This is to certify that the
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DESIGNING A PACKAGE FOR PHARMACEUTICAL TABLETS IN RELATION TO MOISTURE AND DISSOLUTION

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Seungyil Yoon

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Hugh E. Lockhart
Major Professor's Signature

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DESIGNING A PACKAGE FOR PHARMACEUTICAL TABLETS IN RELATION TO MOISTURE AND DISSOLUTION

By

Seungyil Yoon

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ABSTRACT

DESIGNING A PACKAGE FOR PHARMACEUTICAL TABLETS IN RELATION TO MOISTURE AND DISSOLUTION

By

Seungyil Yoon

Dissolution can be used as a measure of bioavailability and as a stability-indicating parameter for pharmaceutical tablets. Therefore, it is very important to predict the dissolution of pharmaceutical tablets in a package in order to design a package for stability testing. In order to predict the dissolution, the relationship between dissolution, storage time and relative humidity must be determined. So, tablets were stored in open dishes at two different temperatures (25 and 40°C) and five different relative humidities (0, 50, 65, 75, 90% RH) for 6 months.

Dissolution was measured every month for 6 months, and the dissolution was plotted with storage time to determine a dissolution retardation rate (R, dissolution change/day). At each relative humidity, tablets have a specific dissolution retardation rate. Therefore, dissolution retardation rates can be plotted as a function of relative humidity to determine the relationship between dissolution retardation rate and relative humidity. Based on that relationship, a dissolution prediction model can be developed. From the dissolution prediction model, dissolution can be calculated at any relative humidity for a given amount of storage time. The relative humidity of the package headspace changes in the unsteady state, so the dissolution of tablets stored at any condition is very hard to estimate. However, computer programs make it possible.

A Windows based dissolution prediction program was developed in this study. The dissolution prediction program can calculate the dissolution change of tablets in a package as a function of storage time. In order to calculate the dissolution change, a proprietary moisture prediction program was also developed in the dissolution prediction program. The moisture prediction program can calculate the moisture content of solids in a package and RH of the package headspace. The program can be used to save time and money in a variety of applications such as determining the amount of desiccant and package barrier requirement for a given shelf life.

The moisture and dissolution prediction programs were verified by using experimental results. Uncoated drug tablets and silica gel were inserted into LDPE bags and HDPE bottles. The moisture content of the tablets and silica gel was measured as a function of storage time, and then this was compared to the results from the moisture prediction program. The differences between predicted and experimental moisture contents ranged from 0% to 0.39% for tablets and 0.11 to 6.50% for silica gel. Also, dissolution results from the dissolution prediction program were compared with the experimental results to verify the program. The differences between predicted and experimental dissolution ranged from 1.3 to 13.5% for LDPE bags and 0 to 18.3% for HDPE bottles. The differences are fairly large because tablets behave in a variety of manners. In this study, a new theory of the relationship between dissolution retardation and relative humidity is proposed.

The open dish study and computer simulation programs are useful in providing an effective way to select an appropriate package for registration stability testing.

DEDICATION

This dissertation is dedicated to my wife Youngmi Shin, my family, and my friends.

ACKNOWLEDGEMENTS

I would like to express my gratitude to all those who gave me the possibility to complete this research. I am deeply indebted to my major professor, Dr. Lockhart whose help, stimulating suggestions and encouragement helped me in all the time of research for and writing of this dissertation. I researched for 6 years with him for master and Ph.D. He guided me right things, and I am sure I followed right things. I am so lucky because I met Dr. Lockhart for my career. I am also grateful to thank Dr. Selke for her prompt and thoughtful discussion of this research. We had meetings very often, sometimes every week or every two weeks. She taught me how to approach the correct things. And, I am also grateful to thank Dr. Burgess and Dr. Worden for their research guidance. Initiating a research correctly is very hard and important. They guided me a right path for this research.

Also, I want to thank Eli Lilly and Company for giving me the permission to use a product and generous supporting equipment and material used for this research. I have furthermore specially to thank the senior packaging engineer at Lilly, Mark and the senior analytical chemist at Lilly, Sharon for discussing my Ph.D. work. They advised me and sometimes encouraged me to go ahead with my dissertation.

Especially, I would like to give my special thanks to my wife Youngmi whose patient love enabled me to complete this work.

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A: surface area
AH: absolute humidity at given temperature, *g H_2O/g dry air*
a_w: water activity
$a_{w(in)}$: water activity of air inside package
$a_{w(out)}$: water activity of air outside package
β: slope of $M(\%)$ and a_w (or $RH(\%)$ or p/p_s)
C_i: concentration of drug initially in tablet (*mg drug initially in tablet/mL medium*)
C_m: concentration of drug dissolved in medium after stirring for time s (*mg drug dissolved in medium/mL medium*)
C_s: concentration of drug still left in tablet after stirring for time s (*mg drug left in tablet/mL medium*)
D: dissolution (%) at 30 minute stirring time
D_i: initial dissolution (%) at 30 minute stirring time
EMC: equilibrium moisture content
K: dissolution reduction rate (day^{-1})
k: dissolution rate ($minute^{-1}$)
k_i: dissolution rate ($minute^{-1}$) of the initial tablet
k_t: dissolution rate ($minute^{-1}$) at storage time t
ℓ: thickness of material
$M(\%)$: moisture content (%) (dry weight), *g H_2O/g dry weight of solid × 100*
$M_w(\%)$: moisture content (%) (wet weight), *g H_2O/g wet weight of solid × 100*
$M_i(\%)$: initial moisture content (%), *g H_2O/g dry weight of solid × 100*
M: moisture content (dry weight), *g H_2O/g dry weight of solid*
M_A: moisture content of solid A, *g H_2O/g dry weight of solid A*
M_{Ai}: initial moisture content of solid A, *g H_2O/g dry weight of solid A*
M_{Af}: final moisture content of solid A, *g H_2O/g dry weight of solid A*
M_B: moisture content of solid B, *g H_2O/g dry weight of solid B*
M_i: initial moisture content, *g H_2O/g dry weight of solid*
M_f: final moisture content, *g H_2O/g dry weight of solid*
M_{wi}: initial moisture content (wet weight), *g H_2O/g wet weight of solid*
m: mass of moisture
m_e: mass of moisture at equilibrium
m_h: mass of moisture in the package headspace
m_i: mass of moisture at initial time
m_T: total mass of moisture inside package
P: permeability of package
P_i: initial weight of product
P_f: final weight of product
p: vapor pressure of water at given temperature
p_{atm}: atmospheric pressure at given temperature
p_{in}: vapor pressure of water inside package at given temperature
p_{out}: vapor pressure of water outside package at given temperature
p_s: saturation vapor pressure of water at given temperature
p/p_s: relative water vapor pressure

R: dissolution retardation rate (*% dissolution change/day*)
$RH(\%)$: relative humidity (%)
s: stirring time
t: storage time
V: volume of the package headspace
W: weight of solid
W_d: dry weight of solid
W_{dA}: dry weight of solid A
W_{dB}: dry weight of solid B
W_f: final weight of solid
W_i: initial weight of solid
w: mass of moisture permeated into the package

INTRODUCTION

Pharmaceutical companies must submit stability data for new drug applications (NDA) to the U.S. Food and Drug Administration (FDA) before pharmaceutical products go to market. The submitted stability data must be approved by FDA. FDA recommends that the length of the studies and the storage conditions should be sufficient to cover storage, shipment and subsequent use. Therefore, FDA recommends that drug products be tested in long-term testing (25±2°C, 60±5% RH) for 12 months and accelerated testing (40±2°C, 75±5% RH) for 6 months in the market package. If a significant change occurs due to accelerated testing, a minimum of 6 months' data from an ongoing 12 months study at an intermediate condition (30±2°C, 60±5% RH) should be included for the initial application. A significant change in dissolution is defined as failure to meet the specification limit for 12 tablets or capsules [USP Stage 2[a]]. If a significant change occurs during intermediate testing, it may not be appropriate to label the drug product for CRT (controlled room temperature) storage with the proposed expiration dating period even if the stability data from the full long-term studies at 25±2°C, 60±5% RH appear satisfactory. After new drug products obtain market approval from FDA, they can launch to market. Stability data in long-term testing (25±2°C, 60±5% RH) must be reported to

[a] If the quantities of active ingredient dissolved from the units tested conform to the accompanying Acceptance Table, the requirements are met. Continue testing through the three stages unless the results confirm at either S_1 or S_2. The quantity, Q, is the amount of dissolved active ingredient specified in the individual monograph (USP <711> Dissolution).

Acceptance Table

Stage	Number Tested	Acceptance Criteria
S_1	6	Each unit is not less than Q + 5%.
S_2	6	Average of 12 units (S_1+ S_2) is equal to or greater than Q, and no unit is less than Q – 15%.
S_3	12	Average of 24 units (S_1+ S_2+ S_3) is equal to or greater than Q, not more than 2 units are less than Q – 15%, and no unit is less than Q – 25%.

FDA annually for the proposed expiration dating period (USP <1196>, 1995 and Guidance for Industry, Stability Testing of Drug Substances and Drug Products, 1998).

A package must be designed properly to meet the FDA requirements for accelerated stability testing. Ideally, the packaged product should meet the stability requirement at the end of the six month accelerated storage period. This study shows how to select a suitable package for pharmaceutical tablets by using an open dish study and computer simulation programs focused on moisture content and dissolution. Dissolution is one parameter that may change as a function of temperature, humidity, and storage time. It has been accepted by the United States Pharmacopeial Convention (USPC) as a measure of bioavailability and as a stability-indicating parameter for solid oral dosage forms.

When solid oral dosage forms are packaged in blisters or plastic bottles, they can be protected from environmental hazards such as light, oxygen, and moisture. However, the packages cannot protect them completely, so the properties of solid dosage forms may deteriorate as a function of storage time. Since dissolution is affected by temperature and moisture, determining the relationship among dissolution, temperature, and moisture is very important in designing a package for solid oral dosage forms that will maintain the specification limit of dissolution.

To measure this relationship and the effect of the package on it, an experimental program can be conducted. It consists of two parts: an open dish study of the product and a separate evaluation of the permeation behavior of the package. This program differs from and is faster than the stability testing program. In the open dish study, the product is brought to equilibrium quickly with a series of temperature and humidity environments.

Once that equilibrium is achieved, the product properties, including dissolution, can be measured. At the same time, the permeability of the package can be measured over the range of temperatures encountered in distribution. Specifically, this information can be obtained for the accelerated storage condition (40°C/75% RH).

Then, using mathematical relationships developed by researchers over the last 20 years, and in this research, product researchers and packagers can select a barrier package that will meet the requirements of the accelerated stability testing program.

More formally, the hypothesis for this research is that there is a general method for design of a barrier package that will protect the dissolution property of a drug product when it is exposed to ICH (International Conference on Harmonization) accelerated stability conditions. The general hypothesis is supported by the following three subordinate hypotheses:

1. The relationship between moisture content and dissolution of drug tablets can be found using open dish studies.
2. Moisture content and dissolution of drug tablets in a permeable package can be predicted based on the unsteady state vapor pressure of the package headspace.
3. A suitable package for stability testing can be chosen using computer simulation programs.

