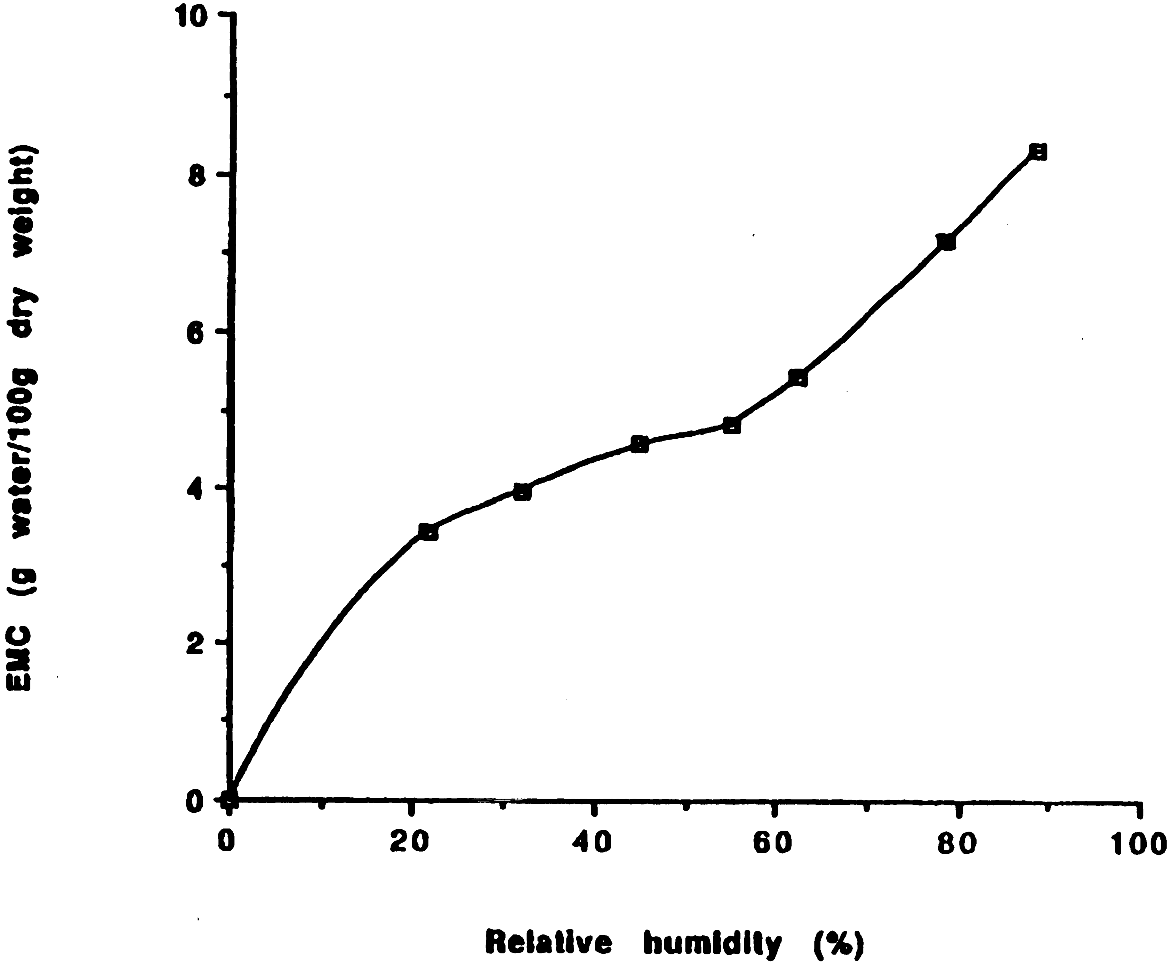

Figure 3 Experimental Moisture Sorption Isotherm of Ibuprofen tablets 21 degrees C

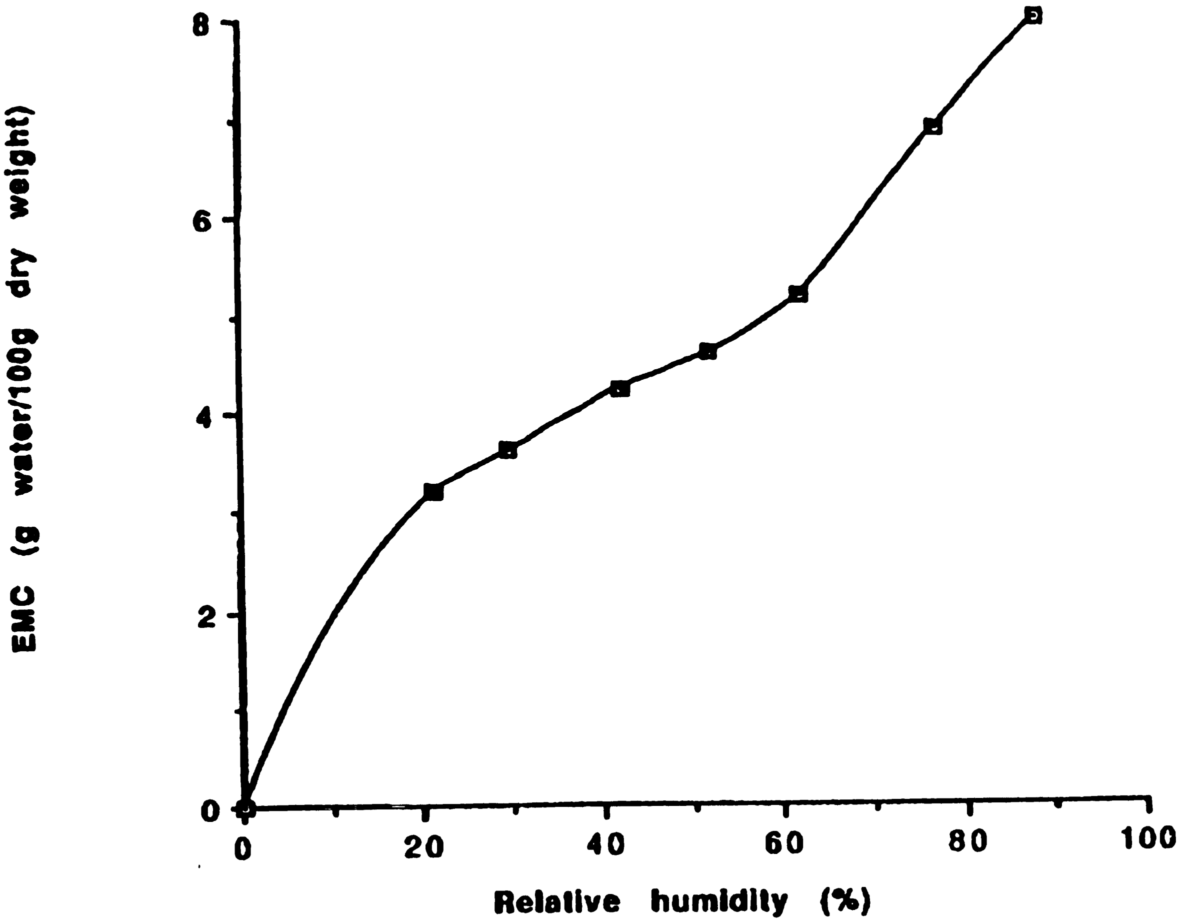

Figure 4 Experimental Moisture Sorption Isotherm of Ibuprofen tablets 33 degrees C

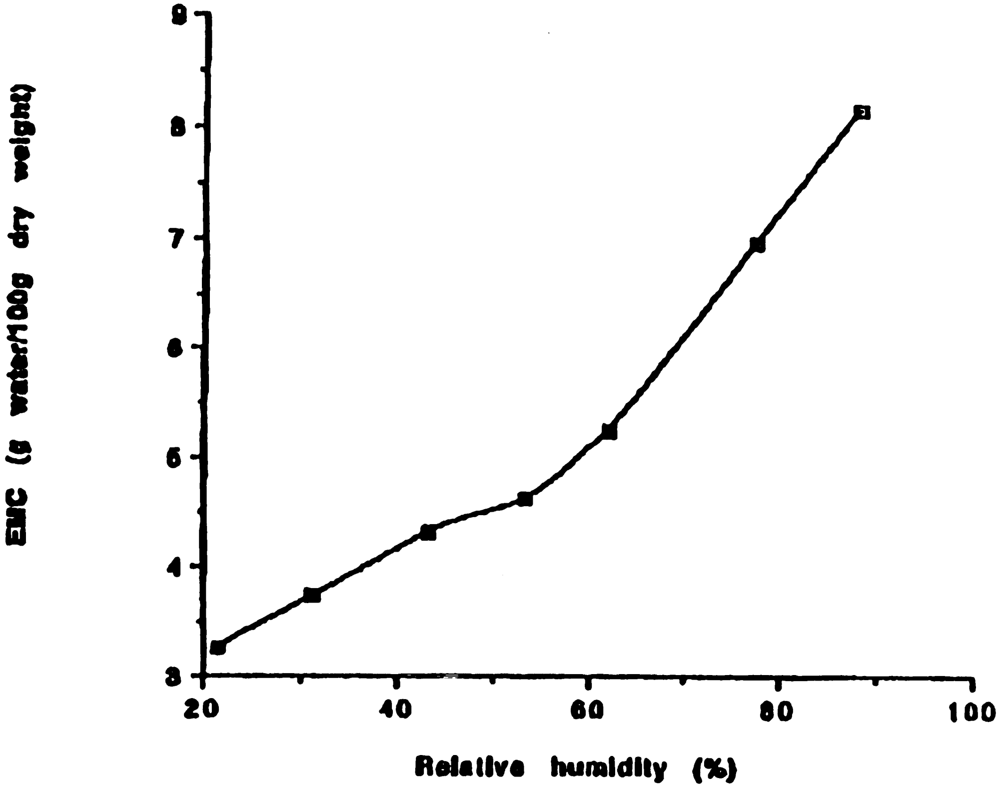

Figure 5 Experimental Moisture Sorption Isotherm of Ibuprofen tablets 28 degrees C

shown in Figures 6 to 14 respectively. The values of the constants are calculated from the slope and y-intercept of the plot. Newtons divided-difference interpolating formula was applied to determine isotherm data at 28 degrees C. The derived constants are as follows:

at 12 degrees C

CHEN model: A = -0.52, K = 2.22

HENDERSON model: N = 2.48, K1 = 0.012

B.E.T model: B = -1713.72, J = 3.1344, Cs = 141

at 21 degrees C

CHEN model: A = -0.51, K = 2.055

HENDERSON model: N = 2.39, K1 = 0.015

B.E.T. model: B = -3411.27, J = 2.98, Cs = 137

at 33 degrees C

CHEN model: A = -0.50, K = 1.97

HENDERSON model: N = 2.31, K1 = 0.019

B.E.T. model: B = 50.18, J = 3.033, Cs = 140

By substituting these values into the isotherm expressions selected for the study, moisture content values were calculated at the respective temperatures, as a function of relative humidity. Plots for the coefficients A, K, N, K1, B, J, Cs as a function of temperature are shown in the Appendix 3.

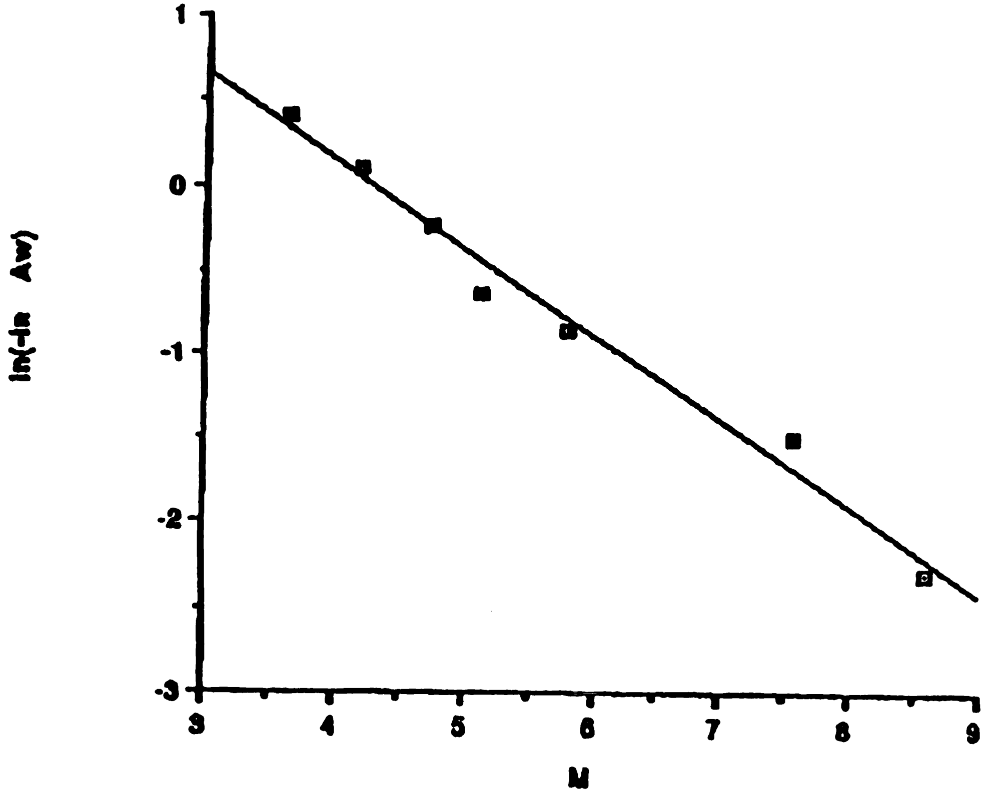

Figure 6 Linearized Isotherm Data : Chen model at 12 degrees C

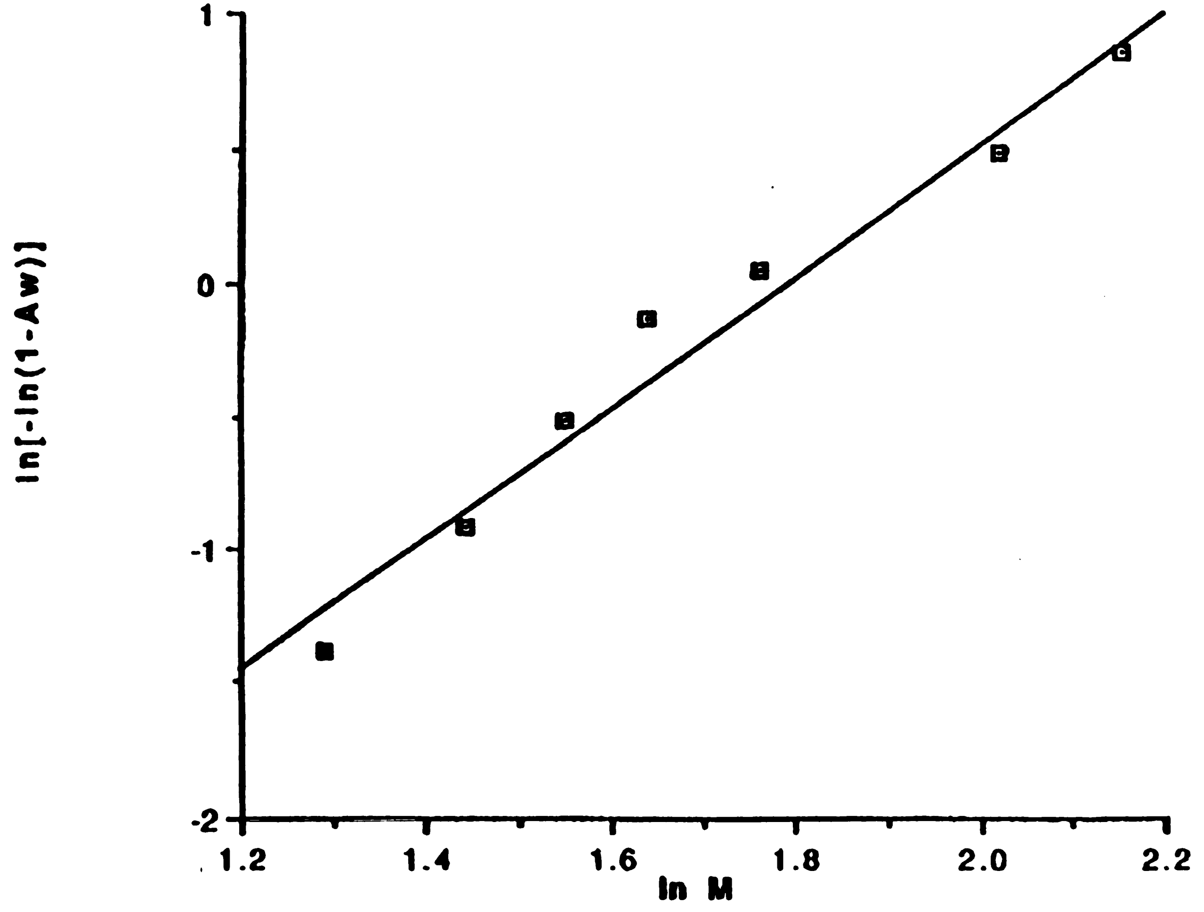

Figure 7 Linearized Isotherm Data : Henderson model at 12 degrees C

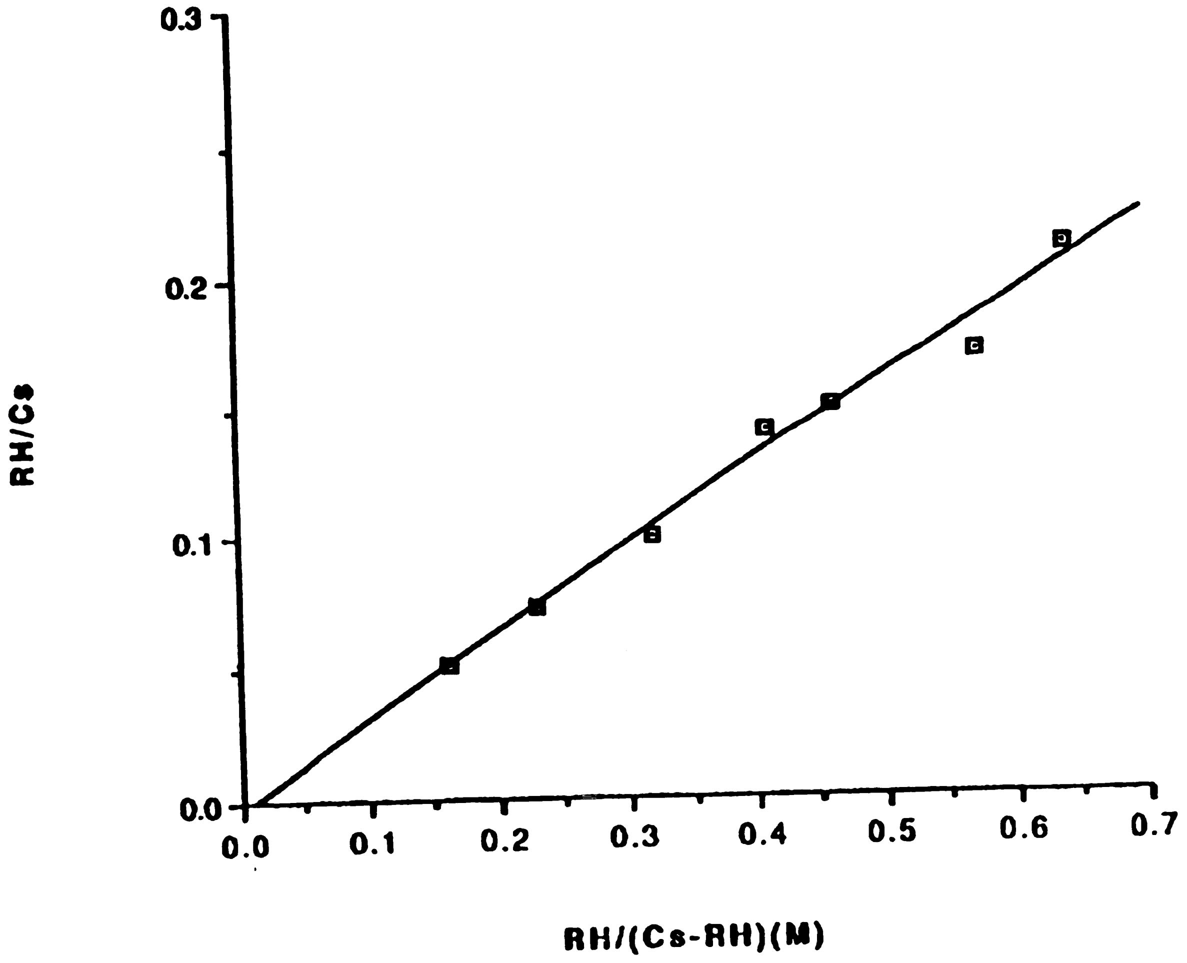

Figure 8 Linearized Isotherm Data : B.E.T. model at 12 degrees C

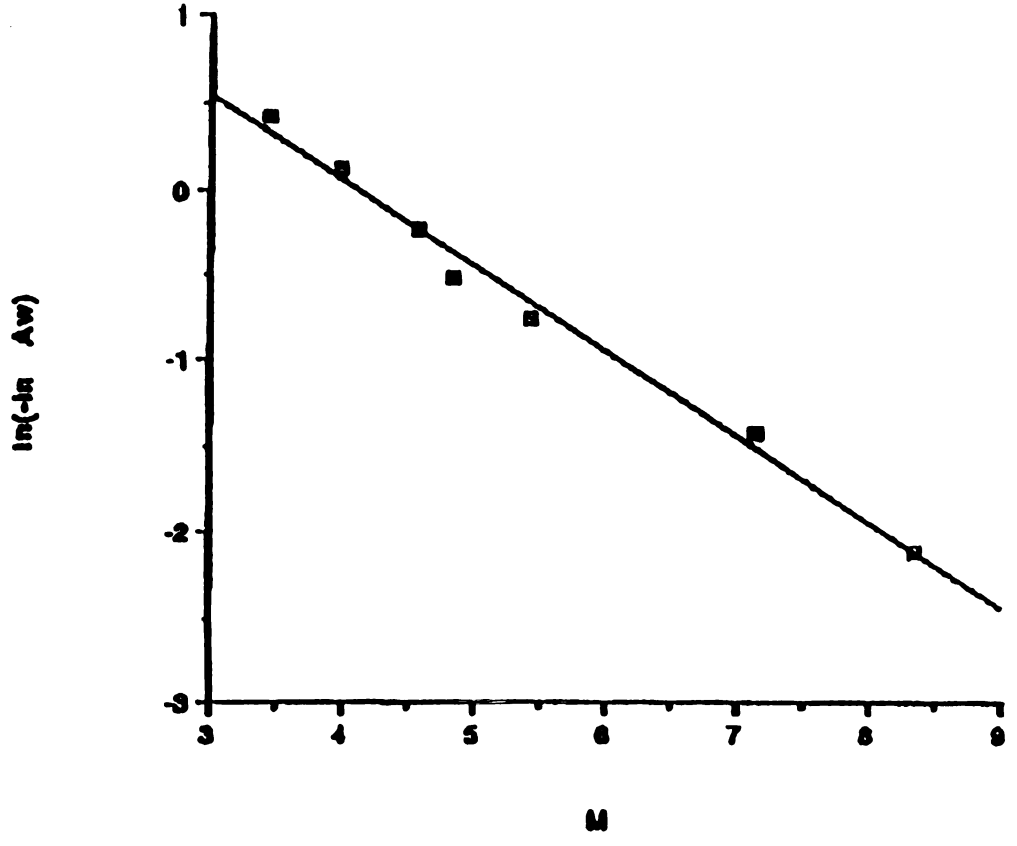

Figure 9 Linearized Isotherm Data : Chen model at 21 degrees C

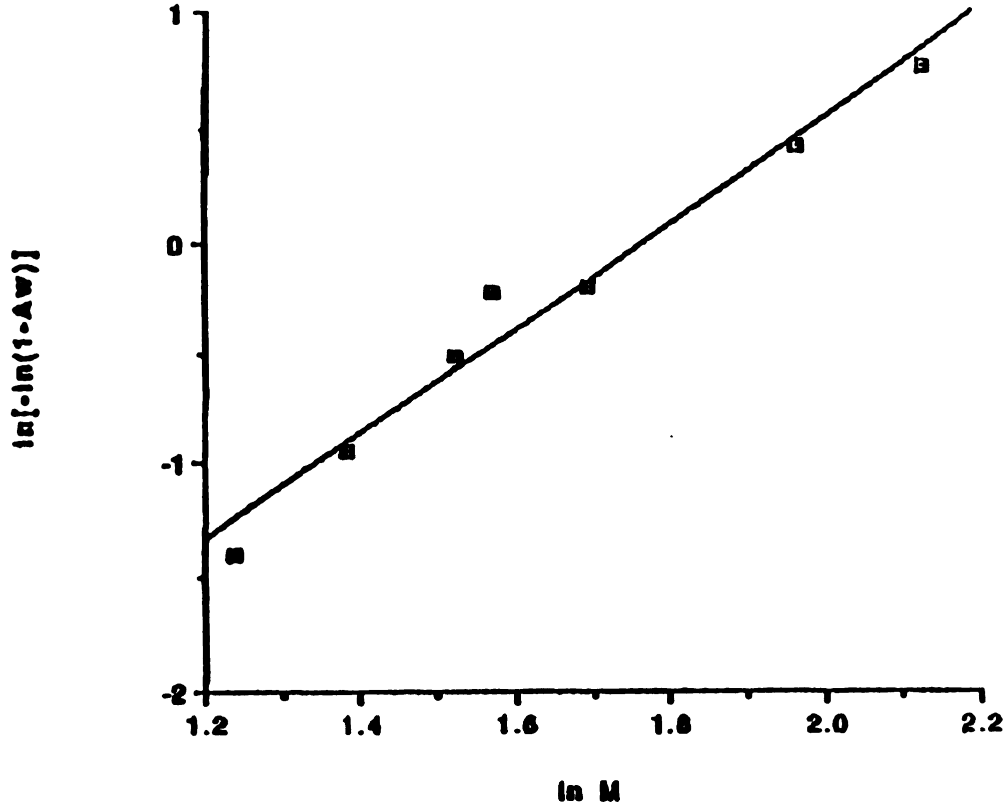

Figure 10 Linearized Isotherm Data : Henderson model at 21 degrees C

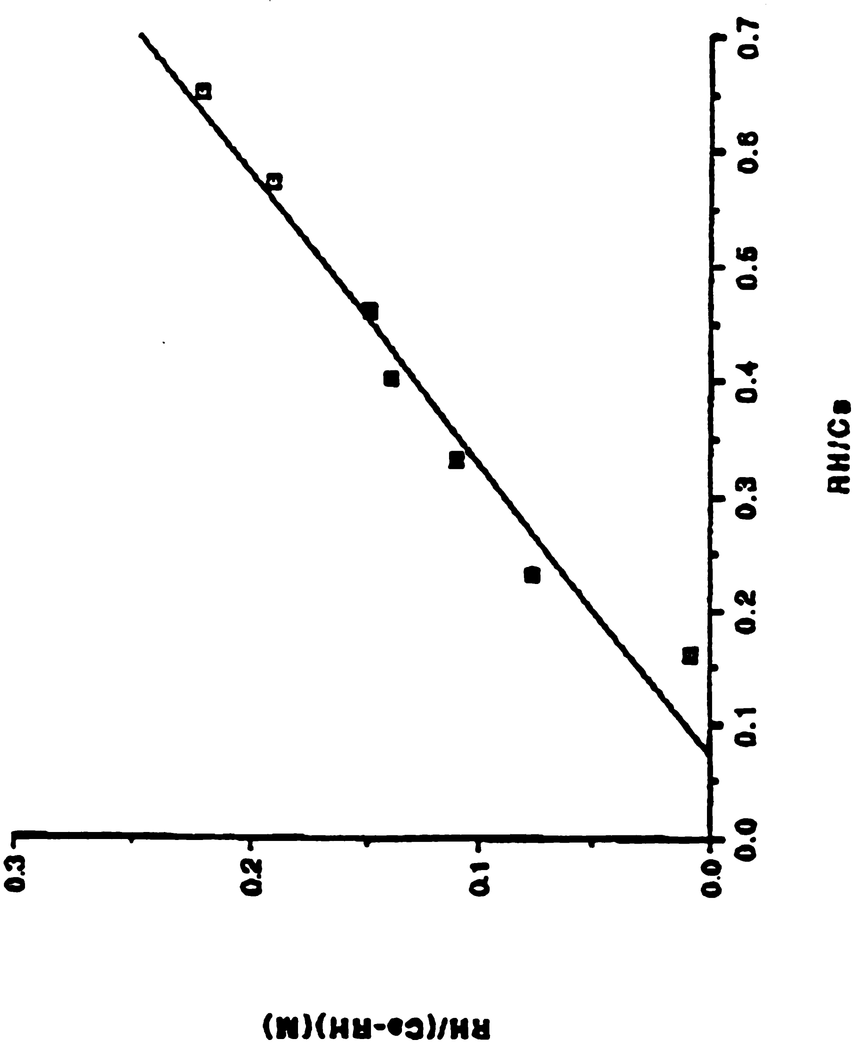

Figure 11 Linearized Isotherm Data : B.E.T. model at 21 degrees C

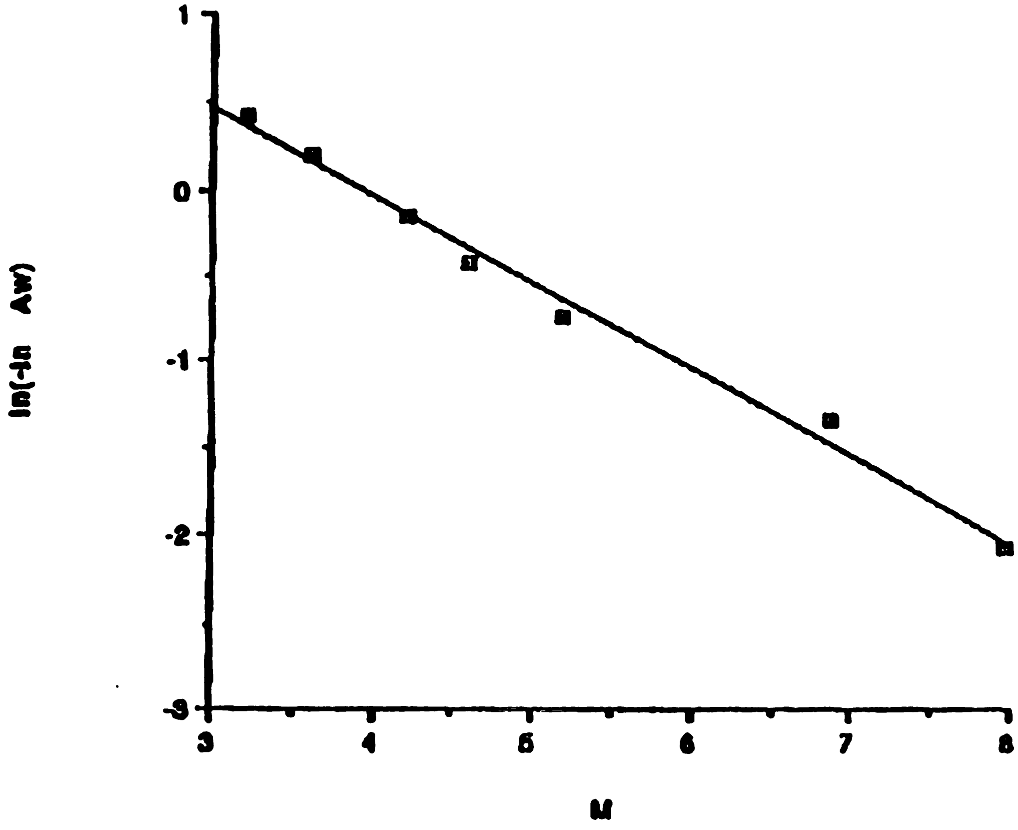

Figure 12 Linearized Isotherm Data : Chen model at 33 degrees C

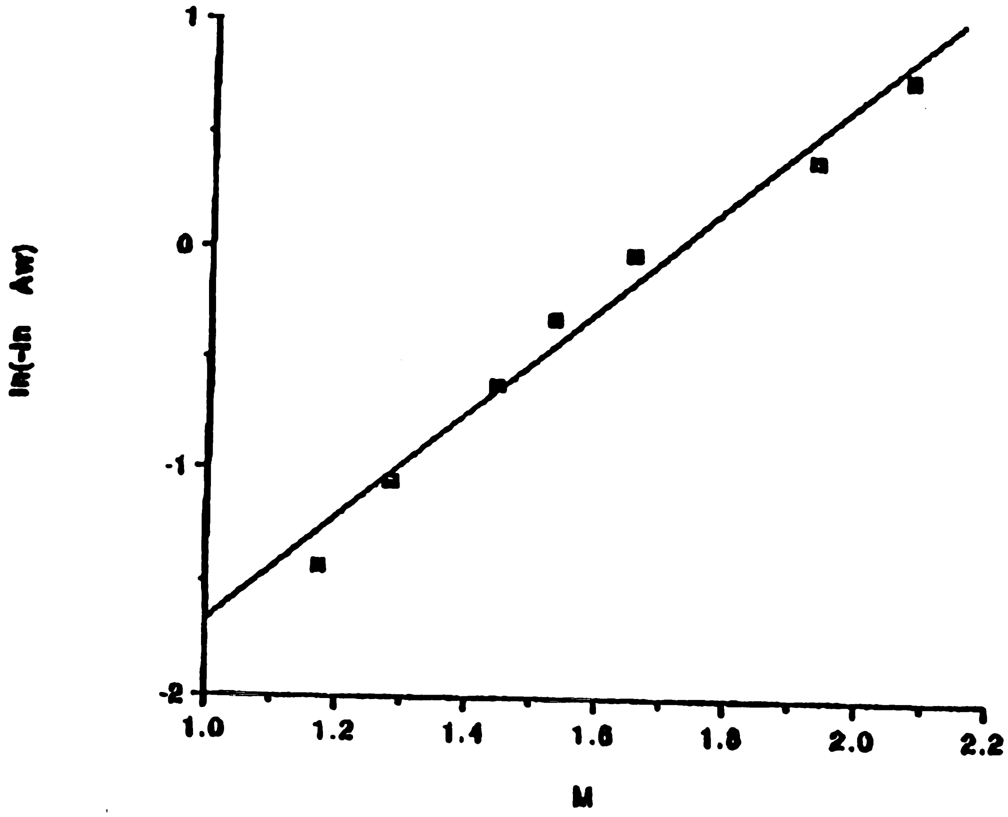

Figure 13 Linearized Isotherm Data : Henderson model at 33 degrees C

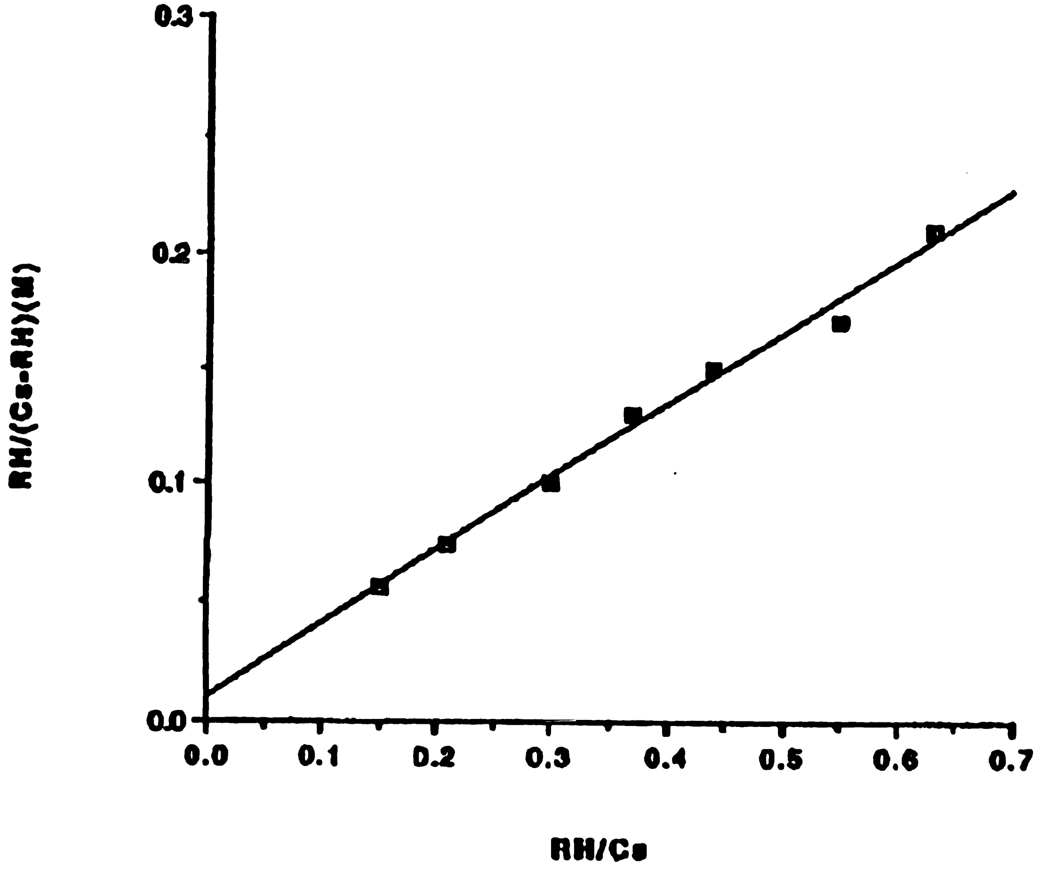

Figure 14 Linearized Isotherm Data : B.E.T. model at 33 degrees C

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Temperature dependency of equilibrium sorption isotherm

As discussed in the Model Development section, using the Newtons divided-difference interpolating formula, the constants of the equations are derived from the isotherms determined at 12, 21 and 33 degrees Celsius respectively. The relationship between the respective constants as a function of temperature T is,

$$A(T) = A1 + B1\ T + C1\ T^2 \tag{26}$$

$$K(T) = A2 + B2\ T + C2\ T^2 \tag{27}$$

$$N(T) = A3 + B3\ T + C3\ T^2 \tag{28}$$

$$K1(T) = A4 + B4\ T + C4\ T^2 \tag{29}$$

$$B(T) = A5 + B5\ T + C5\ T^2 \tag{30}$$

$$J(T) = A6 + B6\ T + C6\ T^2 \tag{31}$$

$$Cs(T) = A7 + B7\ T + C7\ T^2 \tag{32}$$

where T is the temperature in degrees C and A1, B1, C1, A2, B2, C2, A3, B3, C3, A4, B4, C4, A5, B5, C5, A6, B6, C6, A7, B7, and C7 are constants. The values of the constants for 28 degrees

C were obtained as,

A = -0.50, K = 1.99 (Chen model)

N = 2.33, K1 = 0.017 (Henderson model)

B = -109, J = 2.97, Cs = 137.59 (B.E.T. model)