In order to prove the hypotheses, the following steps were taken:

1. Develop mathematical models that can calculate the shelf life, moisture content, and dissolution of drug tablets in a package.

2. Determine moisture sorption isotherm equations.
3. Determine dissolution retardation rates at a variety of relative humidities.
4. Determine permeabilities of packages.

In this study, coated and uncoated drug tablets were placed in open dishes at 25 and 40°C at 0%, 50%, 65%, 75%, and 90% RH, for 6 months. The moisture, dissolution, hardness, and dimensions of the tablets were measured at scheduled times during the open dish study. It was found that dissolution, hardness, and dimensions changed as a function of moisture and storage time. The relationship between moisture and dissolution obtained from the open dish study was used to predict the dissolution of tablets in a package as a function of storage time. The hardness and dimensions were used to explain the theory of dissolution retardation as a function of relative humidity. The permeabilities of packages (LDPE bags and HDPE bottles) at 40°C were measured separately. Tablet properties from the open dish study were used along with package permeabilities to design a suitable package for stability testing.

In order to formulate the relationship between moisture and dissolution, a property called the dissolution reduction rate (K) was developed by Nakabayashi and coworkers (1981). However, their approach did not work for this study because of variation inherent in the dissolution measurements. While logical in theory, the dissolution reduction rate did not work well enough in practical application to be useful. Therefore, a different approach to formulate the relationship between moisture and dissolution was used in this study. This different approach uses the dissolution retardation rate (R), dissolution change/day. Dissolution is dependent on moisture as well

as storage time, so a dissolution retardation rate including storage time is necessary to formulate the relationship with moisture in order to predict the dissolution of tablets in a package as a function of storage time. Dissolution retardation rates must be determined at each relative humidity and temperature.

CHAPTER 1

BACKGROUND AND LITERATURE REVIEW (DISSOLUTION PREDICTION MODELS)

Literature related to dissolution prediction models is reviewed here. Literature related to moisture and shelf life[b] prediction models is reviewed in Appendix A because shelf life and moisture prediction models are not directly related to dissolution prediction for tablets in a package. They are, however, necessary tools for estimating dissolution shelf life or selection of barrier packages, so the necessary background is provided separately.

Dissolution is a critical parameter in determining performance and defining quality control, regulatory compliance, and bioavailability of solid oral dosage forms such as tablets and capsules (see USP <1191>). The U.S. Food and Drug Administration (FDA) requires that any drug product on the market must at all times meet the requirements of the USP monograph or other monographs specifying its properties. Otherwise, it will be recalled from the market. The monograph specifies a dissolution requirement for many products. Compared with the chemical stability of the drug substance in solid dosage forms, the effect of aging on in-vitro dissolution (physical stability) has been neither thoroughly investigated nor fully understood (Chowhan, September 1994).

Dissolution prediction models for drug substance particles have been developed by using the film theory (diffusion layer model). The thickness of a drug particle is assumed, and then the model can be developed from Fick's second law of diffusion. It is a cube-root law as shown in Equation 1 (Higuchi, 1963).

[b] Shelf life is defined as the time required to reach the final moisture content from the initial moisture content.

$$w^{1/3} = w_0^{1/3} - k_{1/3}t \qquad k_{1/3} = \left(\frac{4\pi\rho}{3}\right)^{1/3} DC_s \qquad (1)$$

where w = the particle weight at time t, w_0 = the initial particle weight, k = the composite rate constant, ρ = the density of the particle, D = the diffusion coefficient, C_s = the solubility, h = the diffusion layer thickness

Almeida et al. (1997) demonstrated the inadequacy of the cube-root law (Equation 1) to predict the dissolution of ibuprofen, as the assumptions associated with this model are not valid in the case of multisized powders.

Wang and Flanagan (1999) showed that an assumption used in the derivation of the cube-root law may not be accurate under all conditions for diffusion-controlled particle dissolution. They found the cube-root law was most appropriate when particle size is much larger than the diffusion layer thickness. A two-thirds-root expression (Equation 2) applied when the particle size is much smaller than the diffusion layer thickness. The square-root expression (Equation 3) is intermediate between these two models.

$$w^{2/3} = w_0^{2/3} - k_{2/3}t \qquad k_{2/3} = \left(\frac{4\pi\rho}{3}\right)^{2/3} \frac{2DC_s}{\rho} \qquad (2)$$

$$w^{1/2} = w_0^{1/2} - k_{1/2}t \qquad k_{1/2} = \left(\frac{3\pi\rho}{2}\right)^{1/2} \frac{DC_s}{k'\rho} \qquad (3)$$

where k' = the constant

These models (Equations 1-3) are just for drug substance particles. If a drug is mixed with excipients, and then compressed to form a tablet, the models cannot be

applied to predict the dissolution of the tablet because it is impossible to determine the diffusion layer thickness.

Fu et al. (1976) developed a mathematical model for the estimation of the drug release rate from drug-polymer composite tablets. The drug-polymer composite tablets do not disintegrate in the dissolution medium, but the drug can dissolve into the medium through the polymer. The model (Equation 4) predicts the drug released from a drug-polymer composite tablet as a function of storage time:

$$\frac{M_{(t)}}{M_{(\infty)}} \approx 1 - \frac{8}{\ell^2 a^2} \sum_{m=1}^{10} \frac{exp(-D\alpha_m^2 t)}{\alpha_m^2} \sum_{n=0}^{10} \frac{exp(-D\beta_n^2 t)}{\beta_n^2} \qquad (4)$$

where ℓ = half of the thickness of the drug-polymer composite tablet, a = the radius of the drug-polymer composite tablet, D = the diffusion coefficient of the drug in the drug-polymer composite tablet, t = storage time, α_m = the roots of $J_0(a\alpha) = 0$; J_0 = the zero-order Bessel function, $\beta_n = \frac{(2n+1)\pi}{2\ell}$

Siepmann et al. (1998) also developed a dissolution prediction model for swollen hydroxypropyl methylcellulose (HPMC) tablets numerically by using finite differences. The model was used to calculate the required shape and dimensions of HPMC tablets to achieve desired drug release profiles. The model mentioned above cannot be applied to starch based (or sugar based) tablets because these tablets disintegrate. If tablets lose their original shape, the prediction model cannot be used.

Based on review of the literature, it can be concluded that there is no available dissolution prediction model that can predict the dissolution of aged tablets stored at a specific condition for a certain amount of time. It may be impossible to develop. So, the dissolution behavior as a function of storage time has only been determined by stability

testing.

Taborsky-Urdinola et al. (1981) reported the effects of packaging and storage in multiple-unit and unit-dose containers on the dissolution rate of prednisone tablets. USP prednisone dissolution calibrator tablets that were packaged in polyethylene bags and unpackaged (open dish) tablets were selected to compare their dissolution. Both sets of tablets were placed in a tropical microenvironment of approximately 40 °C and 85% relative humidity for three months. Dissolution was measured at pre-determined intervals during storage. This study clearly demonstrated that packaging and storage affect product integrity. It showed a relationship between dissolution of the pharmaceutical product and the moisture barrier of its packaging. The dissolution of tablets stored in open dishes decreased a lot more quickly than the dissolution of tablets stored in packages. Her study is very useful to understand the dissolution behaviors among opened, low barrier packaged and high barrier packaged tablets. However, she did not explain how much dissolution was different as a function of package barrier and how dissolution changed as a function of storage time. Her study does not predict the dissolution behavior of tablets in a package.

Chowhan (March 1994) reported that the particle size, aqueous solubility, drug substance concentration, excipients and their concentration in the formulation, and the process used in manufacturing all play a significant role in determining drug product dissolution. And, Chowan (September 1994) reported the factors affecting in vitro dissolution of tablets include formulation, manufacturing method, processing variables, in-process controls, and dissolution method. Tablets formulated, manufactured, and processed differently were stored at differing storage conditions for differing storage

times in open dishes. His study is helpful for selecting the initial tablet formulations, but does not predict the dissolution behavior of aged tablets in a package.

As mentioned above, much research on developing pharmaceutical dosage forms has been done, and is still being done for each new product. However, the dissolution behavior of aged tablets in a package has still not been fully investigated and understood. It has been established that the dissolution of tablets in a package is changed as a function of storage conditions and storage time, but little research has been done to find how much the dissolution of tablets in a package is changed as a function of storage conditions and storage time.

When the dissolution shelf life of solid dosage forms was estimated, fit factors, critical storage condition, and dissolution reduction rate were used. Moore and Flanner (1996) presented two new fit factors to compare the difference between the percent drug dissolved per unit time for a test and a reference formulation. The fit factors are denoted by f_1 and f_2, and they can be defined by Equation 5 and Equation 6.

$$f_1 = \left\{ \frac{\sum_{t=1}^{n} |R_t - T_t|}{\sum_{t=1}^{n} R_t} \right\} \times 100\% \qquad (5)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} w_t (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \qquad (6)$$

where, R_t = the reference dissolution at stirring time point t
T_t = the test dissolution at stirring time point t
n = the number of sampling (stirring time) points
w_t = the optional weight factor[c]

[c] It can be used to minimize the analysis error.

Equation 5 is a perturbation of the relative error formula. It can approximate the percent error between reference and test dissolution profiles. The percent error is zero when two profiles are identical and increases proportionally with the dissimilarity between the two profiles. Equation 6 is a logarithmic transformation of the sum of squares error. It takes the average sums of squares of the difference between reference and test dissolution profiles and fits the result between 0 and 100. The fit factor (f_2) is 100 when two profiles are identical and approaches zero as the dissimilarity increases. Moore and Flanner said the fit factor (f_2) may provide a linear relationship if it is plotted as a function of storage time; then the dissolution shelf life can be predicted by extrapolation. However, it is hard to get a linear relationship between either fit factor (f_1 or f_2) and storage time.

The dissolution was used to decide the failure point of solid dosage forms and the moisture content at the failure point was used to estimate the dissolution shelf life (Qian, 1996, Wu, 1996, Kokitkar, 1997, Adams, 1999, Yoon, 2000, Thomas, 2000, Suemag, 2001). Adams (1999) stored hydroxypropyl methyl cellulose coated aspirin tablets in open dishes for 90 days at three different temperatures (25, 30, and 40 °C) and several different relative humidities. Dissolution and moisture content were measured at planned intervals. If the dissolution fell below a specification limit at a condition, that condition was used for a failure storage condition. So, the package was designed to maintain the package headspace below that failure storage condition for a desired dissolution shelf life. However, it has been found that the dissolution is not dependent on moisture content alone. Figure 1 shows dissolution for 3 months storage time for a coated aspirin. The tablets reached equilibrium moisture content in 6 days. Even though the moisture content

at 6 days and 90 days were the same, dissolution at 6 days and 90 days was not the same. Therefore, the dissolution is not dependent on moisture alone. It depends on storage time as well as moisture.