Substituting these values into the respective isotherm expressions, the following calculated values of moisture content were obtained at 28 degrees C and compared to the experimentally derived values. The results are summarized in Tables 7-9 respectively.

Table 7. Experimental and Calculated Equilibrium Moisture Content at 28 degrees C: CHEN model

R.H.	Equilibrium Moisture Content		Difference
	Experimental	Calculated	
%	(gms water/100 gms dry weight)		%
21.4	3.27	3.12	4.58
31.2	3.73	3.69	1.07
43.5	4.32	4.35	-0.69
53.5	4.62	4.94	-6.92
62	5.25	5.48	-4.38
77.5	6.95	6.74	3.02
88	8.15	8.13	0.24

Table 8. Experimental and Calculated Equilibrium Moisture Content at 28 degrees C: HENDERSON model

R.H %	Equilibrium Moisture Content Experimental	 Calculated	Difference %
	(gms water/100 gms dry weight)		
21.4	3.27	3.08	5.81
31.2	3.73	3.72	0.26
43.5	4.32	4.46	-3.24
53.5	4.62	5.06	-9.52
62	5.25	5.59	-6.47
77.5	6.95	6.74	3.02
88	8.15	7.83	3.92

Table 9. Experimental and Calculated Equilibrium Moisture content at 28 degrees C: B.E.T. model

R.H. %	Equilibrium Moisture Content Experimental (gms water/100 gms dry weight)	Calculated	Difference %
21.4	3.27	3.52	-7.64
31.2	3.73	3.84	-2.94
43.5	4.32	4.35	-0.69
53.5	4.62	4.86	-5.19
62	5.25	5.41	-3.04
77.5	6.95	6.81	2.01
88	8.15	8.25	-1.22

For better illustration, the experimental and calculated isotherm data obtained from the Chen, Henderson and B.E.T. expressions, are presented in Figures 15-17 respectively.

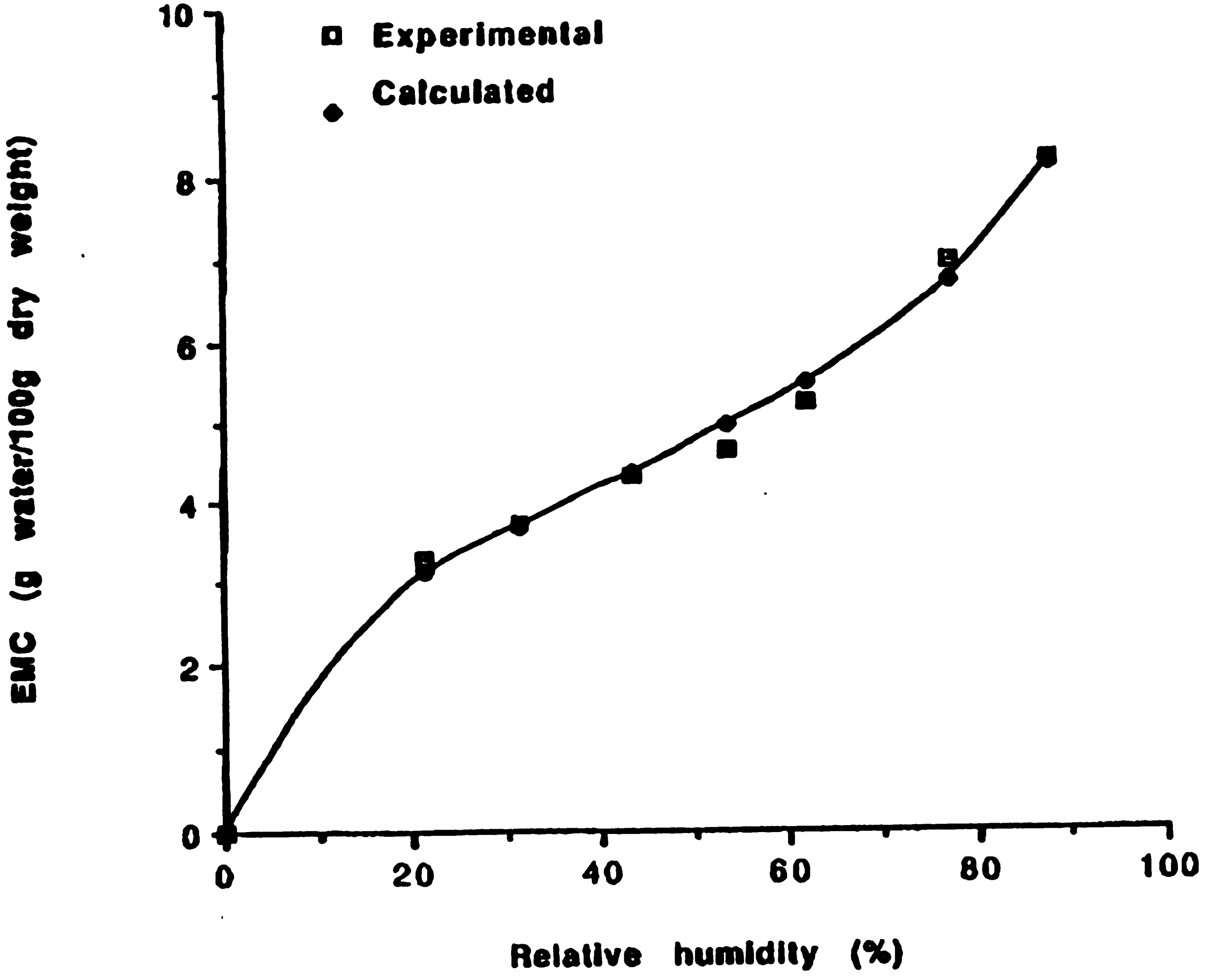


Figure 15 Experimental Isotherm Data and Calculated Isotherm Curve
28 degrees C: Chen model

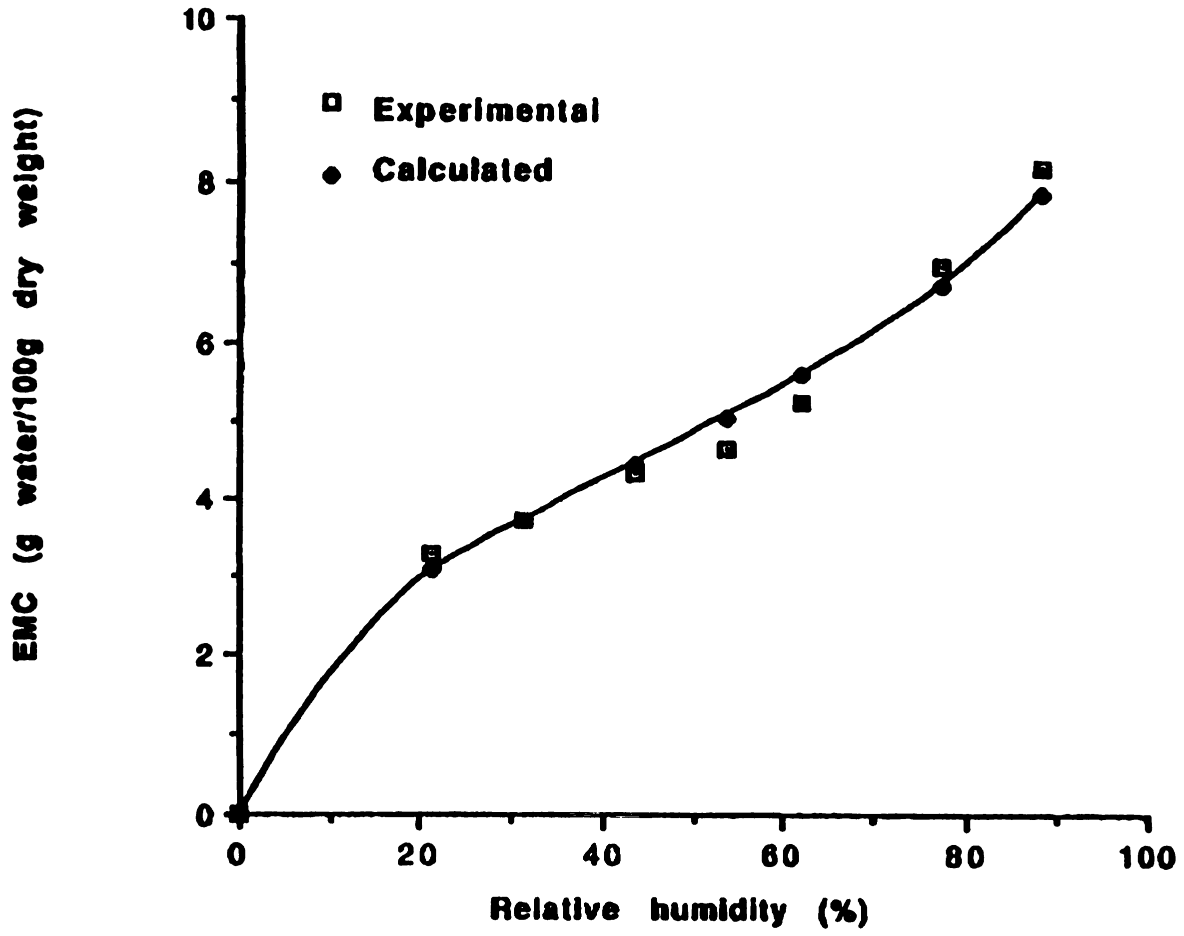


Figure 16 Experimental Isotherm Data and Calculated Isotherm Curve 28 degrees C: Henderson model

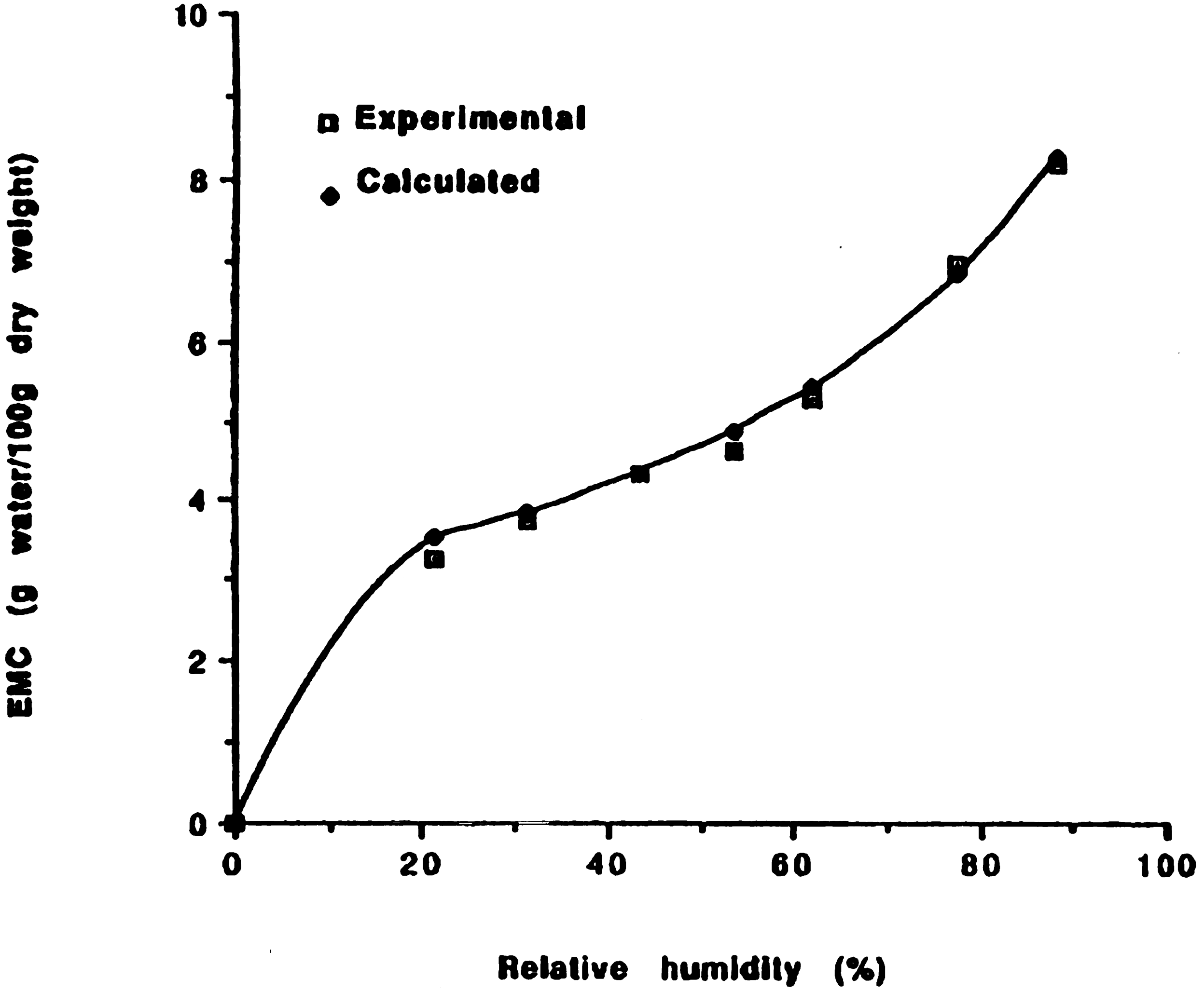


Figure 17 Experimental Isotherm Data and Calculated Isotherm Curve 28 degrees C: B.E.T. model

Statistical selection of best fit model

Correlation coefficient values for the x-y components of the linearized forms of the isotherm expressions and the sums of squares between the experimental and calculated isotherm data, for the respective isotherm models are summarized in Tables 10-12, and were the basis for selecting the best fit isotherm model.