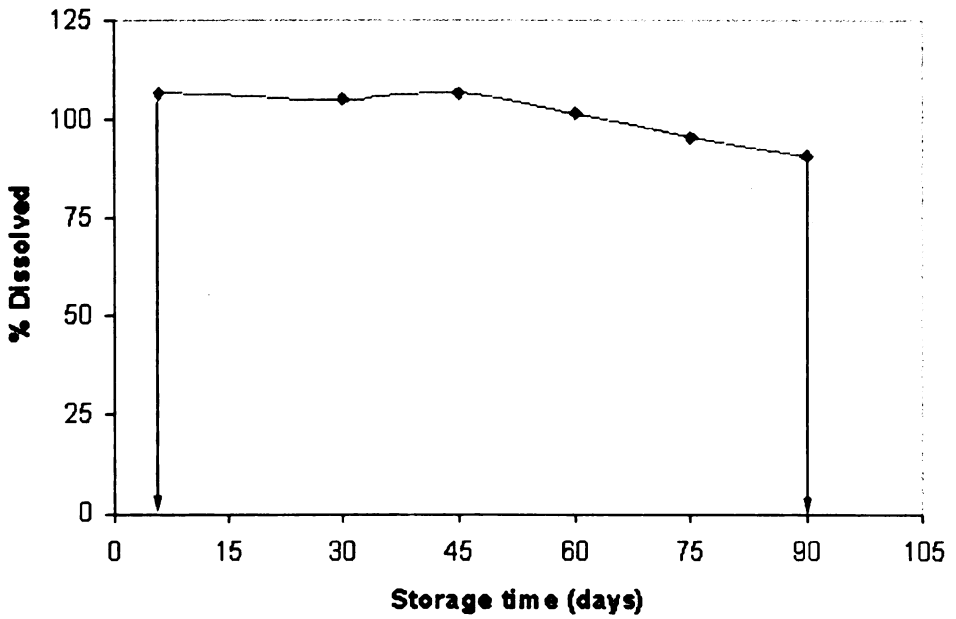


Figure 1 Dissolution of coated aspirin tablets stored for 3 months at 25°C/90% (Figure was plotted with data obtained from Adams, 1999)

Finding the relationship among the dissolution, moisture, and storage time is very important for predicting the dissolution of tablets in a package. Many researchers (Chowan, 1980, Taborsky, 1981, Kadir, 1986, Carstensen, 2000) tried to find the effects of storage conditions (e.g. temperature, RH, storage time) or packaging on the dissolution of solid dosage forms. They found the dissolution is affected by moisture, temperature, packaging, and storage time. However, no one except for Nakabayashi in 1981 explained how much the dissolution is affected by temperature, moisture, and storage time and what the relationship is among them. Nakabayashi tried to predict the dissolution of prednisolone tablets in a package by using the dissolution rate (k) and dissolution

reduction rate (K). In order to understand dissolution rate (k), the mechanism of dissolution in medium should be understood first.

1. Dissolution profile (The mechanism of dissolution)

Abdou (1989) explained the mechanism of tablet dissolution. If a fresh tablet is dropped into a dissolution medium (e.g. water or 0.02N HCl), the tablet is wetted by the medium. Water penetrates through the pores in the tablet, and disintegrants are swollen. The swelling of disintegrants can make boundaries in the tablet weak. Finally, the tablet is disintegrated and deaggregated into fine particles. Stirring by the stirring bar accelerates the tablet disintegration. After that, more drug particles become exposed to the water and dissolution proceeds effectively. If drug particles become exposed quickly to the water, the dissolution value reaches a peak in a short time. Figure 2 shows the S-shaped dissolution curve based on the theory of dissolution.

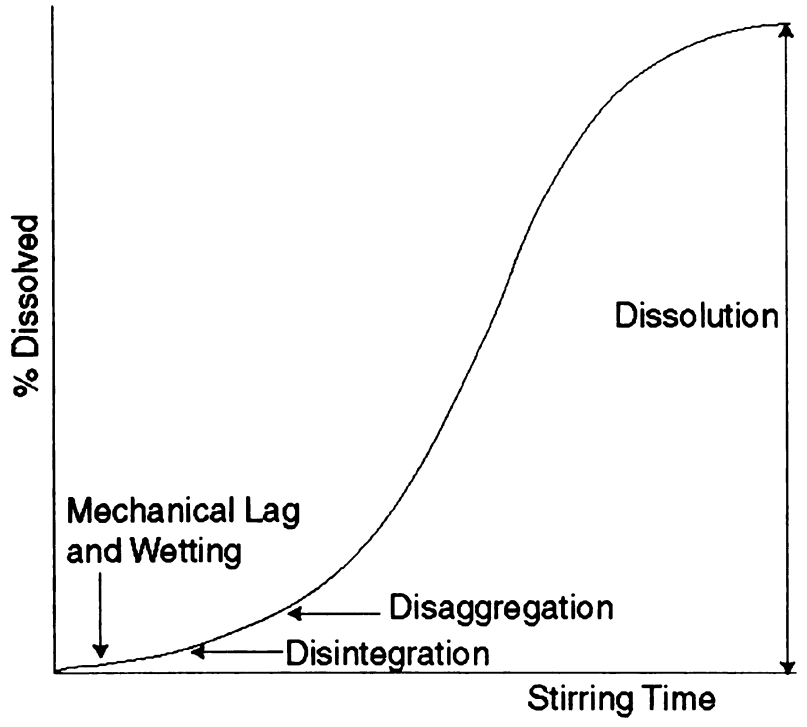


Figure 2 The S-shaped dissolution curve of solid dosage forms (Abdou, 1989)

2. Dissolution rate (k)

Based on the dissolution theory, a dissolution mechanism (I) was proposed by El-Yazigi (1981) as shown below.

$$A \xrightarrow{k_d} A_p \xrightarrow{k_s} A_s \qquad \text{Mechanism (I)}$$

where A is the amount of drug in the tablet, k_d is the disintegration rate constant, A_p is the amount of drug in the small particles (after disintegration). A_s is the amount of drug in solution and k_s is the dissolution rate constant.

When the fresh tablet is dropped into the dissolution medium, it is disintegrated immediately. So, the disintegration rate (k_d) can be ignored for the fresh tablet. The mechanism (I) can be simplified as shown in mechanism (II).

$$A_p \xrightarrow{k} A_s \qquad \text{Mechanism (II)}$$

where k is the dissolution rate.

Equation 7 can be used to determine the dissolution rate (k). The dissolution rate (k) is an apparent first-order kinetic rate.

$$C_s = C_i \cdot e^{-ks} \qquad (7)$$

The dissolution profile shown in Figure 3 is plotted with % undissolved versus stirring time to represent the exponential Equation 7.

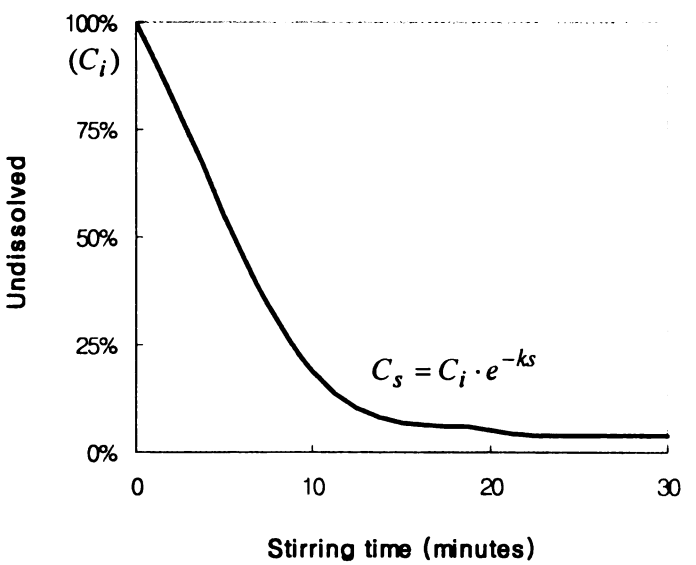


Figure 3 Exponential relationship between % undissolved and stirring time

The concentration of drug (C_s, mg drug left in tablet/mL medium) still left in the tablet after stirring time s can be calculated by Equation 7 and the concentration of drug

dissolved in the medium (C_m, mg drug dissolved in medium/mL medium) after stirring time s can be calculated by Equation 8.

$$C_m = C_i - C_i \cdot e^{-ks} \tag{8}$$

The natural log is applied to both sides of Equation 8, then it is rearranged to get a dissolution rate (k) as shown in Equation 9.

$$\ln\left[\frac{C_i}{C_i - C_m}\right] = ks \tag{9}$$

By plotting the data as $ln[C_i/(C_i-C_m)]$ vs. stirring time (s), a dissolution rate (k) can be determined as shown in Figure 4.

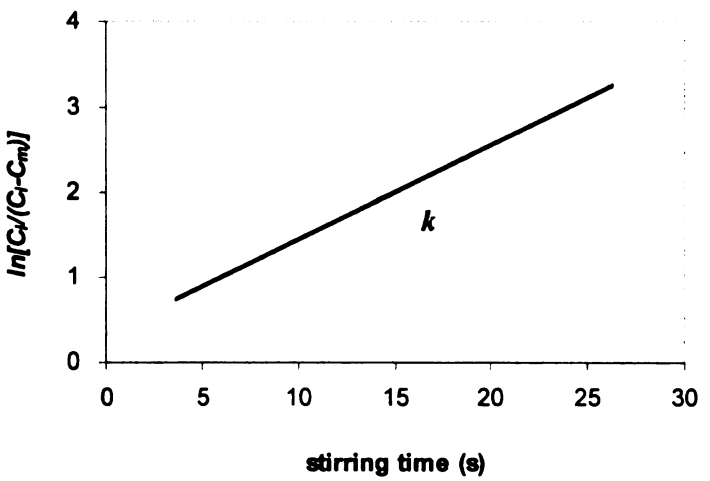


Figure 4 Dissolution rate (k)

3. Dissolution reduction rate (K)

The theory of the dissolution rates as a function of storage time has not been explained clearly yet. So, the relationship between dissolution rate and storage time should be determined experimentally. Nakabayashi used an exponential relationship

(first order kinetics) between dissolution rate and storage time. Obviously, the relationship is very dependent on the product formulation.

Equation 10 can be used to fit the relationship between dissolution rate (k) and storage time (t).

$$k_t = k_i \cdot e^{-K \cdot t} \tag{10}$$

The natural log is applied to both sides of Equation 10, then it is rearranged to get a dissolution reduction rate (K) as shown in Equation 11.

$$\ln\left[\frac{k_t}{k_i}\right] = -K \cdot t \tag{11}$$

By plotting the data as $ln[k_t/k_i]$ vs. storage time (t), a dissolution reduction rate (K) can be determined as shown in Figure 5.

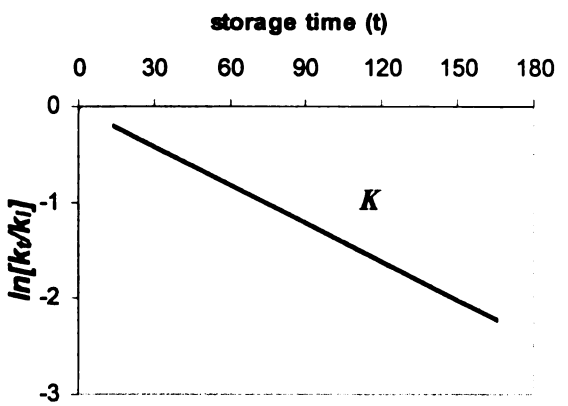


Figure 5 Dissolution reduction rate (K)

4. Relationship between dissolution reduction rate and moisture content

Nakabayshi and coworkers used the multiple regression method to determine the relationship between the dissolution reduction rate, moisture, and temperature. Table 1

shows the dissolution reduction rates for various moisture contents at 25, 40, and 50°C and Equation 12 shows the equation determined from a multiple regression method.

Table 1 Apparent dissolution reduction rate constants (K) of dissolution for prednisolone tablets with various moisture content (Nakabayashi et al., 1981)

Temperature, °C	M (%)	Dissolution Reduction Rate, K
25	4.77	0.0049
25	5.60	0.0091
40	3.54	0.0037
40	4.12	0.0055
40	4.64	0.0092
40	5.41	0.0165
50	3.10	0.0038

The constants of Equation 12 can be determined by using a multiple regression function in a statistics computer program.

$$\ln K = 4.5241 + 3.4936 \cdot \ln M - 4556.0491 / T \qquad (12)$$

where T is the absolute temperature ($^{\circ}K$)

They found that each term of Equation 12 was statistically significant, and the multiple correlation coefficient was as high as 0.994. Thus, Equation 12 was considered to be suitable for expressing the dependence of the K value on moisture and temperature.

CHAPTER 2

EXPERIMENTAL DESIGN, MATERIALS AND METHODS

1. Experimental design

Open dish exposure at various relative humidities causes faster dissolution change than the stability testing that is done with tablets in a package. In this study, therefore, the product and package are tested separately, then their experimental data are combined to predict the product properties in package as a function of storage time. First, tablets were stored in open dishes at 25 and 40°C at 0, 50, 65, 75, and 90% RH for 6 months. They were tested to determine the relationship between moisture content and dissolution for 6 months. Second, the permeabilities of packages (LDPE bags and HDPE bottles) were determined. Finally, the product results (initial moisture content, sorption isotherms, relationship between moisture content and dissolution) and package permeabilities were used to design a barrier package.

The product tablets were 2 years old, so it was necessary to determine if they still met specifications before using them in this study. First, the product quality was tested in terms of moisture, dissolution, and hardness. After determining that the product could be used for this study, initial moisture contents[d] and sorption isotherms were measured. These are better to be measured prior to preparing the storage conditions for the open dish study. Based on the initial moisture content and sorption isotherm, initial equilibrium relative humidity can be determined. Storage conditions above initial equilibrium relative humidity are recommended because tablet deterioration may be more

[d] In this study, initial moisture content is defined as a moisture content of the tablets which are inserted into a package.

severe than at low humidities. After determining the storage conditions, tablets were set up in open dishes for dissolution, hardness, and dimension measurement.

Figure 6 shows the diagram of the experimental design. Careful attention to matching the solid and broken lines with the description in the following text will help the reader to visualize the several relationships that exist among the parts of the work. The solid lines all represent the main theme of the research, from beginning through "Design a Package". The dotted and dashed lines represent the application of theories and procedures which are tools for accomplishing the main task.

Figure 6 also shows the package part of the work (permeability) and the product part of the work (moisture content, dissolution, dimensions, and hardness). Permeability and moisture content are used to verify the shelf life and moisture prediction program. These are all connected by dotted lines. Permeability, moisture content, and dissolution are used to verify the dissolution prediction program. These are all connected by a solid line. Moisture content, dissolution, dimensions, and hardness are used to explain the dissolution behavior as a function of relative humidity. These are connected by dashed lines. Table 2 shows the testing plan for the open dish study. The package permeability and product/package set up for the model verification were started with the open dish study at the same time.

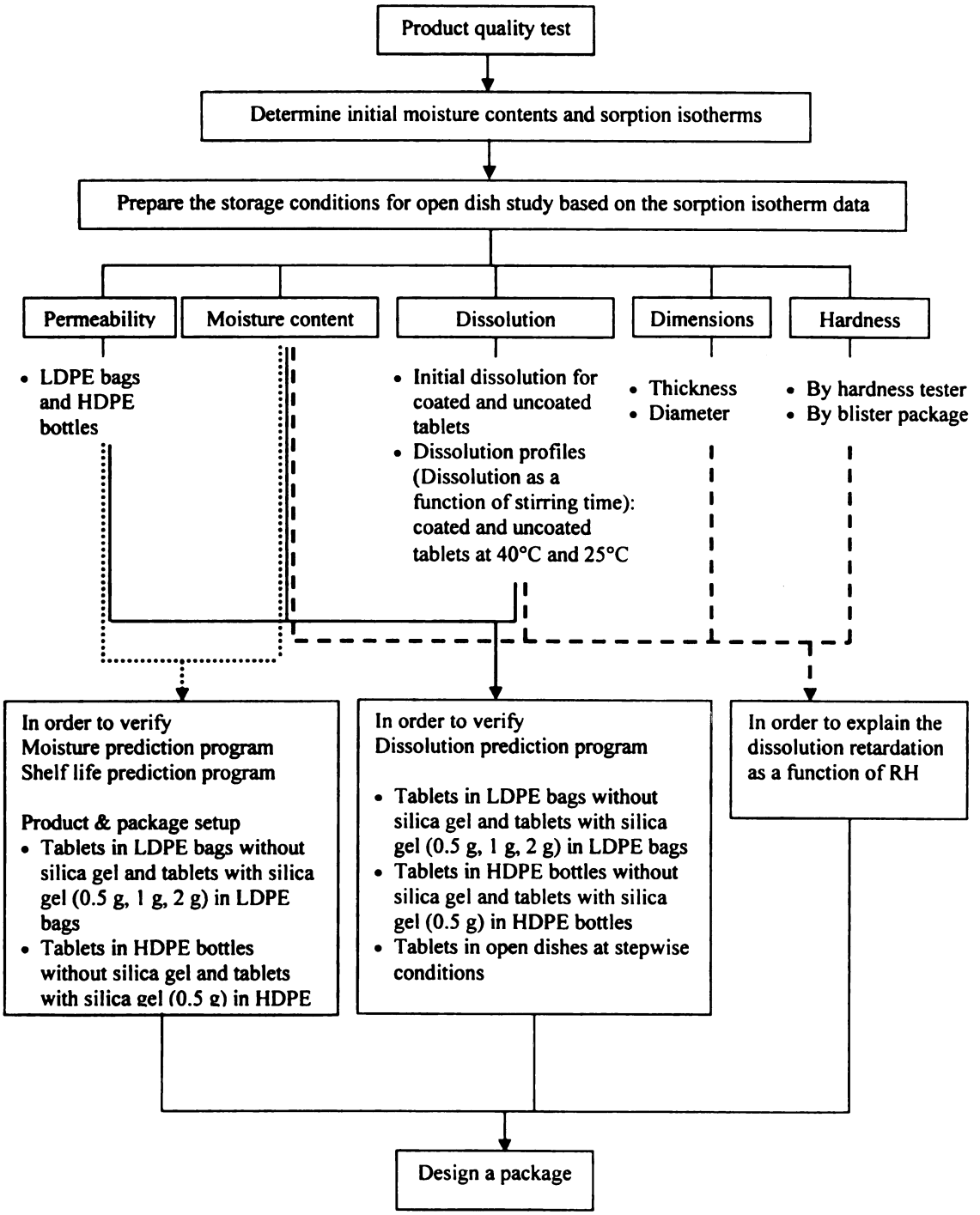


Figure 6 Diagram of the experimental design

Table 2 Testing plan for open dish study

Storage time (months)								
Prior to open dish study			1	2	3	4	5	6
Initial moisture contents (coated and uncoated tablets, silica gel), Moisture sorption isotherms (coated and uncoated tablets, silica gel at 25°C/40°C), Dissolution (calibration curve, initial dissolution profiles for coated and uncoated tablets), Initial hardness, Initial dimension			Package permeability →					
			Product and package were set up for the model verification →					
			Finding the relationship between moisture and dissolution Tests of tablet properties →					
Storage conditions								
40°C	90%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	75%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	65%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	50%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	0%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
25°C	90%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	75%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	65%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	50%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d
	0%		D, H, d	D, H	D, H, d	D, H	D, $D_{(200rpm, 1hr)}$, H	D, H, d

D: the dissolution testing of coated and uncoated tablets using 100rpm for 30 minute stirring (6 samples for each condition at each testing)
$D_{(200rpm, 1hr)}$: the dissolution of coated and uncoated tablets using 100rpm for 30 minute stirring and 200rpm for additional 30 minute stirring (6 samples for each condition)
H: the hardness of coated and uncoated tablets (10 samples for each condition at each testing)
d: the dimension of coated and uncoated tablets (5 samples for each condition at each testing)

During dissolution tests, it was recognized that dissolution of tablets stored at 40°C changed very rapidly as a function of storage time. Dissolution is defined as a physical property of tablets, so dissolution must be explained by physical phenomena such as a physical interaction among ingredients in tablets. Excipient and drug particles compressed into tablets are disintegrated by the dissolution medium. If the disintegration

time increases, the dissolution value will decrease (Carstensen et al., 1980). The dissolution value can be changed physically or chemically. Physically, excipients and drug in tablets can interact such as in crosslinking. Also, a drug can be degraded chemically. This causes the dissolution value of the drug to decrease. In order to make sure that the dissolution changed only by physical interactions, tablets needed to be disintegrated completely in the medium to allow all the drug in the tablet to dissolve into the medium. If the drug in the tablets is dissolved completely, the dissolution value must be the same as for the initial tablets (D = 100%) if there is no chemical degradation. Therefore, tablets at 5 months storage time were stirred using 200 rpm for an additional 30 minutes after the dissolution testing was done to be sure they dissolved completely. Some of the tablets did not reach 100% dissolution because they did not disintegrate completely, but some tablets did disintegrate completely, so they reached 100% dissolution. This meant the drug in 5 month aged tablets did not degrade chemically. See Appendix E. Dissolution Raw Data and Dissolution Profiles at 25°C for more information.

2. Materials and methods

(1) Drug X coated and uncoated tablets

Drug X coated and uncoated tablets were obtained from Eli Lilly and Company (Indianapolis, IN). The tablets were formulated with drug substance X, and the excipients mannitol (63%), microcrystalline cellulose (MCC) (18%), croscarmellose sodium, povidone, purified water, magnesium stearate, and color mixture yellow for coated tablets (see Appendix C for detailed information).

Mannitol can be obtained from hydrogenation of glucose. Glucose is a monosaccharide, so mannitol is a saccharide derivative. Mannitol is used as a diluent in formulating tablets. The superdisintegrant, croscarmellose sodium, was used to make tablets disintegrate quickly in the medium. Magnesium stearate used as a lubricant is hydrophobic but it enhances tablet granulation processing characteristics.