Table 10. Correlation coefficients and sums of squares at 12 degrees Celsius

Model	Sums of Squares	Correlation Coefficients
CHEN	0.3402	-0.9915
HENDERSON	0.5771	0.9837
B.E.T.	0.2156	0.9968

Table 11. Correlation coefficients and sums of squares at 21 degrees Celsius

Model	Sums of Squares	Correlation Coefficients
CHEN	0.2236	-0.9940
HENDERSON	0.5319	0.9836
B.E.T.	0.0911	0.9986

Table 12. Correlation coefficients and sums of squares at 33 degrees Celsius

Model	Sums of Squares	Correlation Coefficients
CHEN	0.1879	-0.9949
HENDERSON	0.3646	0.9890
B.E.T.	0.1037	0.9980

The best fit model is chosen to be the one with the best correlation between the components of x-y axis, and the lowest sums of squares. Here the B.E.T. model shows a consistently low sums of squares and a correlation coefficient very close to 1 at each temperature, and was selected to describe the equilibrium sorption isotherm for the Ibuprofen tablets studied.

This procedure was then applied as a subroutine of the shelf life simulation program to determine the change in moisture content of Ibuprofen tablets, packaged in PVC/ACLAR, PVC/SARAN and PVC blister package systems, and stored at 28 degrees Celsius and 80% R.H.

The permeability constants at 28 degrees C for the respective blister packages are listed below in gm H_2O/day.mm Hg.pkg. (reference for permeability constant values: Wang, 1985, Lee, 1987).

PVC/ACLAR	3.8×10^{-6}	at 28 degrees C
PVC/SARAN	6.2×10^{-6}	at 28 degrees C
PVC	5.5×10^{-5}	at 28 degrees C

The initial moisture content and saturated vapor pressure was entered into the BASIC program to give the storage stability data for the three packaging systems using the B.E.T. model. The results are summarized in Table 13. The weight of the tablet is 0.3 grams.

Table 13. Storage stability data for Ibuprofen tablets at 28 degrees C and 80% RH: B.E.T. model

Moisture Content (gms water/100 gms dry weight)	Time (days)		
	PVC/ACLAR	PVC/SARAN	PVC
3.015	0	0	0
5.65	189	116	13
6.25	232	142	16
6.62	258	158	18
7.13	295	181	20
7.27	305	187	21
7.49	321	196	22

Figure 18 displays the storage stability curves obtained for the respective package systems.

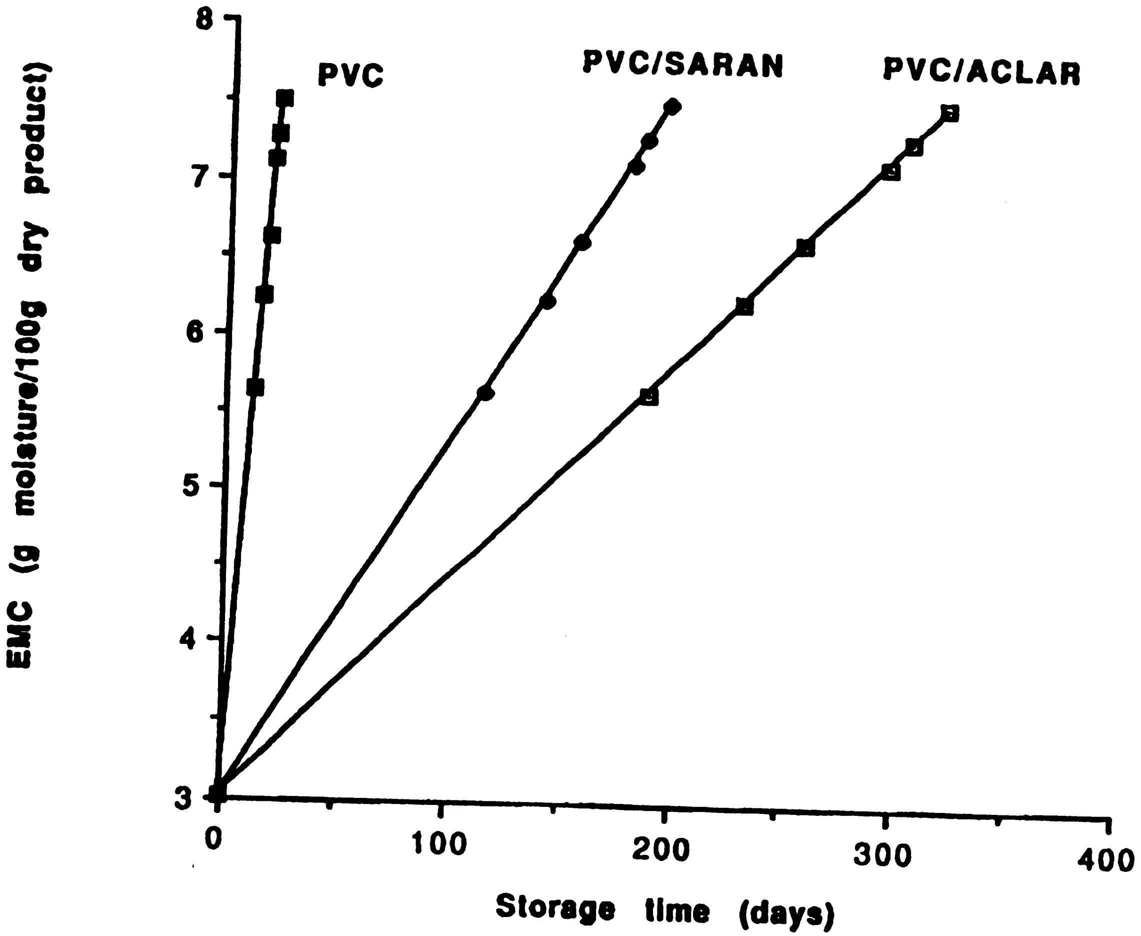


Figure 18 Storage Stability generated for Ibuprofen tablets at 28 degrees C/80 % R.H. B.E.T. model

II. Validity of Simulation Model

The validity of the simulation model was verified by comparing experimentally determined data for an orange flavored multivitamin tablet packaged in a PVC/SARAN blister package and stored at 22 degrees Celsius and 63.3% R.H., with calculated data obtained by the computer simulating model, described in Figure 1. Experimental isotherm and stability data obtained by Lee (1987) were used for these studies. Figure 1 describes, experimental isotherm data at three temperatures, 12.2, 20.6, and 30 degrees Celsius was entered into the computer program. The values of the coefficients for Chen, Henderson and B.E.T. model were calculated by linearizing each of the equations at the three temperatures. Based on statistical analysis, the B.E.T. expression was found to best describe the sorption isotherm of the multivitamin product. The derived B.E.T. constants are summarized below.

at 12.2 degrees C

Cs = 78

B = -23.69

J = 0.58

at 20.6 degrees C

Cs = 79

B = -35.34

J = 0.57

at 30 degrees C

Cs = 77

B = -24.40

J = 0.50

The correlation coefficients between the components of x and y axis of the linearized equation were stored at this point. The constants were then used to calculate moisture content values for the product as a function of relative humidity at respective temperatures of test. The calculated and experimental moisture content values are listed in Tables 14-16.

Table 14 Experimental and Calculated equilibrium moisture content for multivitamin tablet: B.E.T. model 12.2 degrees C

Relative Humidity %	Moisture Content Experimental (g water/100 g dry weight)	Moisture Content Calculated (g water/100 g dry weight)	Difference %
12	0.768	0.896	14.28
22.6	0.962	0.914	- 5.2
31	1.101	1.032	- 6.6
49	1.569	1.606	2.3
55	2.000	2.011	0.5
64.5	3.407	3.395	- 0.3

Table 15 Experimental and Calculated equilibrium moisture content for multivitamin tablet: B.E.T. model 20.6 degrees C

Relative Humidity %	Moisture Content Experimental	(g water/100 g dry weight) Calculated	Difference %
10.7	0.710	0.817	13.0
23.4	0.911	0.881	- 3.4
31.2	1.150	1.000	-15.0
42.2	1.309	1.274	- 2.74
53.2	1.704	1.797	5.17
60.9	2.591	2.548	- 1.68

Table 16 Experimental and Calculated equilibrium moisture content for multivitamin tablet: B.E.T. model 30 degrees C

Relative Humidity %	Moisture Content Experimental	 Calculated	Difference %
	(g water/100 g dry weight)		
11.0	0.680	0.781	12.9
22.3	0.837	0.791	- 5.8
30.5	0.910	1.892	- 0.9
41.7	1.190	1.142	- 4.2
50.7	1.428	1.511	5.49
58.9	2.212	2.177	- 1.6

Comparing the experimental and calculated moisture content values, the sums of squares listed in Table 17 were obtained.

Table 17 Correlation coefficients and sums of squares for B.E.T. model

Temperature degrees C	Sums of Squares	Correlation Coefficients
12.2	0.0251	0.9982
20.6	0.0266	0.9961
30.0	0.0233	0.9957

Equation 19 for predicting shelf life (t) was then solved using the Newton-Raphson method and trapezoidal rule for storage of the packaged product at 22 degrees Celsius and 63.3% R.H. The results by computer simulation according to this model gave good agreement with the experimental storage stability data as shown in Table 18, and graphical representation as shown in Figure 19. The difference is 0-6 days.

Table 18 **Storage stability curve generated for multivitamin tablet and experimental data: B.E.T. equation. (stored at 22 degrees C. and 63.3% R.H.)**

EMC (g moisture/ 100 gms dry weight)	Storage time (days) Computer	Experimental	Difference days
1.236	0	-	-
1.248	3	2	1
1.260	7	4	3
1.265	8	8.9	1
1.271	10	10.7	1
1.297	17	13.9	3
1.305	19	17	2
1.311	21	19	2
1.316	22	21.9	0
1.402	48	49	1
1.414	49	53	4
1.426	52	58	6

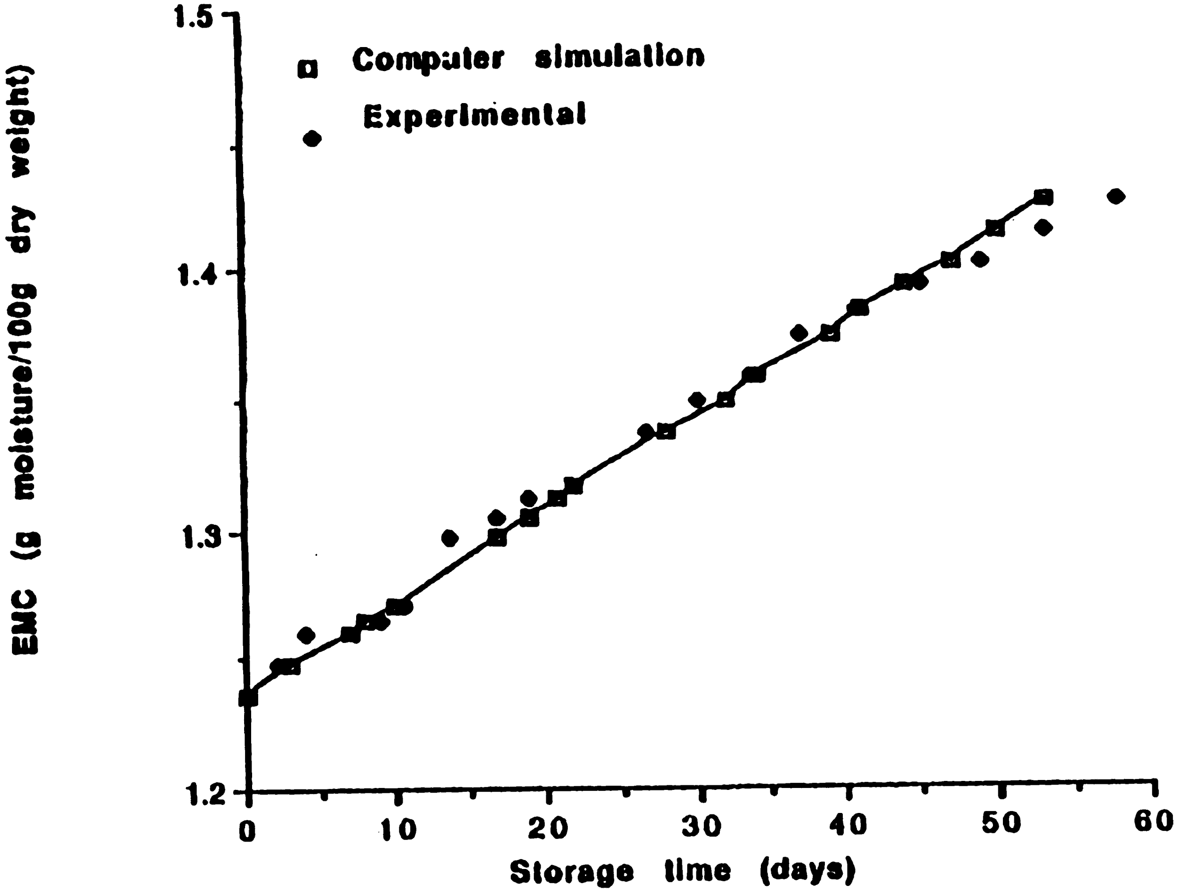


Figure 19 Storage Stability generated for Multivitamin tablet and experimental data

STATISTICAL DISCUSSION

The geometric configuration of the sorption isotherms is of significance in this study. The shape of the curve is defined by the product moisture gain and the fit is described by the equation chosen. Seven data points, i.e., relative humidity and its corresponding moisture content, were used to describe the curve in this study. Three replicates were used for each value. The number of data points and number of replicates are a matter of precision. Precision is the ability of an experiment to detect a true treatment effect. It can be improved by such action as (i) taking additional measurements, and (ii) increased replication.

(i) Additional measurements: One of the techniques for reducing error in an experiment is to remove the variability in the dependent variable associated with some independent variable x, here the relative humidity. In order to determine the coefficients, the equation of the curve is linearized and the slope and abscissa are determined through simple linear regression. The correlation coefficient between the x and y coordinates is scrutinized to determine the fit of the curve. The calculated values of moisture content were then compared to the experimental values to determine sums of squares. In the case of a linear function it would be reasonable to assume that the greater the number of data points used to estimate the line, the more precise the experiment will be in detecting differences between fitted and true means. The correlation coefficient and sums of squares are the statistical tools used to determine which equation fits best for the given data. (ii) Increased replication: The precision of an experiment can always be increased by additional replicates, but the degree of improvement falls off rapidly as the number of replications increases. For example, compared to an experiment with four replications, to double the degree of precision with which two means can be separated requires 16 replications. This follows from the effect of the number of replications (n) on the difference required to separate 2 means at a given level of significance, LSD = $t/(2SxS/n)^{1/2}$. This is not exactly so because, as n increases, t becomes slightly smaller, but it is close enough to use as a rule of thumb (Little and Hills, 1977).