Table 3 shows that the physical properties of drug X 2 year old tablets are close to those of drug X fresh tablets.

Table 3 Comparison of physical properties between drug X fresh tablets and 2 year old tablets

	Moisture content		Dissolution at 30 minutes		Hardness	
	Coated	Uncoated	Coated	Uncoated	Coated	Uncoated
Fresh	≈ 2%	*	100%	*	9 kp	*
2 years old	2.31%	1.93%	95.9%	96.2%	9.21 kp	8.9 kp

*Data for uncoated tablets were not available.

(2) Storage conditions

Two different temperatures (25 and 40°C) and 5 different relative humidities (0, 50, 65, 75, 90%) were used for the open dish study. The relative humidities (50, 65, 75, and 90%) were prepared by saturating deionized water with salts (Fisher Scientific, PA) and 0% RH was prepared by using calcium chloride ($CaCl_2$, desiccant) in glass desiccators. Table 4 shows the list of the salts used to provide the desired range of relative humidities. ASTM E 104-85 shows how to prepare the salt solutions and the expected RH values for selected salt solutions.

Table 4 Salt solutions used to provide the required range of relative humidities

		25°C		
Salts	Amount used	Nominal RH	Actual RH by humidity sensor	Actual RH by moisture content
Calcium Chloride ($CaCl_2$)	N/A	0%	N/A	1.3 – 1.5%
Magnesium Nitrate ($Mg(NO_3)_2 \cdot 6H_2O$)	1300g/500ml DI water	52.9%±0.2%	50%	N/A
Sodium Nitrite ($NaNO_2$)	350g/500ml DI water	64.3%	65%	N/A
Sodium Chloride (NaCl)	300g/500ml DI water	75.3%±0.1%	75%	N/A
Potassium Nitrate (KNO_3)	500g/500ml DI water	93.6%±0.6%	93%	N/A
		40°C		
Salts	Amount used	Nominal RH	Actual RH by humidity sensor	Actual RH by moisture content
Calcium Chloride ($CaCl_2$)	N/A	0%	N/A	2.9 – 4.1%
Magnesium Nitrate ($Mg(NO_3)_2 \cdot 6H_2O$)	1300g/500ml DI water	48.4%±0.4%	50%	47 – 52%
Sodium Nitrite ($NaNO_2$)	350g/500ml DI water	61.3%	64%	63 – 66%
Sodium Chloride (NaCl)	300g/500ml DI water	74.7%±0.1%	75%	73 – 74%
Potassium Nitrate (KNO_3)	500g/500ml DI water	89%±1.2%	89%	86 – 89%

N/A: It was not measured.

Environmental chambers (25 and 40°C) in which temperature and relative humidity are controlled automatically were used. Desiccators were stored in those 25 and 40°C chambers. In order to make sure that each saturated salt solution reached the desired relative humidity, a humidity sensor was placed in the lid of the desiccator until equilibrium was reached. The stick-shaped humidity sensor was fitted with a rubber stopper. Then it was placed in the top of desiccator as shown in Figure 7.

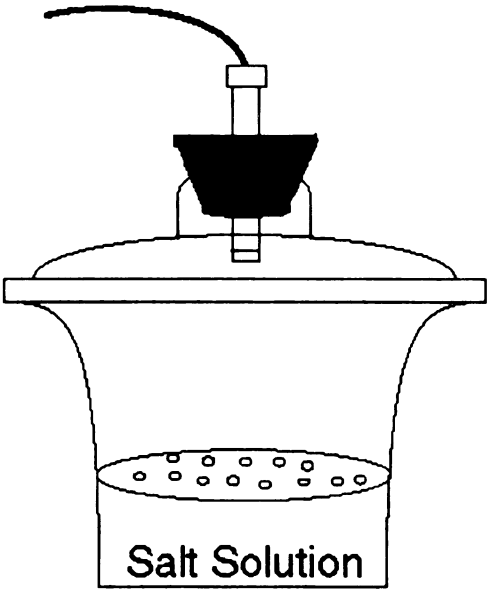


Figure 7 Graphical representation of the humidity sensor placed on the top of desiccator

The humidity sensor is connected to a humidity transducer by wire. The humidity transducer detects the voltage change from the sensor. The accuracy of the humidity sensor is ±3% from 0-90% RH between 15 °C and 50 °C (59 to 122 °F). The humidity is detected by the voltage change (4.0 mA to 20.0 mA). The 4.0 to 20.0 mA output is proportional to 0% RH to 100% RH.

Also, the relative humidities for 6 months were measured by using the moisture content of tablets and moisture sorption isotherm curve. Periodically, the moisture

content of tablets was measured, and applied to the moisture sorption isotherm curve to determine the equilibrium relative humidity. Table 4 shows actual relative humidities determined by this method. There is good agreement. It means desiccators kept the desired RH well.

(3) Sealing, integrity testing, and volume measuring of packages

The LDPE bags (3" × 3") were heat sealed by an impulse heat sealer (24SC, Sencorp Inc.). The LDPE film sheet was cut and folded, and then two sides were impulse heat sealed for two seconds. After tablets were inserted into the LDPE bags, the top was also heat sealed. The HDPE bottles (50 mL) were induction heat sealed by an induction heat sealer (LM328502, ENERCON Inc.) after the tablets were inserted into the bottles.

In order to make sure packages were sealed properly, the integrity of packages was tested visually for induction heat sealed HDPE bottles and by using methylene blue for impulse heat sealed LDPE bags. After each moisture and dissolution test, the methylene blue was injected into LDPE bags until it covered the seal all around the package. The methylene blue was allowed to remain in contact with the seal edge for approximately 10 seconds. The sealed area was visually examined.

In order to determine the volume of LDPE bags and HDPE bottles, water was injected into LDPE bags and poured into HDPE bottles, and then water was poured into a 100 mL volume flask to measure the volume. The bag was visually flattened to make the bag volume the same as the actual bag volume containing tablets.

(4) Permeability

The permeabilities of LDPE bags and HDPE bottles were measured using calcium chloride. See procedures ASTM D 895-94 or USP 24 <671> for more information. Calcium chloride ($CaCl_2$) was regenerated at 110°C for 24 hours to have 0% water vapor pressure, and inserted into the LDPE bags and HDPE bottles. It was assumed that the internal water vapor pressure was zero. Five LDPE bags containing calcium chloride and two LDPE bags containing glass beads were stored in a 90% RH desiccator in the 40°C chamber, and five HDPE bottles containing calcium chloride and two HDPE bottles containing glass beads were stored in the 40°C/75% chamber. There was not enough space for HDPE bottles in the 90% RH desiccator, so the bottles were stored in the 40°C/75% chamber. The bags and bottles were taken out periodically and the moisture gain was measured using a balance (R300S, Sartorius Inc., sensitivity: ±0.00005g).

(5) Moisture content

(a) Initial moisture content

The initial moisture contents of tablets and silica gel were determined by using a Computrac MAX 2000 (Arizona Instrument Inc., AZ) at a temperature of 103°C for 6 hours. Tablets were ground by mortar and pestle, and then placed on the weighing pan. The granules of silica gel were not ground. The Computrac MAX 2000 has the heating pan on the top and the balance on the bottom. Therefore, drying and weighing tablets and silica gel can be achieved at the same time. The moisture change is expressed by using a graph (weight change vs time) on the screen.

(b) Moisture sorption isotherms

The moisture sorption isotherms of tablets and silica gel were constructed using a SGA-100 Symmetrical Gravimetric Sorption Analyzer (VTI Corporation, FL) (see Figure 8).

The SGA-100 Symmetrical Gravimetric Sorption Analyzer is a continuous gas flow adsorption instrument for obtaining moisture sorption isotherms at temperatures ranging from 5°C to 60°C at ambient pressure. It has the capability of performing sorption isotherms at relative humidities from 0% to 98%. The SGA-100 has an option to dry the sample to determine the initial moisture content. However, 60°C is not a high enough temperature to dry out the tablet and silica gel completely. Therefore, the initial moisture content would be better to be determined before samples were placed on weighing pan in the analyzer, and then Equation 20 in Appendix A can be used to calculate the equilibrium moisture content if the initial moisture content, and the initial and final weights of the tablet and silica gel are available.

The tablet is placed on the quartz sample holder, then the sample holder is attached to a hang down wire connected to a sensitive microbalance. The temperature is controlled by a constant temperature bath (sensitivity: ±0.01°C) which circulates water inside the walls of the aluminum block. The humidity is controlled by the wet Mass Flow Controller (MFC 1 in Figure 8). The humidifier is maintained at constant temperatures (25 or 40°C) to make a saturated stream of humidity.

At the beginning of each run, the equilibrium criteria must be determined. For example, if a weight % change does not occur for a given time (e.g., 10 minutes), then the relative humidity is increased to the next step. Therefore, the user must determine the

weight % change and the specific amount of time. These conditions are maintained until the sample weight reaches equilibrium.

There is a way to determine the minimum equilibrium weight gain. The noise level for SGA-100 is 1 microgram (0.001 mg), so any reading at that level is noise. For example,

$$\frac{0.001\ mg\ (noise\ level)}{200\ mg\ (sample\ weight)} \times 100 = 0.0005\%$$

If a 200 mg sample is used, 0.0005% weight change can happen as a result of background noise. Therefore, a larger weight % change than 0.0005% must be selected.

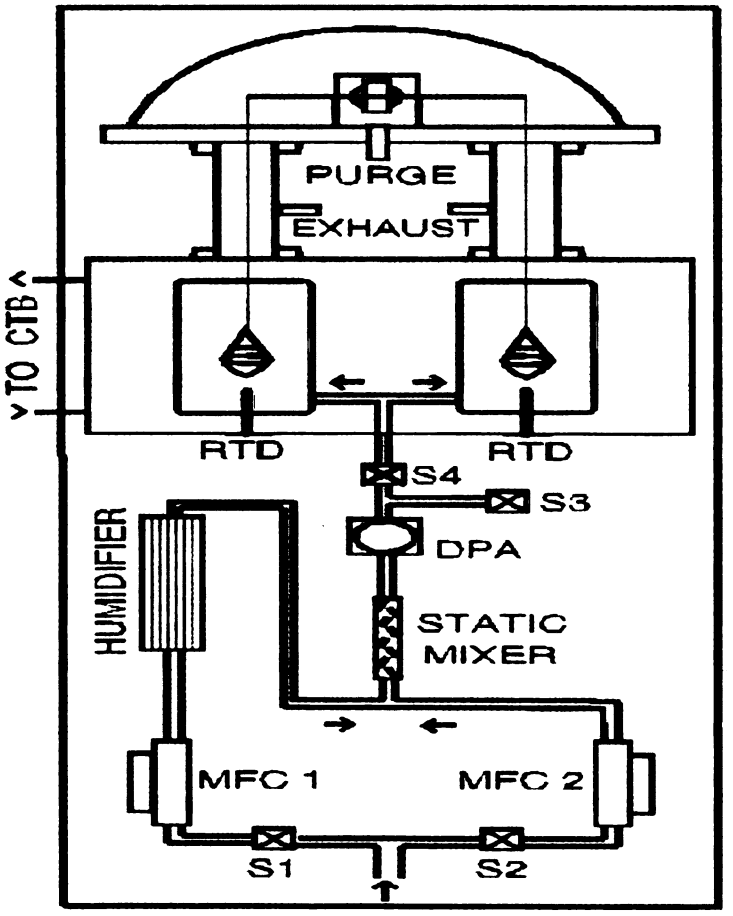


Figure 8 The sketch of the symmetrical gravimetric analyzer (SGA-100)
(The sketch was obtained from VTI, and it is modified to simplify.)

where,

S1, S2, S3, and S4 = Solenoid Valves
MFC 1 and MFC 2 = Mass Flow Controllers
DPA = Dew Point Analyzer
RTD = Resistance Platinum Thermometer
CTB = Constant Temperature Bath

Principles of operation for SGA-100

A dry gas source (nitrogen, air) passes through a 2 micron filter and splits into two lines. One of the lines, called the purge line, is connected to the microbalance chamber. The flow rate of the gas continuously purging the microbalance chamber is regulated by a rotameter. The second line is connected to two solenoid valves which are provided for shutting on and off the flow to the mass flow controllers which are used to accurately control the flow of the dry gas. One of the streams (MFC 1) flows through the humidifier. The second mass flow controller (MFC 2) provides a dry gas stream (see Figure 8).

The gas leaving the humidifier is mixed with the dry stream via a static mixer. The dew point of the mixed stream is measured with the dew point analyzer (DPA). Two solenoid valves downstream from the DPA redirect the stream either to the aluminum block or to the vent. The stream entering the aluminum block is equilibrated with the temperature of the block and is equally divided into two streams. One of the streams enters the sample compartment of the aluminum block. The other stream enters the reference compartment of the block[c]. In each of the compartments, a 100 Ohm Resistance Platinum Thermometer (RTD) is provided for measuring temperature of the

[c] If the weight of a sample is larger than the capacity of the balance, a counter weight is used. The balance measures the difference in weight between the two pans, and the software adds the counter weight to the difference to get the actual sample weight.

process stream. Based on the temperature and dew point, the relative humidity is determined.

The sample weight changes during adsorption are measured with a Cahn D-200 microbalance (sensitivity: ±0.001mg) and recorded in a computer with Flow System software. The Cahn balance has a capacity of 3.5 grams and is sensitive to changes as small as 1 microgram.

(c) Verification of moisture simulation program

Packages (LDPE bags and HDPE bottles) were used to verify the shelf life and moisture prediction models. The uncoated tablets and silica gel were inserted into the LDPE bags and HDPE bottles, and they were stored at 40°C/90%. Table 5 shows the combination of components[f] in each package. Seven different LDPE bags and HDPE bottles were used for each combination. See Appendix D for raw data of the weight of components in LDPE bags and HDPE bottles.

Table 5 The combination of components in LDPE bags and HDPE bottles used to verify the moisture and shelf life prediction program

	LDPE bags				HDPE bottles	
Contents	Tablets only	Tablets + 0.5 g silica gel	Tablets + 1 g silica gel	Tablets + 2 g silica gel	Tablets only	Tablets + 0.5 g silica gel

Before the tablets and silica gel were inserted into the package, the initial weights of tablets, silica gel and package were measured using a balance (sensitivity: ±0.00005g). At each weighing time, the total weight of the package and contents was measured first, then the package was opened, and the tablets were removed for weighing.

[f] It is defined as dry solids such as tablets, capsules, and desiccant.

The moisture gain of LDPE bags alone was determined by blanks when the permeability was determined. It was 0.02 g, and assumed to be the same for all tests. See Appendix D for raw data. The moisture gain of HDPE bottles alone was also determined by blanks when the permeability was determined. Figure 9 shows the moisture gain of empty HDPE bottles as a function of storage time. As explained, the moisture gain of each of the packages and the tablets was determined. If they are subtracted from the total moisture gain, the moisture gain of the silica gel can be calculated without measuring the weight of silica gel. The silica gel in LDPE bags and HDPE bottles is hard to remove for measuring the weight because it is small granules. (see example calculations below.)

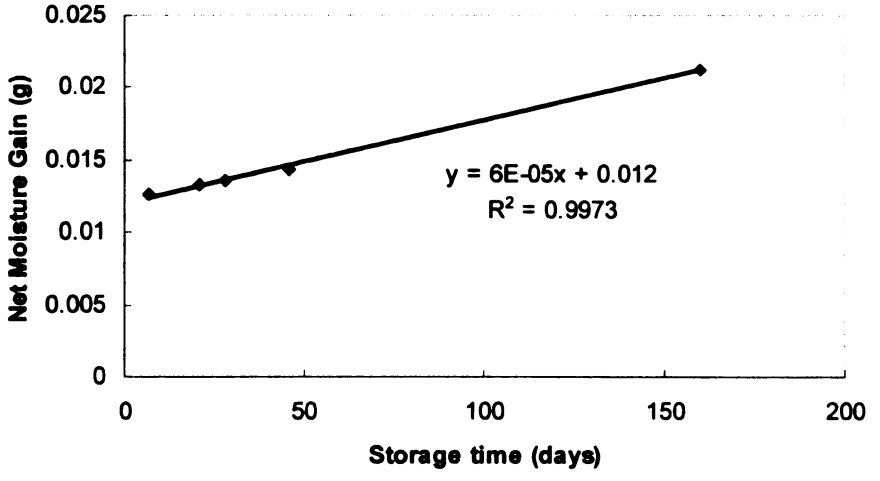


Figure 9 The moisture gain of HDPE bottles

The following example calculation shows how to calculate the moisture content of tablets and silica gel by using Equation 23 from page 125, rewritten here for convenience.

Moisture content based on the dry weight of solid: $M(\%) = \left[\frac{W_f \cdot (M_i + 1)}{W_i} - 1\right] \times 100$

Calculation of the moisture content of tablets and silica gel in the packages

Example 1. Tablets and silica gel in LDPE bags

Initial weight	Final weight
• Package: 1.1690g • Tablets: 3.7642 g • Silica gel: 0.5010g • Total: 5.4342 g • Initial moisture content (tablet: 1.9312%, silica gel: 3.03%)	• Package (calculated): 1.1890g • Tablets: 3.7872 g • Silica gel (calculated): 0.6063g • Total: 5.5825g

The final weight of package = 1.1690g + 0.02 g = 1.1890g (moisture gain of LDPE bag: 0.02 g)

The final weight of silica gel = 5.5825g – 3.7872 g – 1.1890g = 0.6063g

By using the moisture content equation, the *M(%)* of tablets and silica gel can be calculated.

$$M(\%)_{tablets} = \left[\frac{3.7872 \cdot (1 + 0.019312)}{3.7642} - 1\right] \times 100 = 2.55\%$$

$$M(\%)_{silica\ gel} = \left[\frac{0.6063 \cdot (1 + 0.0303)}{0.5010} - 1\right] \times 100 = 24.68\%$$

Example 2. Tablets and silica gel in HDPE bottles

Initial weight	Final weight
• Package: 13.9370g • Tablets: 3.7643g • Silica gel: 0.5032 g • Total: 18.2045g • Initial moisture content (tablet: 1.9312%, silica gel: 3.03%)	• Package (calculated): 13.9498g • Tablets: 3.7431 g • Silica gel (calculated): 0.5386g • Total: 18.2315g

The final weight of package = 13.9370g + 0.01284g = 13.9498g (moisture gain of HDPE bottle after 14 days = 0.00006 × 14 days + 0.012 from the equation in Figure 9)

The final weight of silica gel = 18.2315g – 3.7431 g – 13.9498g = 0.5386g

By using the moisture content equation, the *M(%)* of tablets and silica gel can be calculated.

$$M(\%)_{tablets} = \left[\frac{3.7431 \cdot (1 + 0.019312)}{3.7643} - 1\right] \times 100 = 1.36\%$$

$$M(\%)_{silica\ gel} = \left[\frac{0.5386 \cdot (1 + 0.0303)}{0.5032} - 1\right] \times 100 = 10.28\%$$

(6) Dimensions

The dimensions of tablets stored at all conditions (25 and 40°C at 0%, 50%, 65%, 75% and 90%) were measured by using a digital caliper (CD-6" BS, Mitutoyo Inc., sensitivity: ±0.005mm). Each time, five tablets were selected to measure the dimensions (thickness and diameter) for each condition. The tablet has a score. The dimensions were always measured at the same position relative to the score. The dimensions were measured initially, and these dimensions were compared to the dimensions of aged tablets. See Appendix F for raw data of tablet dimensions.

(7) Hardness

The hardness of tablets stored at all conditions (25 and 40°C at 0%, 50%, 65%, 75% and 90%) was measured by HT-300 Hardness tester (Key International, Inc., NJ). Each time, ten tablets were selected to measure the hardness at each storage condition. As with the dimensions, the score was used as an index to assure that the hardness was

always measured at the same position. See Appendix G for raw data of the tablet hardness.

Figure 10 shows a sketch of the HT-300 hardness tester. The plunger moves at a constant speed towards the specimen. As soon as the plunger touches the specimen and produces a force on the load cell, a linearly increasing force is produced until the specimen breaks. Then the decreasing signal from the load cell indicates to the microprocessor to determine the hardness value.

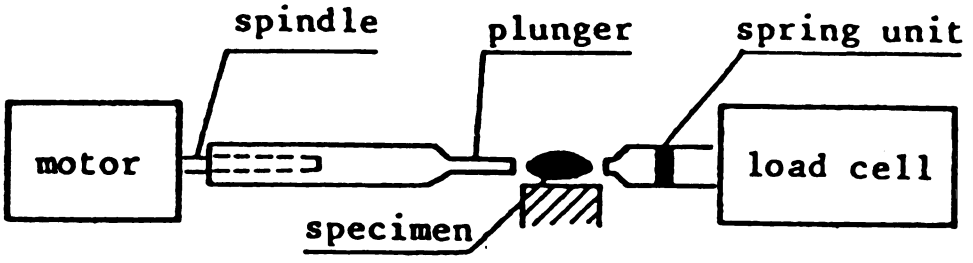


Figure 10 Sketch of the HT-300 hardness tester
(The sketch was obtained from the company brochure, and it was modified to simplify.)

Measuring range: 0.5-30 kp (kilopond) or 5-300 N (1kg = 9.807N)
Resolution: 0.1 kp
Accuracy: ±1% over the entire readout measuring range

Also, the effect of hardness of tablets on opening blisters was tested using PVC blister packages. A Klockner – Pentapack blister thermoform-fill-sealer was used to thermoform PVC blisters, fill tablets, and seal blisters. PVC film (10 mil) was used to thermoform blisters and 1.9 mil aluminum foil laminated with paper was used for the backing film. Tablets at equilibrium at each condition (25 and 40°C at 0, 50, 65, 75 and 90% RH) were packaged into the blister. One tablet was placed in each blister, and then the blister was heat-sealed to the backing film by the thermoform-fill-sealer. The tablets

packaged into the blister were used to test whether they had enough hardness to be pushed out of the blisters without breaking.