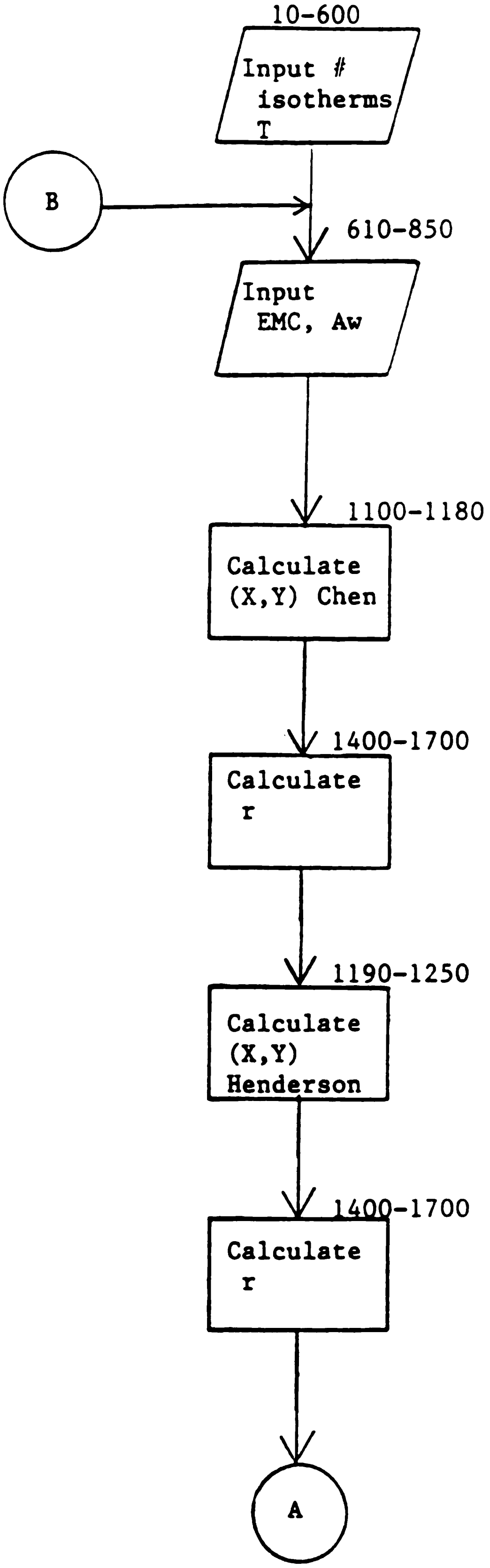
The number of experimental data points necessary to fully describe a sorption moisture isotherm for its application to shelf life prediction, cannot be recommended from this study. Since the isotherm curve is characteristic to the product, the specific relative humidities at which the experimental moisture content is determined is critical. These data points will define the fit of the experimental data to the model. This computer program may be applied to a global error analysis so that such a number may be determined for various products. Future work should consider non-linear regression as a means to fit the parameters in the three models. Future study should also determine design points in the temperature and relative humidity space that allow the experiment to discriminate most efficiently among the three models. In this context, the question of numbers of levels and replications can be better addressed.

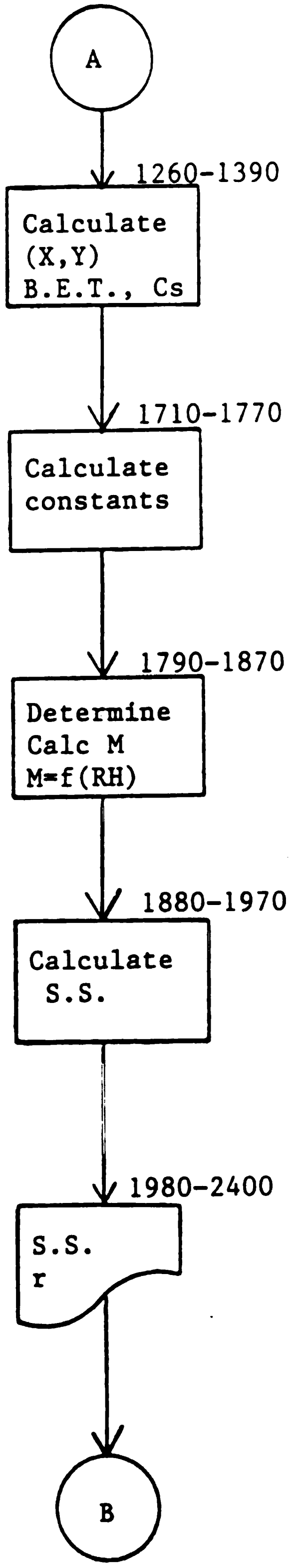
SUMMARY AND CONCLUSION

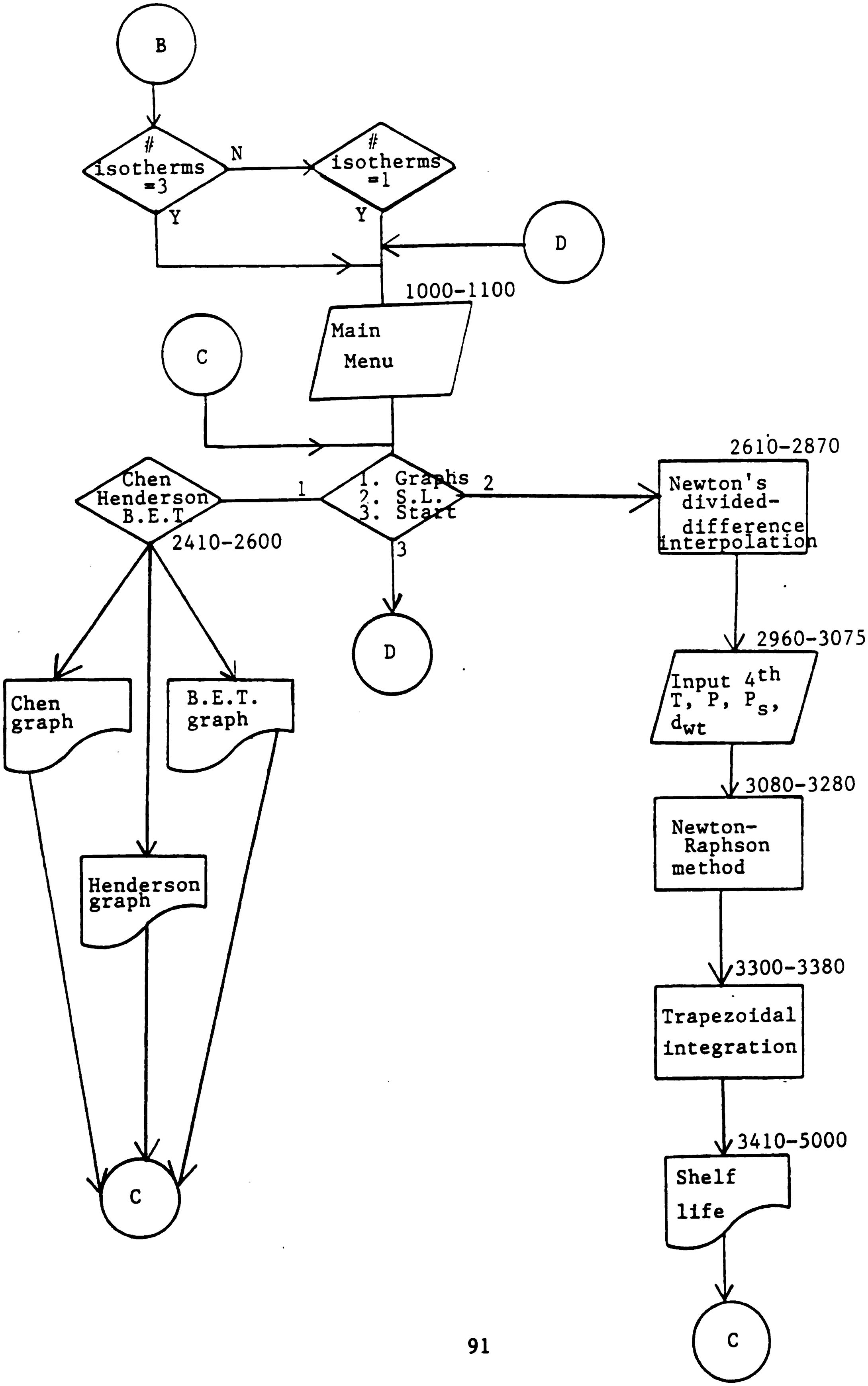
The simulation approach developed in this study to predict the shelf life of a packaged moisture sensitive solid drug product over a range of temperature and relative humidity values, provides reliable storage stability data as shown. The storage stability curves obtained for the orange flavored multivitamin tablet generated from computer simulation, showed good agreement when compared to experimental data from Lee's study (1987). According to the model, experimental isotherm data for three temperatures is required to predict the shelf life at any temperature within the range. The computer program helps select the best fit equation for the isotherm from among three models provided, based on sums of squares and correlation coefficients. The effect of temperature on the coefficients of the equation selected is determined, by describing a quadratic equation as a function of temperature. This allows calculation of the moisture content of the product as a function of relative humidity at the desired temperature. The shelf life equation is then solved for the required temperature, without actually having to obtain experimental sorption isotherms for that temperature. A model that best fits the experimental data is selected. Experimental sorption data is necessary at only three temperatures. This model may be modified for isocratic conditions, or incorporate fluctuating temperature and humidity environments. Also different products must be considered and fit to other moisture isotherm equations.

APPENDIX I

Flow chart


10-600
Input #
isotherms
T
B
610-850
Input
EMC, Aw
1100-1180
Calculate
(X,Y) Chen
1400-1700
Calculate
r
1190-1250
Calculate
(X,Y)
Henderson
1400-1700
Calculate
r
A


A
1260-1390
Calculate (X,Y) B.E.T., Cs
1710-1770
Calculate constants
1790-1870
Determine Calc M M=f(RH)
1880-1970
Calculate S.S.
1980-2400
S.S. r
B


B
#
isotherms
=3
N
Y
#
isotherms
=1
Y
D
1000-1100
Main
Menu
C
Chen
Henderson
B.E.T.
2410-2600
1
1. Graphs
2. S.L.
3. Start
2
3
2610-2870
Newton's
divided-
difference
interpolation
D
Chen
graph
B.E.T.
graph
2960-3075
Input 4th
T, P, Ps,
dwt
3080-3280
Newton-
Raphson
method
Henderson
graph
3300-3380
Trapezoidal
integration
3410-5000
Shelf
life
C
C

APPENDIX II

```
10 REM ************************* RESEARCH.BAS *******
**************************
20 ' Program description: This program simulates the
shelf life of a drug product. It combines the express
ion for the isotherm as a function of
30 ' temperature and the expression for the water
vapor permeability of the
40 ' package as a function of temperature
with the equation for predicting the
50 ' moisture uptake of the product as a function of
time and storage environment.
60 REM ***********************************************
**************************
100 CLS: FOR Z=1 TO 3: PRINT: NEXT Z
110 PRINT "
*****************************************************"
120 PRINT "
*                                                   *"
130 PRINT "
*              SHELF LIFE PREDICTION                *"
140 PRINT "            *                      OF A
                       *"
150 PRINT "            *           PACKAGED MOISTURE
SENSITIVE             *"
160 PRINT "            *                       DRUG PRODUCT
                    *"
170 PRINT "            *                     OVER A RANGE OF
                   *"
175 PRINT "            *        TEMPERATURE AND RELATIVE
HUMIDITY          *"
177 PRINT "            *                          VALUES
                    *"
180 PRINT "            *
                   *"
181 PRINT "            *                             by
                   *"
183 PRINT "            *                     Monica Kirloskar
               *"
187 PRINT "            *                     Ruben Hernandez
                 *"
190 PRINT "            *                     Jack Giacin
                  *"
192 PRINT "            *
                  *"
193 PRINT "            *                  SCHOOL OF PACKAGI
NG                 *"
195 PRINT "            *               MICHIGAN STATE UNIVE
RSITY              *"
200 PRINT "            *********************************
*********************"
203 LOCATE 23,22: INPUT "Strike RETURN key to proceed...
```

```
",KKK
205 CLS: PRINT: PRINT: PRINT
210 PRINT "                    SHELF LIFE PREDIC
TION"
220 PRINT: PRINT: PRINT: PRINT
225 PRINT "          This program simulates the shelf
life of a packaged moisture"
230 PRINT "          sensitive drug product.  It comb
ines the expression for the"
235 PRINT "          isothem as a function of tempera
ture and the expression for"
240 PRINT "          the water vapor permeability of
the package as a function of"
245 PRINT "          temperature with the equation for
predicting the moisture"
247 PRINT            uptake of the product as a funct
ion of time and storage"
248 PRINT "          environment."
250 PRINT: PRINT: PRINT
255 LOCATE 23,22: INPUT "Strike RETURN key to proceed..
.",KKK
400 CLS: LOCATE 10,10: INPUT "Do you want to send
output to the printer (Y/N) ", KKK$
402 PRINT CHR$(0);
405 IF KKK$="N" OR KKK$="n" OR KKK$="y" OR KKK$="Y"
THEN GOTO 500
410 GOTO 400
500 KEY OFF:CLS
510 LOCATE 10,5:INPUT "Please input the number of
sorption isotherms to be processed (1 or 3): ", MON:
MON1=1: IF MON=0 OR MON=2 OR MON>3 THEN 500: IF MON=1
THEN GOTO 530
520 CLS: LOCATE 10,20: DIM T(MON+1)
530 FOR Z=1 TO MON
540 CLS:LOCATE 10,15: PRINT "Input the";
550 IF Z=1 THEN Z$=" 1" ELSE IF Z=2 THEN Z$=" 2" ELSE
IF Z=3 THEN Z$=" 3"
560 IF Z=1 THEN PRINT Z$;"st ";:INPUT "isotherm
temperature in Celsius please: ", T(Z)
570 IF Z=2 THEN PRINT Z$;"nd ";:INPUT "isotherm
temperature in Celsius please: ", T(Z)
580 IF Z=3 THEN PRINT Z$;"rd ";:INPUT "isotherm
temperature in Celsius please: ", T(Z)
590 IF T(Z)=0 THEN GOTO 540
600 NEXT Z:CLS
610 LOCATE 10,20:INPUT "Input the number of data point
s: ", DPTS:IF DPTS = 0 THEN GOTO 610
620 DIM AW(DPTS), EXPM(DPTS), CALCM(3,DPTS), SS(3), X
(3,DPTS), Y(3,DPTS), SXY(3,DPTS), SX(3,DPTS), SY(3,DPT
S),YINT(3),SLOPE(3), R(3), D(3,DPTS)
630 DIM A(MON), K(MON), N(MON), K1(MON), B(MON), J(MON
```

```
), CS(MON)
640 CLS:LOCATE 3,25:PRINT "EXPERIMENTAL SORPTION ISOTH
ERM DATA"
650 LOCATE 4,25:PRINT "-----------------------------------"
660 LOCATE 6,10: PRINT "Temperature: ";T(MON1);" degre
es Celsius"
670 LOCATE 8,10: PRINT "Equilibrium Moisture Content (EMC)"
680 LOCATE 8,52: PRINT "Water Activity"
690 LOCATE 9,12: PRINT "(g Moisture/100g Dry Product)"
:LOCATE 9,52:PRINT "% Rel. humidity/100"
700 LOCATE 10,10: PRINT "----------------------------
----------------------------------"
710 FOR I =1 TO DPTS
720      LOCATE 10+I,10
730      PRINT I;")"
740      LOCATE 10+I,20
750      INPUT "", EXPM(I)
760      LOCATE 10+I,56
770      INPUT "", AW(I)
780 NEXT I
790 LOCATE 12+I,20
810 PRINT "
                ";
830 LOCATE 12+I,10: INPUT "DO YOU WANT TO CHANGE ANY
DATA? INPUT NUMBER (0 TO ESCAPE): ", YORN
840 IF YORN>DPTS THEN GOTO 790: IF YORN=0 THEN GOTO 880
842 IF YORN=0 THEN GOTO 880
845 LOCATE 10+YORN,20: PRINT "     ": LOCATE 10+YORN,56
: PRINT "     ": AW(YORN)=0:EXPM(YORN)=0
850 LOCATE 10+YORN,20: INPUT "", EXPM(YORN): LOCATE 10+
YORN,56: INPUT "", AW(YORN)
860 GOTO 830
880 CLS: LOCATE 24,1:COLOR 7,0: PRINT "Processing";T(MO
N1);" degrees Celsius"
890 LOCATE 24,1: COLOR 23,0: PRINT "Please wait";
900 GOSUB 1120                           ' Calculate X,
Y for Chen equation
910 GOSUB 1400                           ' Calculate c
orrelation coefficient
920 GOSUB 1190                           ' Calculate X,
Y for Henderson equation
930 GOSUB 1400                           ' Calculate c
orrelation coefficient
940 GOSUB 1260                           ' Calculate X,
Y for B.E.T equation
950 GOSUB 1710                           ' Calculate c
onstants
960 GOSUB 1790                           ' Calculated
moisture contents
970 GOSUB 1880                           ' Calculate
sums of squares
```

```
980 GOSUB 1980                                   ' Display output
990 COLOR 7,0
1000 IF MON > 1 AND MON1<=MON THEN GOTO 2790
1005 CTR=1
1010 CLS: LOCATE 6,27: PRINT "M A I N    M E N U"
1020      LOCATE 7,27: PRINT "------------------"
1030      LOCATE 9,27: IF MON=3 THEN PRINT "1.  NOT AV
AILABLE **" ELSE IF MON=1 THEN PRINT "1.  GRAPHS: SORPTI
ON ISOTHERM"
1050      LOCATE 10,27: PRINT "2.  SHELF LIFE DETERMIN
ATION":LOCATE 11,27:PRINT "3.  START SCREEN":LOCATE 12
,27: PRINT "4.  EXIT PROGRAM"
1060      LOCATE 20,15:IF MON=1 THEN GOTO 1070 ELSE IF
MON=3 THEN PRINT "** GRAPHICS ARE AVAILABLE ONLY WITH 1
TEMPERATURE"
1070      LOCATE 14,27: PRINT "                           ":
LOCATE 14,27: INPUT "ENTER CHOICE: ", M2: IF M2 =0 OR M2
 > 5 THEN GOTO 1070
1080 IF MON=3 AND M2=1 THEN GOTO 1070
1090 IF M2=1 THEN GOSUB 2410: ELSE IF M2=2 THEN GOTO 2880
:ELSE IF M2=3 THEN GOTO 1110: ELSE IF M2=4 THEN END
1100 GOTO 1010
1110 LOAD "research",R
1120 REM *********************** Calculate X, Y for CHEN
 equation *************
1130 FOR I=1 TO DPTS
1140     X(1,I)=EXPM(I)
1150     Y(1,I)=LOG(-LOG(AW(I)))
1160 NEXT I
1170 J=1
1180 RETURN
1190 REM *********************** Calculate X, Y for HEND
ERSON equation ********
1200 FOR I=1 TO DPTS
1210      X(2,I)=LOG(EXPM(I))
1220      Y(2,I)=LOG(-LOG(1-AW(I)))
1230 NEXT I
1240 J=2
1250 RETURN
1260 REM ************************ Calculate X, Y for B.E
.T equation ***********
1270 R1=0
1280 FOR CS=76 TO 150
1290     FOR I=1 TO DPTS
1300         X(3,I)=(AW(I)*100)/CS
1310         IF ((CS-(AW(I)*100))*EXPM(I))=0 THEN 1330
1320         Y(3,I)=(AW(I)*100)/((CS - (AW(I)*100))*EXPM(I))
1330     NEXT I
1340     J=3
1350     GOSUB 1400
1360     IF R(3)>R1 THEN GOSUB 1680
```

```
1370 NEXT CS
1380 R(3)=R1: SLOPE(3)=SLOPE1: YINT(3)=YINT1
1390 RETURN
1400 REM ********************Calculate Sx, Sy, Sxy ***
*******************
1410 XM=0: YM=0
1420    FOR I=1 TO DPTS
1430      XM=XM+X(J,I)
1440      YM=YM+Y(J,I)
1450    NEXT I
1460    YM1=YM/DPTS
1470    XM1=XM/DPTS
1480    A=0: B=0: C=0: SUMXSQ=0: SUMXY=0
1490    FOR I=1 TO DPTS
1500      A1=(X(J,I)-XM1)*(X(J,I)-XM1)
1510      A=A+A1
1520      B1=(Y(J,I)-YM1)*(Y(J,I)-YM1)
1530      B=B+B1
1540      C1=(X(J,I)-XM1)*(Y(J,I)-YM1)
1550      C=C+C1
1560      SUMXSQ=SUMXSQ+(X(J,I)*X(J,I))
1570      SUMXY=SUMXY+(X(J,I)*Y(J,I))
1580    NEXT I
1590    SX=SQR(A/(DPTS-1))
1600    SY=SQR(B/(DPTS-1))
1610    SXY=C/(DPTS-1)
1620    R(J)=SXY/(SX * SY)
1630    REM *** CALCULATE SLOPE ***
1640    SLOPE(J)=((DPTS)*(SUMXY)-(XM)*(YM))/((DPTS)*(
SUMXSQ)-(XM)*(XM))
1650    REM *** CALCULATE Y-INTERCEPT ***
1660   YINT(J)=((YM)*(SUMXSQ)-(XM)*(SUMXY))/((DPTS)*(
SUMXSQ)-(XM)*(XM))
1670 RETURN
1680 REM ************************ SAVE VALUES OF X Y
AND R *********************
1690 R1=R(3): CS1=CS: SLOPE1=SLOPE(3): YINT1=YINT(3)
1700 RETURN
1710 REM ************************ CALCULATE CONSTANTS
 IN THE EQUATION **********
1720 A =SLOPE(1)
1730 K =YINT(1)
1740 N =SLOPE(2)
1750 K1=EXP(YINT(2))
1760 B =(SLOPE(3)/YINT(3))+1
1770 J =1/(YINT(3)*B)
1780 RETURN
1790 REM *************************** CALCULATED VALUE
S OF M ********************
1800 FOR I=1 TO DPTS
1810    AW1=AW(I)*100
```

```
1830    CALCM(1,I)=(YINT(1)-LOG(-LOG(AW(I))))/-SLOPE(1)
1840    CALCM(2,I)=EXP((1/SLOPE(2))*(LOG((-1)*LOG(1-A
W(I)))-LOG(EXP(YINT(2)))))
1850    CALCM(3,I)=(B*J*AW1)/((CS1-AW1)*(1+(B-1)*(AW1
/CS1)))
1860 NEXT I
1870 RETURN
1880 REM *********************** CALCULATE SUMS OF S
QUARES ******************
1890 FOR Q=1 TO 3
1910 SS(Q)=0
1920   FOR I=1 TO DPTS
1930     D(Q,I)=(EXPM(I) - CALCM(Q,I))^2
1940     SS(Q)=SS(Q) + D(Q,I)
1950   NEXT I
1960 NEXT Q
1970 RETURN
1980 REM *********************** DISPLAY OUTPUT ****
***************************
1990 COLOR 7,0:CLS
2000 LOCATE 3,20:PRINT "STATISTICAL DATA FOR THE MQDE
LS":LOCATE 4,20:PRINT "-------------------------------"
2010 LOCATE 6,10:PRINT "TEMPERATURE ";T(MON1);"degree
s Celsius"
2020 LOCATE 9,10: PRINT "Model"
2030 LOCATE 8,30: PRINT " Sum of "
2040 LOCATE 8,50: PRINT " Correlation "
2050 LOCATE 9,30: PRINT " Squares"
2060 LOCATE 9,50: PRINT " Coefficient"
2070 LOCATE 10,9: PRINT "-------"
2080 LOCATE 10,29: PRINT " ---------"
2090 LOCATE 10,49: PRINT " -------------"
2100 LOCATE 12,10: PRINT "Chen"
2110 LOCATE 14,10: PRINT "Henderson"
2120 LOCATE 16,10: PRINT "B.E.T"
2130 LOCATE 12,31: PRINT USING "#.####"; SS(1)
2140 LOCATE 12,53: PRINT USING "#.####"; R(1)
2150 LOCATE 14,31: PRINT USING "#.####"; SS(2)
2160 LOCATE 14,53: PRINT USING "#.####"; R(2)
2170 LOCATE 16,31: PRINT USING "#.####"; SS(3)
2180 LOCATE 16,53: PRINT USING "#.####"; R(3)
2190 LOCATE 18,10: INPUT "Strike RETURN key to contin
ue...",KKK
2191 IF KKK$="N" OR KKK$="n" THEN RETURN
2192 IF KKK$="Y" OR KKK$="y" THEN 2194
2194 IF MON1=1 THEN LPRINT CHR$(12): IF MON1=1 THEN L
PRINT "        S T A T I S T I C A L   D A T A   F
 O R   T H E   M O D E L S"
2195 IF MON1=1 THEN LPRINT "          ===============
===============================================" 
2196 LPRINT: LPRINT "         TEMPERATURE ";T(MON1);"
```

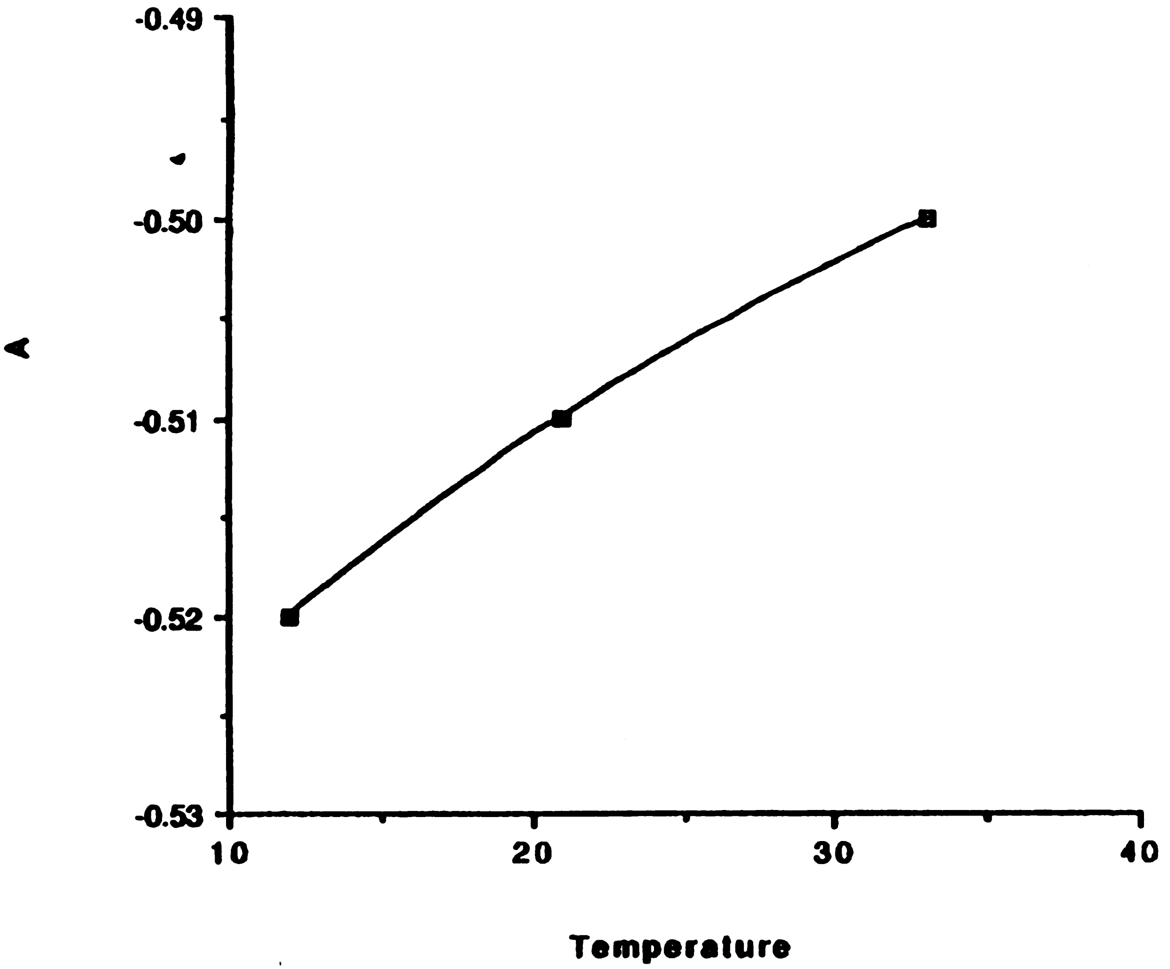
```
degrees Celsius"
2197 LPRINT: LPRINT "                                        Sum
of                  Correlation"
2198 LPRINT "          Model               Squares
          Coefficient"
2199 LPRINT "          -----               -------
          -----------"
2200 LPRINT: LPRINT USING "         Chen
   #.####                  #.####";SS(1),R(1)
2205 LPRINT: LPRINT USING "         Henderson
   #.####                  #.####";SS(2),R(2)
2207 LPRINT: LPRINT USING "         B.E.T
   #.####                  #.####";SS(3),R(3)
2210 LPRINT:LPRINT:LPRINT
2400 RETURN
2410 REM *********************** Graphics ***********
*************************
2420 GOSUB 2560
2430 FOR I=1 TO DPTS
2440     PSET (AW(I) ,EXPM(I))
2450 NEXT I
2460 FOR I=1 TO DPTS-1: LINE (AW(I),EXPM(I))-(AW(I+1)
,EXPM(I+1)): NEXT I
2470 LOCATE 23,5: INPUT "(C)hen, (H)enderson, (B)ET,
(Q)uit: ", CG$
2480 IF CG$="c" OR CG$="C" THEN J=1: ELSE IF CG$="h"
OR CG$="H" THEN J=2: ELSE IF CG$="b" OR CG$="B" THEN
J=3: ELSE IF CG$="q" THEN GOTO 2550: ELSE GOTO 2470
2490 GOSUB 2560
2500 FOR I=1 TO DPTS
2510    PSET(AW(I), CALCM(J,I))
2520    PSET (AW(I), EXPM(I))
2530 NEXT I
2540 GOTO 2470
2550 SCREEN 2,0:SCREEN 0,0: RETURN
2560 SCREEN 1,0: CLS
2570 WINDOW(0,0)-(1,INT(EXPM(DPTS)+1))
2580 LINE (0,0)-(1,0)
2590 LINE (0,0)-(0,INT(EXPM(DPTS)+1))
2600 RETURN
2605 REM ************** NEWTON'S DIVIDED DIFFERENCE IN
TERPOLATION *******************
2610 PP=(Q(2)-Q(1))/(T(2)-T(1)):QQ1=(Q(3)-Q(2))/(T(3)
-T(2)):QQ2=PP:QQ=(QQ1-PP)/(T(3)-T(1)):A1=Q(1)-PP*T(1)
+QQ*T(1)*T(2)
2620 B1=PP-QQ*T(1)-QQ*T(2)
2630 C1=QQ
2640 ASP=A1+B1*T(4)+C1*T(4)*T(4)
2650 RETURN
2660 Q(1)=A(1): Q(2)=A(2): Q(3)=A(3): RETURN
2670 SLOPE(1)=ASP: RETURN
```

```
2680 Q(1)=K(1): Q(2)=K(2): Q(3)=K(3): RETURN
2690 YINT(1)=ASP: RETURN
2700 Q(1)=N(1): Q(2)=N(2): Q(3)=N(3): RETURN
2705 SLOPE(2)=ASP: RETURN
2710 Q(1)=K1(1): Q(2)=K1(2): Q(3)=K1(3): RETURN
2715 YINT(2)=ASP: RETURN
2720 Q(1)=B(1): Q(2)=B(2): Q(3)=B(3): RETURN
2725 B=ASP: RETURN
2730 Q(1)=J(1): Q(2)=J(2): Q(3)=J(3): RETURN
2735 J=ASP: RETURN
2740 Q(1)=CS(1): Q(2)=CS(2): Q(3)=CS(3): RETURN
2745 CS1=ASP: RETURN
2750 RETURN
2760 CLS: LOCATE 10,25:PRINT "SORRY, NOT ENOUGH
TEMPERATURES"
2770 LOCATE 11,25: PRINT "Press RETURN key to continu
e...";:INPUT KKK
2780 RETURN
2790 A(MON1)=A
2800 K(MON1)=K
2810 N(MON1)=N
2820 K1(MON1)=K1
2830 B(MON1)=B
2840 J(MON1)=J
2850 CS(MON1)=CS1
2860 MON1=MON1+1
2870 IF MON < MON1 THEN GOTO 1010 ELSE GOTO 640
2880 REM ************************** SHELF LIFE DETERMI
NATION ************
2890 IF MON<3 THEN 2760
2900 CLS
2960 LOCATE 10,10: INPUT "1. Please input the 4th tem
perature (degrees Celcius): ", T(4): IF T(4)=0 THEN G
OTO 2960
2965 LOCATE 11,10: PRINT "2. Please input (C)hen, (H)
enderson or (B).E.T: ";:INPUT B$
2970 IF B$<>"c" AND B$<>"C" AND B$<>"h" AND B$<>"H" A
ND B$<>"B" AND B$<>"b" THEN  GOTO 2965
2980 LOCATE 12,10: PRINT "3. Please input the externa
l Water Activity (rh/100): ";:INPUT "",MEXT
2990 LOCATE 13,10: INPUT "4. Please input dry weight
(in grams) of the product: ", DWT
3000 LOCATE 23,15: PRINT "* (g Water/day. mm Hg. pkg.
)"
3010 LOCATE 14,10: PRINT "5. Please input the package
 permeability constant*: ";:INPUT " ",PPRM
3015 LOCATE 23,15: PRINT "
       ":LOCATE 23,15:PRINT "* (mm Hg)"
3020 LOCATE 15,10: PRINT "6. Please input the saturate
d vapor pressure of water *: ";: INPUT " ",STVP
3030 LOCATE 23,15: PRINT "* (g Water/100 grams dry pr
```