(8) Dissolution

In accordance with the USP monograph for drug X, experiments were carried out with 1000 mL of 0.02N HCl dissolution medium, apparatus 1 (rotating basket), and 100 rpm speed for the stirrer. One tablet was used per vessel and six vessels were used for each storage humidity and temperature combination.

(a) Dissolution medium (0.02N HCl)

In order to prepare 1 liter 0.02N HCl, 1.7 mL of concentrated HCl (37%) was added to a flask and diluted to 1 liter with purified water. The dissolution medium was deaerated using helium sparging before testing.

(b) Reference standard solution

For the drug X tablets, the linearity of the response was determined using eight standard preparations of drug X in the concentration range of 6% to 164% of the 20mg dose. If 20mg drug X is dissolved in the 1000 mL medium completely, the concentration of drug X in the medium is 100%. The drug X reference standard was weighed, then transferred into a 1000 mL volumetric flask. Table 6 shows the concentrations (mg/mL) to make the entire concentration (%) range. The drug X reference standard was dissolved in 0.02N HCl dissolution medium by using a sonicator. The absorbance of the solutions

was measured by using a UV spectrophotometer (HP8453, Agilent Inc.), then plotted as absorbance vs. % concentration as shown in Figure 11.

Table 6 Dissolution calibration data of drug X

Concentration (%)*	Concentration (mg/mL)	Response (absorbance)
6.58%	0.001315	0.0396795
16.44%	0.003287	0.0988455
32.87%	0.006573	0.192289
65.73%	0.013146	0.395215
92.91%	0.018581	0.561377
98.60%	0.019719	0.583967
131.46%	0.026292	0.775347
164.33%	0.032865	0.979527

* Concentration (%) = Dissolution (%)

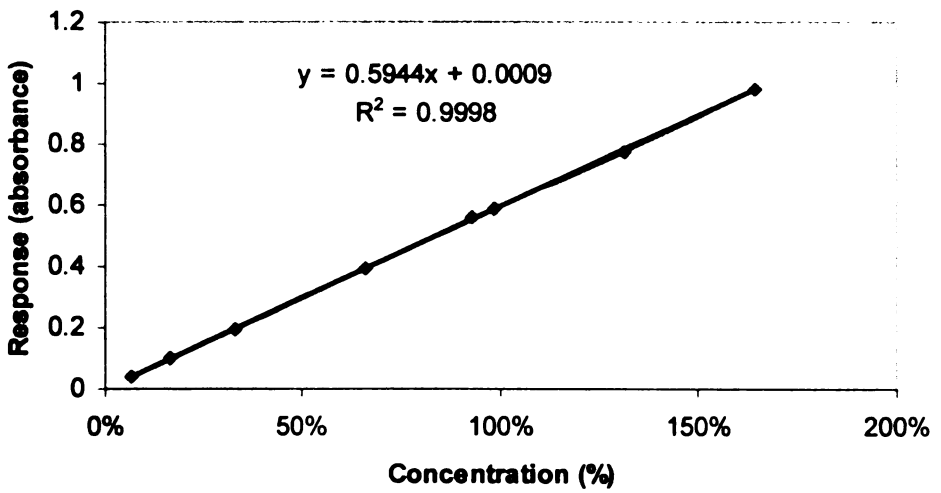


Figure 11 The calibration curve for the spectrophotometer using drug X

Calculation of % dissolution

Example. The absorbance of tablets at the 30 minute stirring time: 0.5724. Therefore, by the equation in Figure 11, dissolution can be calculated.

$$\%\ Dissolution = \frac{0.5724 - 0.0009}{0.5944} \times 100 = 96.14\%$$

(c) Dissolution sampling

A VK 7010 six vessel dissolution sampling apparatus (Vankel, NC) was used for sampling drug solution. The prepared dissolution medium (0.02N HCl) was poured into the vessels, then they were covered to increase the temperature to 37±0.5°C. The temperature was checked with a Curette thermometer (20-40°C, ±0.15°C) (YSI Inc., OH). Tablets were placed into 40 mesh standard baskets (Vankel, NC), then they were immersed into the medium (see USP <711> for information about dissolution). After the dissolution sampling apparatus was run, the vessels were covered again to keep the constant temperature. Samples were collected every 10 minutes with 10 mL syringes (Becton Dickinson and Company, NJ). A 0.5 μm pore size hydrophilic PTFE filter (Millipore Inc., MA) was attached to the syringe, then about 3 mL sample was flushed through the filter because there may be dust from a manufacturing process. By flushing the filter, the dust can be removed. Then, the remaining 7 mL sample was collected into 10 mL disposable glass tubes. The new filter was used in collecting samples each time.

About 10 mL dissolution medium was removed from the vessel at each sampling and it was not replaced. For the second sampling, the volume of the dissolution medium was 990 mL, and for the third sampling, the volume of the dissolution medium was 980 mL. Therefore, the percent dissolution at 20 and 30 minutes stirring time should be corrected by using Equation 13.

$$Corrected\ \%\ Dissolution = C_n \frac{[V_m - (n-1)\cdot V_s]}{V_m} + \frac{V_s}{V_m}\sum_{i=1}^{n-1} C_i \qquad (13)$$

where, C_n = uncorrected concentration at sample interval n
V_m = original medium volume (mL)
n = sample interval
V_s = sample volume (mL)

C_i = uncorrected concentrations of previously removed sample aliquots

Calculation of the corrected % dissolution

Example. Dissolution at 10 minutes stirring time: 68.23%
Dissolution at 20 minutes stirring time: 93.97% (uncorrected)
Dissolution at 30 minutes stirring time: 96.15% (uncorrected)

$$Corrected\ \%Dissolution = 93.97\frac{[1000mL-(2-1)\cdot 10mL]}{1000mL}+\frac{10mL}{1000mL}68.23 = 93.71$$

$$Corrected\ \%Dissolution = 96.15\frac{[1000mL-(3-1)\cdot 10mL]}{1000mL}+\frac{10mL}{1000mL}(68.23+93.97) = 95.85$$

The dissolution of tablets stored at 25 and 40°C at 0, 50, 65, 75 and 90% RH was measured at every month for 6 months. The resulting data were used to determine the dissolution retardation rate (R).

(d) Dissolution measuring (absorbance)

Based on the USP monograph for drug X tablets, the UV spectrophotometer was used to measure the UV absorbance at the wavelength of maximum absorbance, 275 nm, of filtered portions of the solution under test. The cell having 1 cm path length was used. The absorbance of the blank obtained from the dissolution medium was measured first, then it was subtracted from the absorbance of the initial and aged tablets to get the true absorbance of drug X.

(e) Verification of dissolution prediction model

In order to verify the dissolution prediction model, uncoated tablets were placed in open dishes using stepwise storage conditions. Also, they were packaged into LDPE bags and HDPE bottles for continuous storage conditions.

i. Tablets in open dishes - stepwise storage conditions

The uncoated tablets were placed in open dishes at 40°C/50% initially, and they were transferred to 40°C/65% after one month, and so on as shown in Table 7. When they were transferred to another condition, the dissolution was measured.

Table 7 Stepwise storage conditions used to verify the dissolution prediction model

Storage time (months)	Storage Conditions
1	50%(1 month)
2	50%(1 month), 65%(1 month)
3	50%(1 month), 65%(1 month), 75%(1 month)
4	50%(1 month), 65%(1 month), 75%(2 months)
4	50%(1 month), 65%(1 month), 75%(1 month), 90%(1 month)
5	50%(1 month), 65%(1 month), 75%(3 month)
5	50%(1 month), 65%(1 month), 75%(1 month), 90%(2 month)

ii. Tablets in packages - continuous storage conditions

The uncoated tablets were packaged into LDPE bags and HDPE bottles to verify the dissolution prediction model. They were the same as those used to verify the moisture prediction model. After the moisture gains of tablets were measured, they were tested for dissolution. Each package has the same number of tablets, 15 tablets, but each package has a different total tablet weight because of the variation of individual tablet weights. To make a single continuous smooth plot, the average weights of tablets were used for the moisture content and dissolution prediction.

CHAPTER 3

RESULTS AND DISCUSSION

Figure 12 shows the outline of the whole experiment that has been done for this research. It is placed here because it is especially relevant to the discussion in this chapter. Parts of the figure refer to this chapter only. Other parts are found in other places in the dissertation. Their location and relevance to the whole are described in the following text and the figure. Careful attention to matching the solid and broken lines with the description in the following text will help the reader to visualize the several relationships that exist among the parts of the work. The solid lines all represent the main theme of the research, from beginning through "Design a Package". The dotted and dashed lines represent the application of theories and procedures which are tools for accomplishing the main task.

Figure 12 shows the package part of the work (permeability) and the product part of the work (moisture content, dissolution, dimensions, and hardness). Permeability and moisture content were used to verify the shelf life and moisture prediction program. These are all connected by dotted lines. Permeability, moisture content, and dissolution were used to verify the dissolution prediction program. These are all connected by a solid line. Moisture content, dissolution, dimensions, and hardness were used to explain the proposed theory of dissolution retardation as a function of relative humidity. These are connected by dashed lines. Dimensions and hardness are not directly related to the main purpose of this research (dissolution shelf life), so they are attached as Appendices. The verification for the moisture and shelf life prediction programs is attached in Appendix B, and the verification for the dissolution prediction program appears in

Chapter 4. Experimental results and discussion of permeability, moisture content, and dissolution are presented in this chapter.