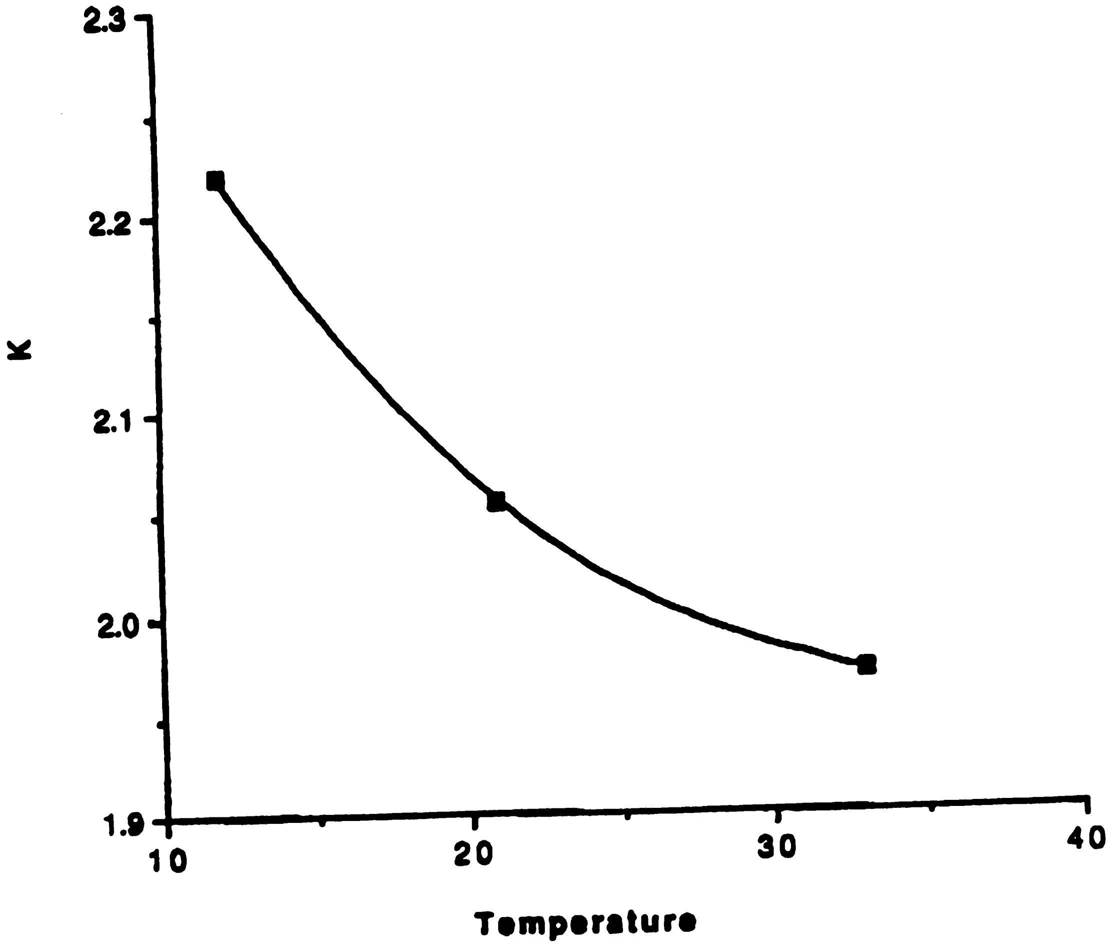
```
oduct weight)"
3040 LOCATE 16,10: INPUT "7. Please input the initial
 moisture content *: ",MINC
3050 LOCATE 17,10: INPUT "8. Please input the critica
l moisture content *: ",MCC
3060 IF B$="C" THEN GOTO 3070: IF B$="H" THEN GOTO 30
73: IF B$="B" THEN GOTO 3075: GOTO 2920
3070 GOSUB 2660: GOSUB 2610: GOSUB 2670: GOSUB 2680:
GOSUB 2610: GOSUB 2690: GOTO 3080
3073 GOSUB 2700: GOSUB 2610: GOSUB 2705: GOSUB 2710:
GOSUB 2610: GOSUB 2715: GOTO 3080
3075 GOSUB 2720: GOSUB 2610: GOSUB 2725: GOSUB 2730:
GOSUB 2610: GOSUB 2735:GOSUB 2740: GOSUB 2610: GOSUB
2745:GOTO 3080
3080 DEF FNM1(AW)=(YINT(1)-LOG(-LOG(AW)))/SLOPE(1)
3090 DEF FNM2(AW)=EXP((1/SLOPE(2))*(LOG((-1)*LOG(1-AW
))-LOG(EXP(YINT(2)))))
3100 DEF FNM3(AW)=(B*J*AW2)/((CS1-AW2)*(1+((B-1)*AW2/
CS1)))
3110 DEF FNDM1(AW)=-1/(SLOPE(1)*AW*LOG(AW))
3120 DEF FNDM2(AW)=(FNM2(AW)/N)*(-1/((1-AW)*LOG(1-AW)
))
3130 DEF FNDM3(AW)=(FNM3(AW)*AW2)-((B*J*AW2)*((CS1-2*
AW2)*(1+(B-1)/CS1))/((CS1-AW2)*(1+(B-1)*(AW2/CS1))))
3140 REM *********************** Newton-Raphson metho
d ************************
3145 IF CTR>1 THEN GOTO 3160
3150 DIM AW1(5),Y1(5): GOTO 3160
3160 AW=.5
3170 ES=.001
3180 FOR NI=1 TO 5
3190 IF B$="B" THEN AW2=AW*100
3195 IF B$="C" THEN XN=AW-(FNM1(AW)/FNDM1(AW)): GOTO
3210
3200 IF B$="H" THEN XN=AW-(FNM2(AW)/FNDM2(AW)): GOTO
3210
3205 IF B$="B" THEN XN=AW-(FNM3(AW)/FNDM3(AW)): GOTO
3210
3210 IF XN=0 THEN 3240
3220 EA=ABS((XN-AW)/XN)*100
3225 AW1(NI)=ABS(XN)
3240 REM AW=ABS(XN)
3270 NEXT NI
3280 NI=NI-1
3300 REM ******************************** trapezoidal ru
le *********************
3310 FOR I=1 TO NI
3320 Y1(I)=(DWT/(PPRM*STVP))*(1/(MEXT-AW1(I)))
3330 NEXT I
3340 SU=Y1(1)
3350 FOR I=2 TO NI: SU=SU+2*Y1(I): NEXT I
```

```
3360 HT=(SU+Y1(NI))/(2*(NI+1))
3365 IN=(MCC-MINC)*HT
3366 IF IN<0 THEN IN=0
3370 CLS: LOCATE 10,10:PRINT "The shelf life of the p
roduct is ";: PRINT USING "######"; IN;:PRINT " days"
3380 LOCATE 23,10: INPUT "Strike RETURN key to contin
ue...",KKK
3400 IF KKK$="n" OR KKK$="N" THEN GOTO 5000
3410 LPRINT CHR$(12)
3420 LPRINT "                    SHELF LIFE DETERMINAT
ION OF THE DRUG PRODUCT"
3430 LPRINT "                    =====================
=========================="
3440 LPRINT: LPRINT: LPRINT
3450 LPRINT "          TEMPERATURE:";T(4);"degrees Cel
sius";
3460 LPRINT "          MODEL: ";:IF ZZ$="C" OR ZZ$="c"
 THEN LPRINT "Chen": IF ZZ$="h" OR ZZ$="H" THEN LPRIN
T "Henderson": IF ZZ$="b" OR ZZ$="B" THEN LPRINT "B.E.T"
3465 LPRINT
3468 LPRINT "          External Water Activity
  ";MEXT
3470 LPRINT "          Dry Weight
  ";DWT;"g"
3475 LPRINT "          Package permeability constant
  ";PPRM;"g Water/day. mm Hg"
3480 LPRINT "          Saturated vapor pressure
  ";STVP;"g Water/day. mm Hg"
3485 LPRINT "          Initial moisture content
  ";MINC;"g Water/100 g dry product weight"
3490 LPRINT "          Critical moisture content
  ";MCC;"g Water/100 g dry product weight"
3500 LPRINT
3510 LPRINT "          The shelf life of the product i
s";IN;"days"
5000 CTR=2: GOTO 1010
6000 REM ****** error handling ******
6005 STOP
6010 IF ERR=24 THEN GOTO 6020
6020 LOCATE 17,10:PRINT "Please check the printer...T
ry again"
6030 LOCATE 18,10:PRINT "Strike RETURN key to continu
e....",KKK
6040 RESUME 402
```

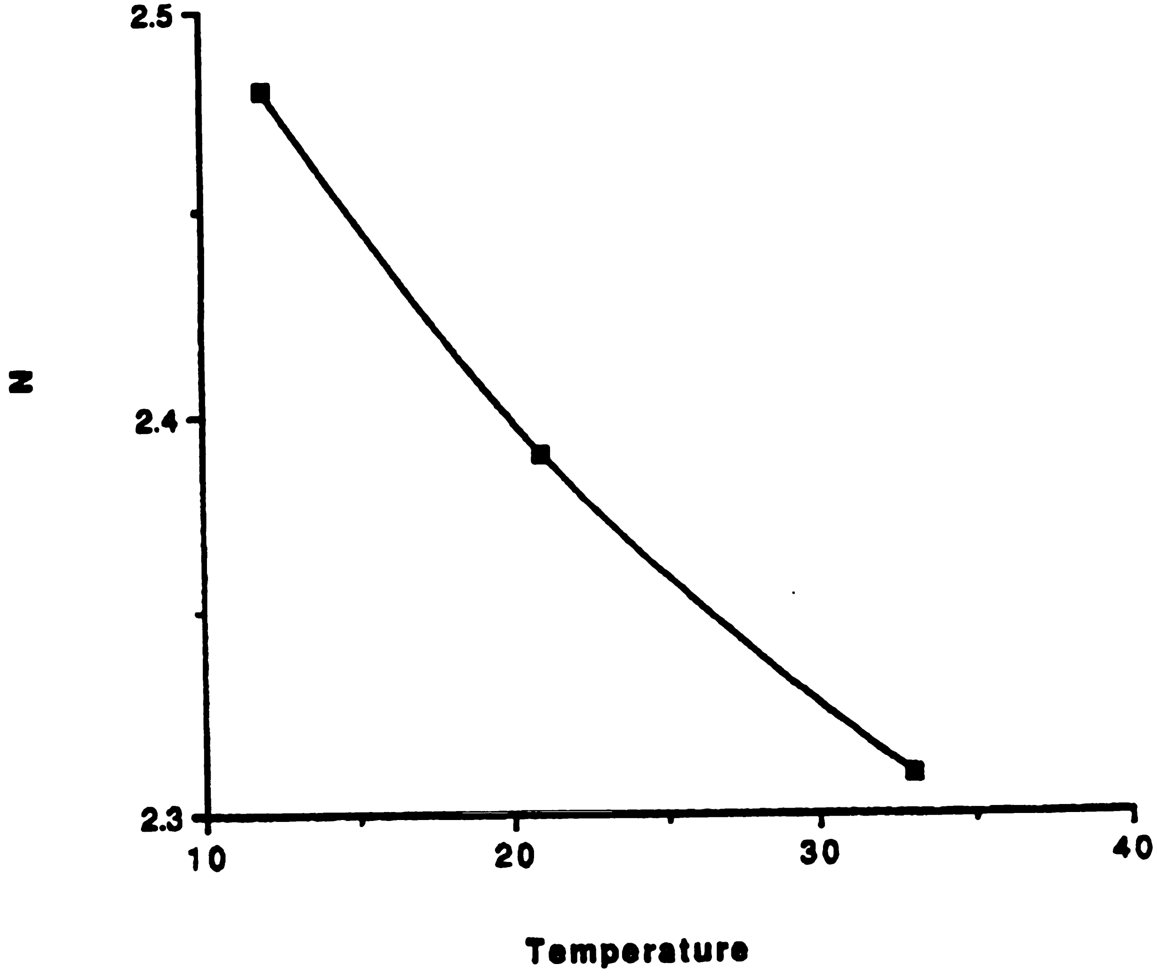
APPENDIX III



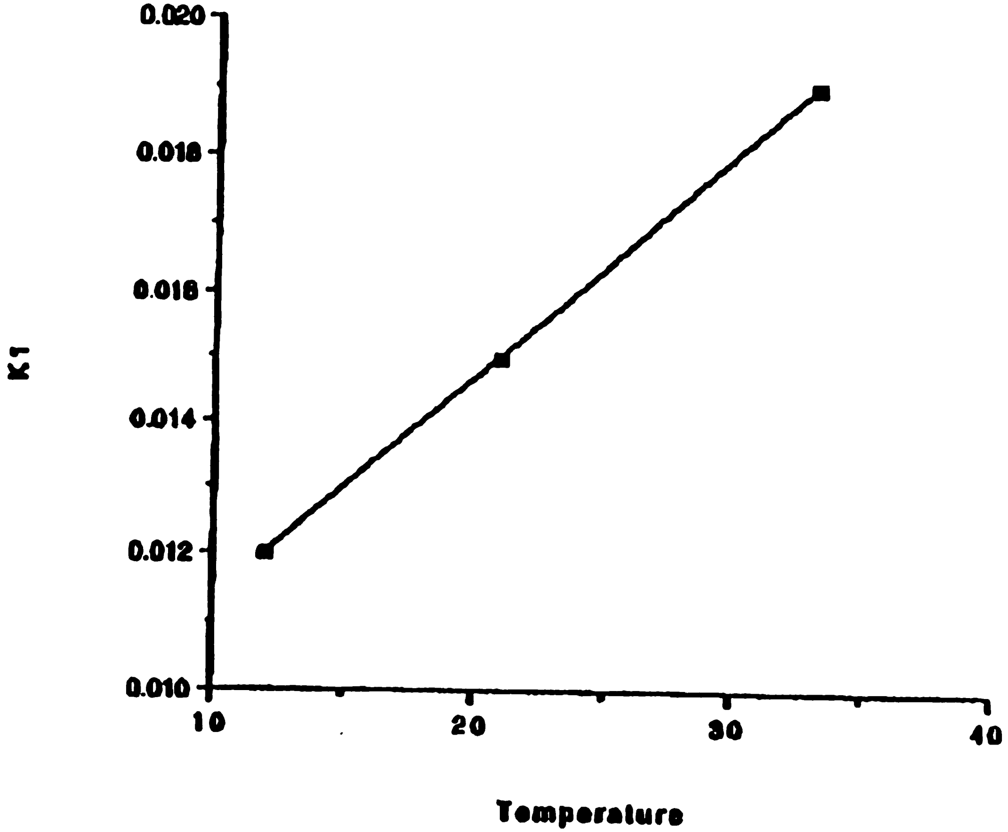
A versus Temperature (degrees C): Chen model



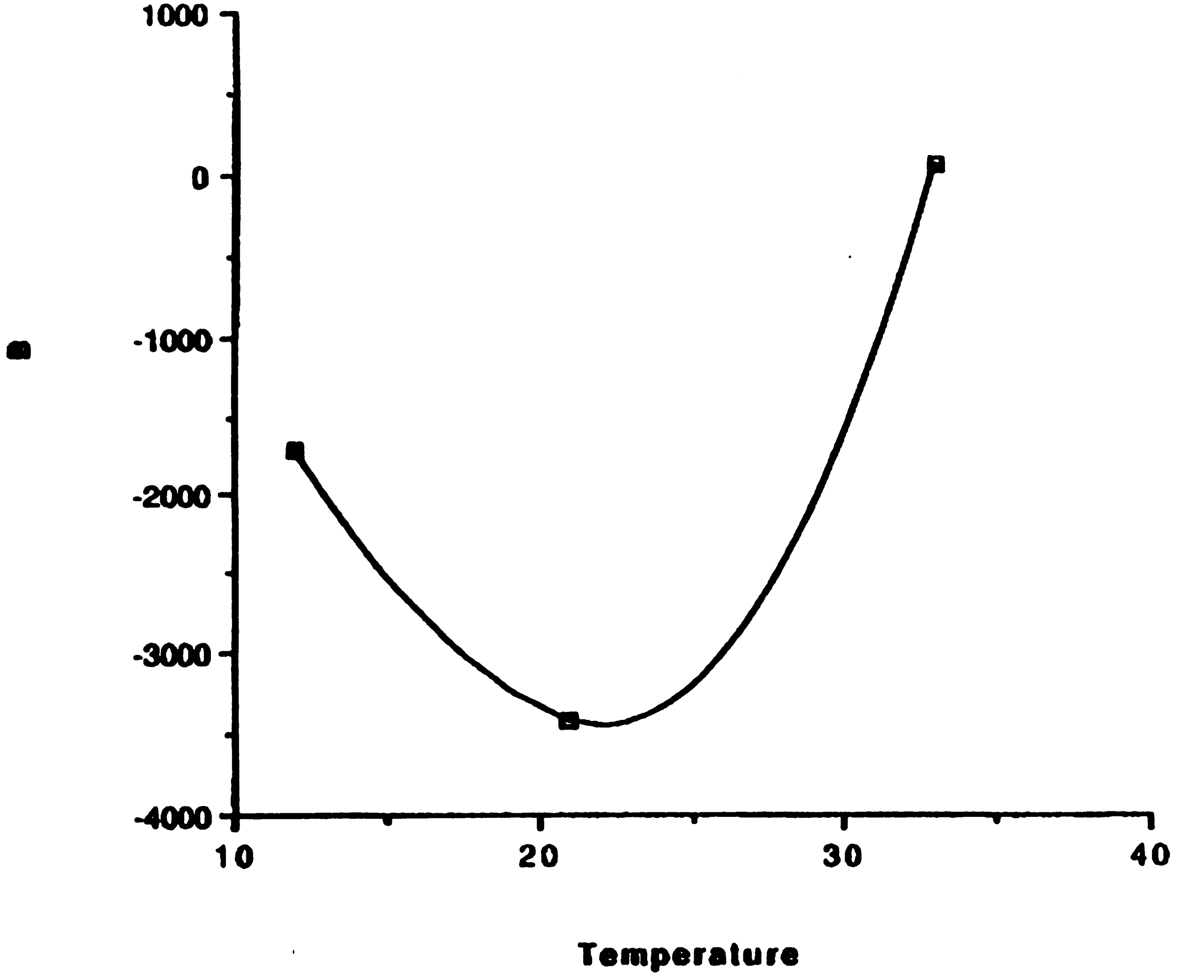
K versus Temperature (degrees C): Chen model



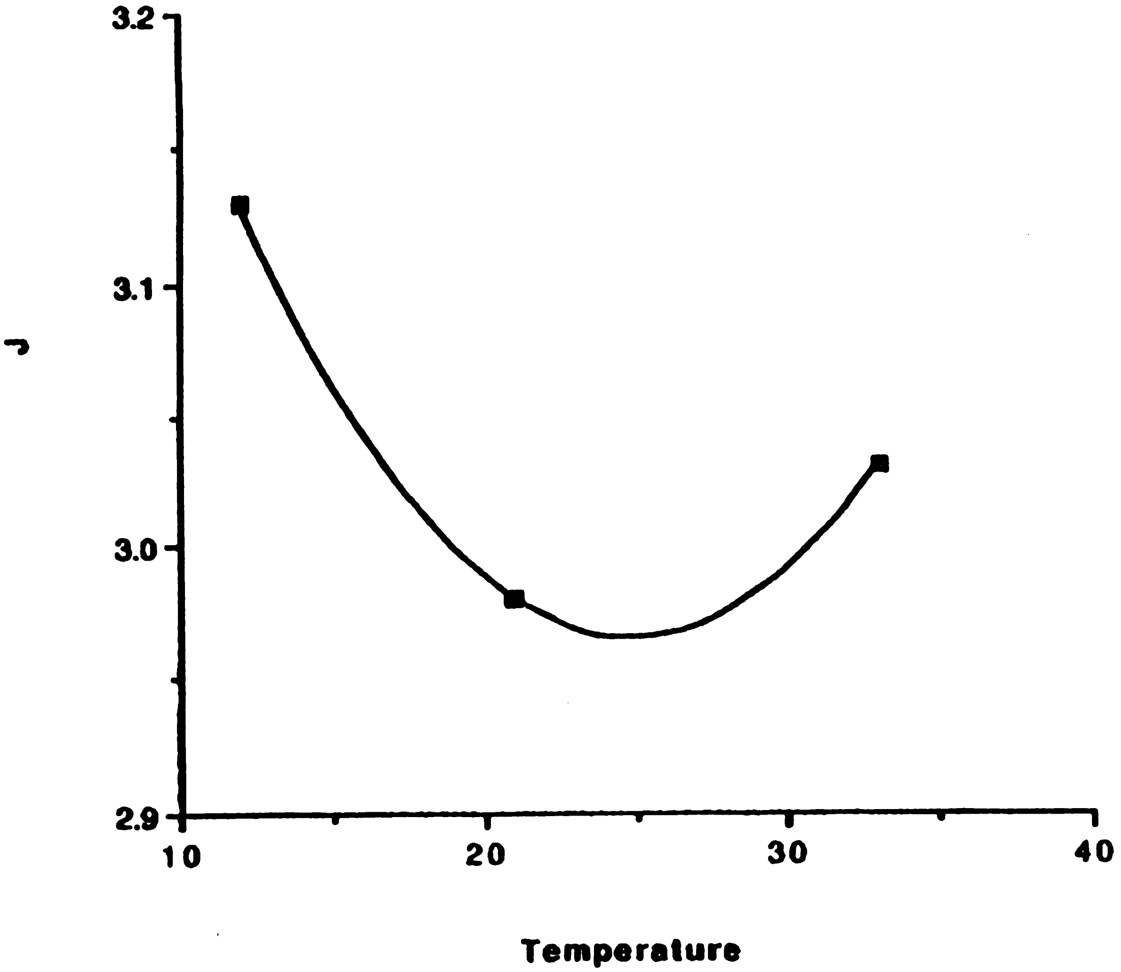
N versus Temperature (degrees C): Henderson model



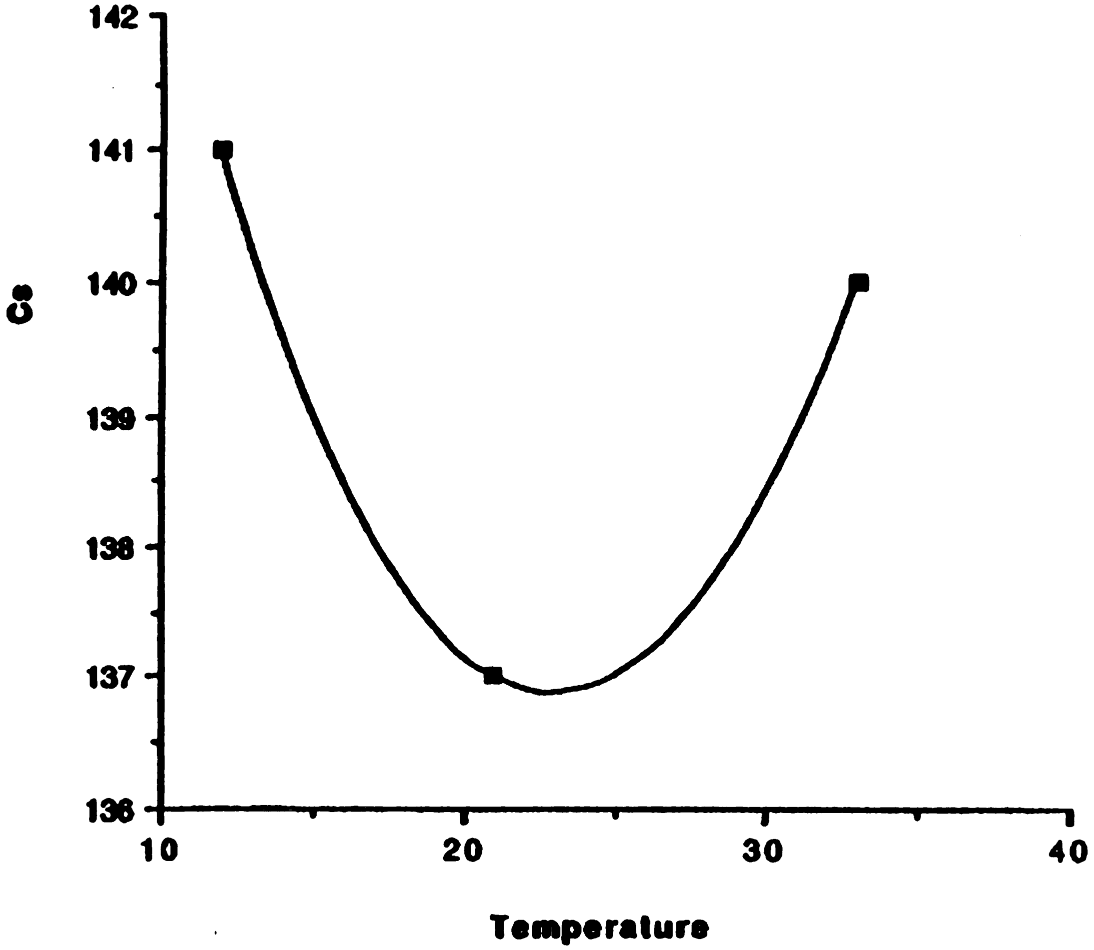
K1 versus Temperature (degrees C): Henderson model



B versus Temperature (degrees C): B.E.T. model



J versus Temperature (degrees C): B.E.T. model



Cs versus Temperature (degrees C): B.E.T. model

LIST OF REFERENCES

BOURNE, M. C. 1986. Effects of Water Activity on Textural Properties of Food. Institute of Food Technologists; Proceedings, tenth Basic Symposium.

BRUNAUER, S., EMMETT, P. H., and TELLER, E. 1938. Adsorption of Gases in Multimolecular Layers. J. Am. Chem. Soc. 60:309

CAURIE, M. 1970. A New Model Equation for Predicting Safe Storage Moisture Levels for Optimum Stability of Dehydrated Foods. J. Fd. Technol. 5, 301

CAURIE, M., LEE, T.C., SALOMON, M., and CHOCHESTER, C. O. 1976. A Rearranged B.E.T. Plot for a More Direct Estimation of B.E.T. Constants. J. Fd. Sci. 41,448

CHAPRA, S. C. and CANALE, R. P. 1985. Numerical methods for engineers with personal computer applications. McGraw-Hill, Inc. Pages 316-317.

CHEN, C. S. 1971. Equilibrium Moisture Curves for Biological Materials. Trans. of the ASAE. 14,924

CHEN, C. S. and CLAYTON, J. T. 1971. The Effect of Temperature on Sorption Isotherms of Biological Materials. Trans. of the ASAE. 14,927

CHIRIFE, J. and IGLESIAS, H. A. 1978. Equations for fitting water sorption isotherms of foods: Part I-a review. J. Fd. Technol. 13,159-174

DAVIS, E. G. 1970. Evaluation and Selection of Flexible Films for Food Packaging. Food Technol. Aust 22:62

DUCKWORTH, R. B. and SMITH, G. M. 1963. Recent Advances in Food Science. Proc. Nutr. Soc. 22, 182.

FELT, C. E., BUECHELE, A. C., BORCHARDT, L. F., KOEHN, R. C., COLLATZ, F. A., and HILDEBRAND, F. C. 1945. Determining Shelf Life of Packaged Cereals. Cereal Chem. 22:261.

FENNEMA, O. 1985. Water and Ice. Chapter 2 in Principles of Food Science, second edition, Marcel Dekker Inc.

HEISS, R. (1958). Shelf Life Determinations. Modern Packaging. 8:119

HENDERSON, S. M. 1952. A Basic Concept of Equilibrium Moisture. Agric. Engng. 33,29

IGLESIAS, H. A. and CHIRIFE, J. 1976a. B.E.T. Monolayer Values in Dehydrated Foods and Food Components. Lebensm. Wiss. U. Technol. 9,107

IGLESIAS, H. A. and CHIRIFE, J. 1976b. Equilibrium Moisture Contents of Air Dried Beef. Dependence on Drying Temperature. J. Fd. Technol. 11,565

IGLESIAS, H. A. and CHIRIFE, J. 1976c. Prediction of the Effect of Temperature on Water Sorption Isotherms of Food Materials. J. Fd. Technol. 11,109

IGLESIAS, H. A., BOQUET, R. and CHIRIFE, J. 1977a. On the Evaluation of B.E.T. Constants from the B.E.T. Isotherm Equation. J. Fd. Sci.

IGLESIAS, H. A., CHIRIFE, J., and VIOLLAZ, P. 1977. Evaluation of Some Factors Useful for the Mathematical Prediction of Moisture Gain by Packaged Dried Beef. J. Food Technol. 12,505

IGLESIAS, H. A., VIOLLAZ, P., and CHIRIFE, J. 1979. Technical Note: A Technique for Predicting Moisture Transfer in Mixtures of Packaged Dehydrated Foods. J. Food Sci. 14:89-93.

KAREL, M., and LABUZA, T. P. 1969. Optimization of Protective Packaging of Space Foods. U.S. Air Force Contract.

KENTALA, M. D., LOCKHART, H. E., GIACIN, J. R. and ADAMS, R. 1982. Computer Aided Simulation of Quality Degradation of Oral Solid Drugs Following Repackaging. Pharm. Technol. 6:46.

LABUZA, T. P. 1968. Fd. Technol., Champaign, 22,263

LABUZA, T. P., MIZRAHI, S., and KAREL, M. 1972. Mathematical Models for Optimization of Flexible Film Packaging of Foods for Storage. Trans. ASAE. 15:150

LABUZA, T. P., and RIBOH, D. 1982. Theory and Application of Arrhenius Kinetics to the Prediction of Nutrient Losses in Foods. Food Technol. 36(10):66-74.

LABUZA, T. P. 1982. Open Shelf Life Dating of Foods. Food and Nutrition Press, Inc. Westport, CT.

LEE, C. H. 1987. Temperature Dependency of the Equilibrium Sorption Isotherm and its Utility in Shelf Life Simulation of a packaged moisture sensitive pharmaceutical tablet. M.S. thesis, Michigan State University.

Le MAGUER, M. 1986. Mechanics and Influence of Water Binding on Water Activity. Institute of Food Technologists; Proceedings, tenth Basic Symposium.

LEUNG, H. K. 1986. Influence of Water Activity on Chemical Reactivity. Institute of Food Technologists; Proceedings, tenth Basic Symposium.

LITTLE T. M. and HILLS F.J. 1977. Agricutural Experimentation. Design and Analysis. John Wiley and Sons.

McLAREN, A. D. and ROWEN, J. W. 1952. J. Polymer Sci. 7,289.

MIZRAHI, S. and KAREL, M. 1977a. Accelerated Stability Tests of Moisture Sensitive Products in Permeable Packages by Programming Rate of Moisture Content Increase. Journal of Food Sci. 42(4)

MIZRAHI, S. and KAREL, M. 1977b. Accelerated Stability Tests of Moisture Sensitive Products in Permeable Packages at High Rates of Moisture Gain and Elevated Temperatures. Journal of Food Sci. 42(6)

NAKABAYASHI, K., SHIMAMOTO, T., and MIMA, H. 1980 a. 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., and MIMA, H. 1980 b. 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., and MIMA, H. 1980 c. Stability of Packaged Solid Dosage Forms. III. Kinectic 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., SHIMAMOTO, T., and MIMA, H. 1981 a. 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. 29:2027-2034.

NAKABAYASHI, K., SHIMAMOTO, T., MIMA, H., and OKADA, J. 1981 b. Stability of Packaged Solid Dosage Forms. V. Prediction of the Effect of Aging on the Disintegration of Packaged Tablets Influenced by Moisture and Heat. Chem. Pharm. Bull. 29: 2051-2056

NAKABAYASHI, K., HANATANI, S., and SHIMAMOTO, T. 1981 c. Stability of Packaged Solid Dosage Forms. VI. Shelf Life Prediction of Packaged Prednisolone Tablets in Relation to Dissolution Properties. Chem. Pharm. Bull. 29:2057-2061.

OSWIN, C. R. 1945. The Kinectics of Package Life. J. Soc. Chem. Ind. Trans. 64:419.

PARROT, E. L. 1970. Pharmaceutical Technology. Fundamental Pharmaceutics. University of Iowa. Burgess Publishing Company.

PIRES, L. C. 1988. The Storage Stability of a Moisture Sensitive Oral Solid Drug Product in Bulk and Blister Packages. The Effect of Repetitive Opening and Closing of Bulk Packages. M.S. thesis, Michigan State University.

QUAST, D. G., and KAREL, M. 1972a. Effect of Environmental Factors on the Oxidation of Potato Chips. J. Food Sci. 37:584.

QUAST, D. G., KAREL, M., and RAND, W. M. 1972b. Development of a Mathematical Model for Oxidation of Potato Chips as a function of Oxygen Pressure, Extent of Oxidation and Equilibrium Relative Humidity. J. Food Sci. 37:673

QUAST, D. G., and KAREL, M. 1972c. Computer Simulation of Foods undergoing Spoilage by Two Interacting Mechanisms. J. Food Sci. 37:679

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. 34:35-42.

REAMER, J. T., and GRADY, L. T. 1978. Moisture Permeation of Newer Unit Dose Repackaging Materials. Am. J. Hosp. Pharm. 35:787-793.

RIMER, J., and KAREL, M. 1978. Shelf Life Studies of Vitamin C during Food Storage. Prediction of L-ascorbic Acid Retention in Dehydrated Tomato Juice. J. Food Proc. Pres. 1:293

SALWIN, H. 1959. Defining Minimum Moisture Contents for Dehydrated Foods. Food Technol. 13:594-595

SALWIN, H. and SLAWSON, V. 1959. Moisture Transfer in Combination of Dehydrated Foods. Food Technol. 13:715

SINGH, R. P., HELDMAN, D. R., and KIRK, J. R. 1974. Computer Simulation of Quality Degradation in Liquid Foods During Storage. Proceedings, fourth Int. Congress Food Science and Technol. 1V:407-416.

THOMAS, G. B., Finney, R. L. 1981. Calculus and Analytic Geometry. Addison-Wesley Publishing Company. Pages 86-87.

UNITED STATES PHARMACOPEIA (USP XXII) "Stability Considerations in Dispensing Practice", page 1703, 1990, United States Pharmacopeial Convention, Inc. Rockville, MD 20852
"Current Good Manufacturing Practice for Finished Pharmaceuticals" 21 CFR, Part 211, Section 211.37, Expiration dating and Section 211.166, Stability

Testing; Office of the Federal Register, National Archives and Records Administration, U.S. Government Printing Office, Washington D.C.

VEILLARD, M., BENTEJAC, R., DUCHENE, D., and CARSTENSEN, J. T. 1979. Moisture and Transfer Tests in Blister Package Testing. Drug Dev. Ind. Pharm. 5:227-244

WANG, M. J. M. 1985. Prediction of Moisture Uptake by a Packaged Moisture Sensitive Pharmaceutical Product Stored Under Fluctuating Temperature and Humidity Environments. M.S. thesis Michigan State University.

WANNIGER, L. A. 1972. Mathematical Model Predicts Stability of Ascorbic Acid in Food Products. Food Technol. 26(6):42