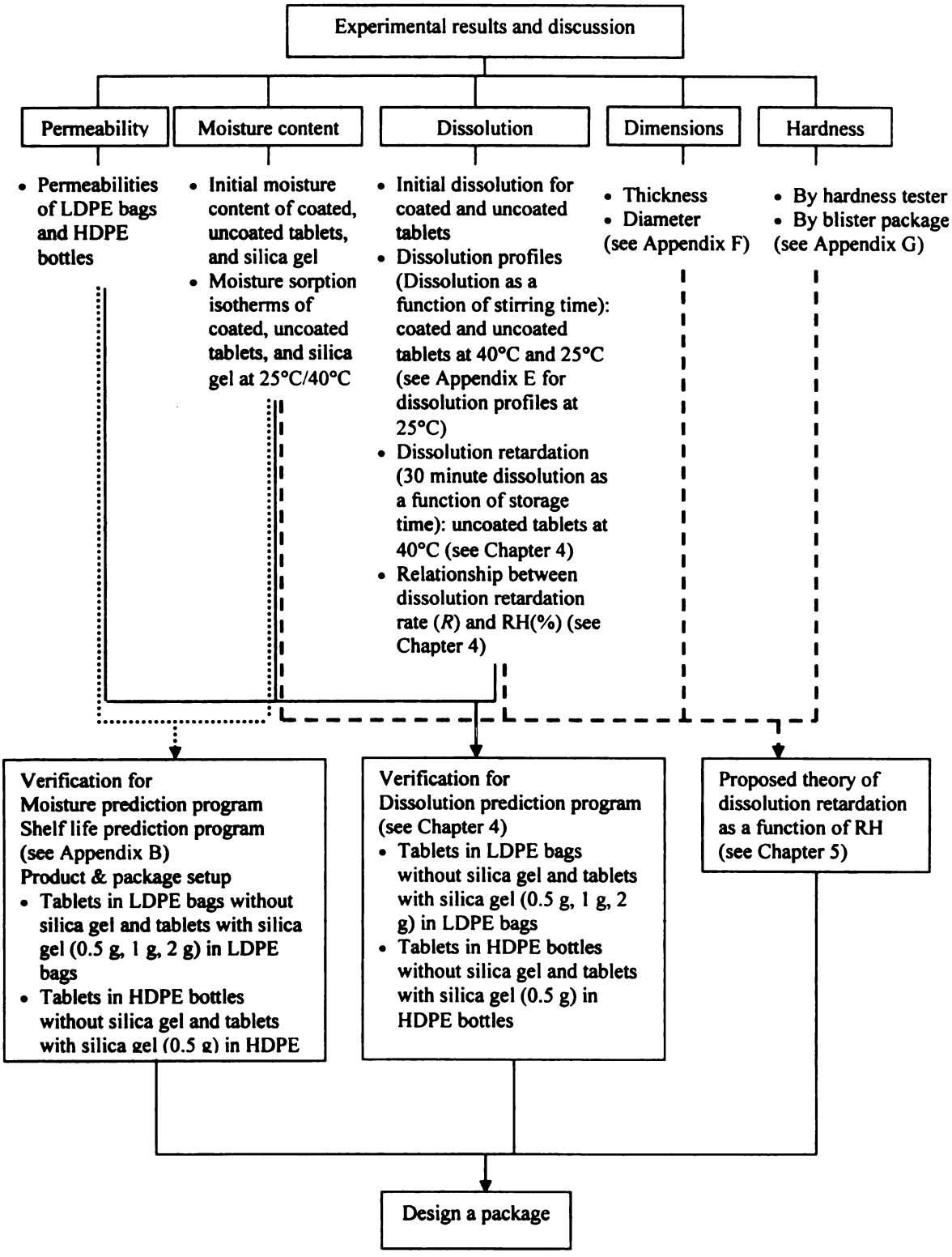


Figure 12 Outline of the experiment

1. Permeability

Raw data used to determine WVTR are attached in Appendix D.

Figure 13 shows a standardized traditional relationship among water vapor transmission rate (WVTR), permeance, thickness normalized WVTR, and permeability. This relationship assumes a homogeneous material in sheet form of some thickness ℓ. WVTR is divided by the partial pressure difference between the inside and outside of the package to calculate the permeance, and then the permeance is multiplied by the package wall thickness to calculate the permeability (see ASTM E96).

The permeability for a given material is a constant value at the same temperature. If the package is stored at a high relative humidity, the WVTR will be high due to the large partial pressure difference, and vice versa. Therefore, the permeability is always the same at the same temperature.

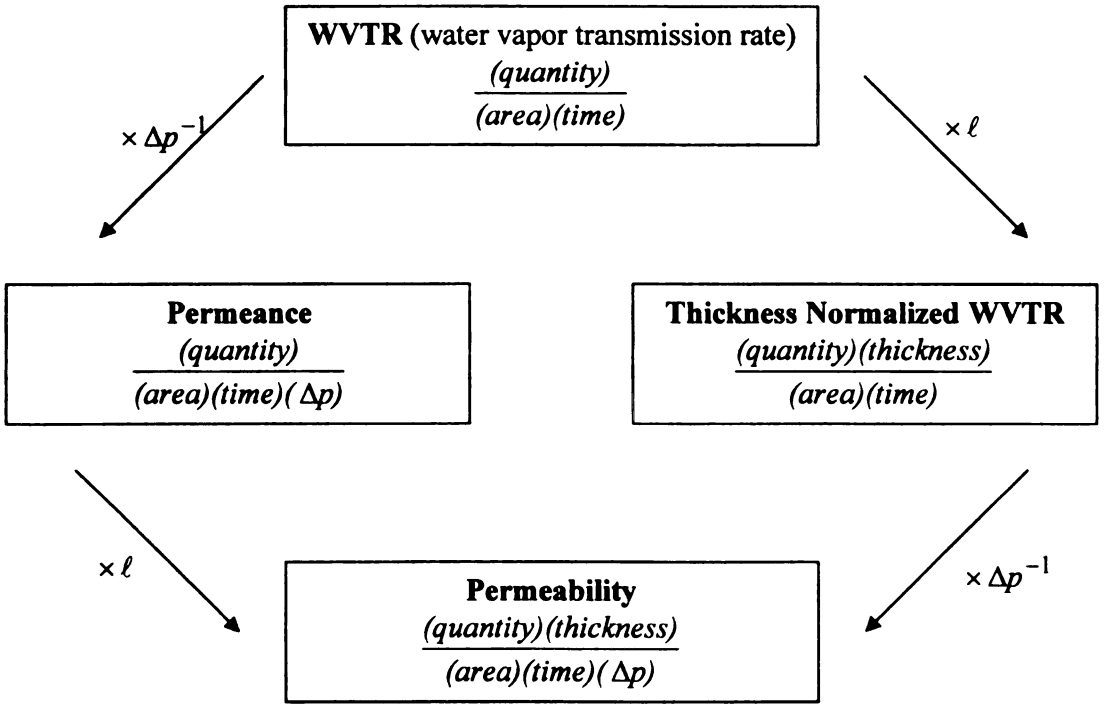


Figure 13 Relationship between water vapor transmission rate (WVTR), permeance, thickness normalized WVTR, and permeability

The pharmaceutical industry does not follow the traditional practice of assuming the package to be a homogeneous sheet of some thickness ℓ. Bottles are a complex combination of varying bottle wall thickness and closure combinations. Blisters are thermoformed from sheet, and therefore have varying wall thickness always less than that of the starting sheet. Furthermore, barrier blisters are not homogeneous in construction, but rather have two or more materials laminated or coextruded. Use of the model for packages made of a homogeneous sheet has no practical value. Therefore, the pharmaceutical industry practice is to use the whole package unit instead of the thickness and area of the package to determine WVTR and permeability.

USP <671> Containers-Permeation sets the common practice for the drug industry. Bottles, pouches and blisters are all tested as whole package units without reference to thickness or closure. They are also tested at a single temperature and humidity, which mandates a single partial pressure differential (Δp). Thus, the USP test yields a water vapor transmission rate (WVTR) which is labeled as "Permeation" in USP terms. This construction is very limited in comparison with the relationship described in Figure 13. It is also too limited for use in development of the theories and application treated in this research.

USP <671> has a built-in discontinuity which makes it very difficult to compare blister or pouch permeation with bottle permeation. Blister and pouch permeation is reported as weight gain per package (single pouch or single blister) per day. Bottles are reported as weight gain per liter (of bottle volume) per day. A bottle tested may contain any number of product units (e. g. 7 to 500) and it may be of any volume, 45 mL to 500 mL, for example. In any case, bottle permeation (a WVTR) is reported as mg/L/day. A

blister or pouch usually contains only one product unit. Blister permeation (WVTR) is reported as mg/cavity/day; the cavity is the equivalent of 1 unit of product (capsule, tablet, etc.). This makes it very difficult to compare permeation performance between bottles and blisters. The need to compare these values is great when planning package changes between bottles and blisters. Industry practice is moving toward the comparison of bottles and blisters on a permeation per product unit basis. This trend is anticipated in this research.

This research is intended for application to bottles, blisters and pouches at any relative humidity at a single temperature. Therefore, the permeance property of packages is modeled in Figure 14. In this research WVTR was determined as a quantity per whole package per a unit of time, so the units for WVTR and permeance are not the same as in Figure 13. In this work permeance is treated as the permeability of the package.

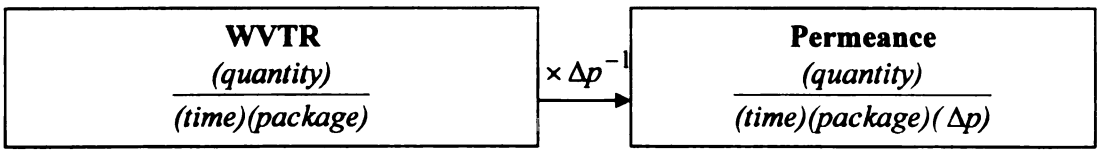


Figure 14 Relationship between water vapor transmission rate (WVTR) and permeance using whole package instead of thickness and area

In this study, WVTR was determined as a quantity per whole package per unit of time instead of quantity per package area per unit of time. Then this WVTR was divided by partial pressure differential to obtain permeance as quantity per package per unit partial pressure differential per unit time.

The total weight increase of each package was measured for 5 LDPE bags and 5 HDPE bottles at each testing time, then it was reduced by the weight increase of the blank to calculate the net moisture gain. The net moisture gain was plotted as a function

of storage time. WVTR was determined by a trend line as shown in Figure 15 and Figure 16. When the WVTR was determined, the point (0,0) was not included because at this point the package was not yet at steady-state conditions at 40°C.

(1) LDPE bags

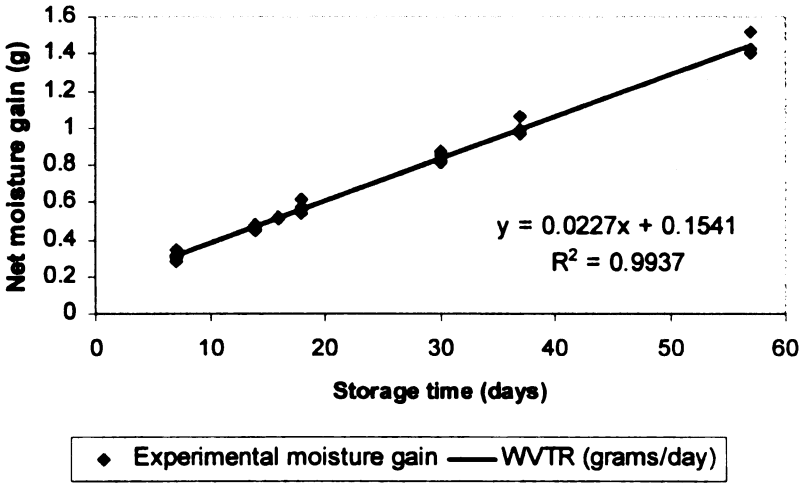


Figure 15 WVTR of LDPE bags at 40°C/90% RH

Calculation of the permeability of the LDPE bags

WVTR = 0.0227 grams/day·package

Vapor pressure difference = 90% RH - 0% RH = 90% RH (or 0.9 p_s)

Therefore,

$$Permeability = 0.0227 \frac{g}{day \cdot package} \times \frac{1}{0.9\ p_s} = 0.0252 \frac{g}{day \cdot package \cdot p_s} \ at\ 40°C$$

(2) HDPE bottles

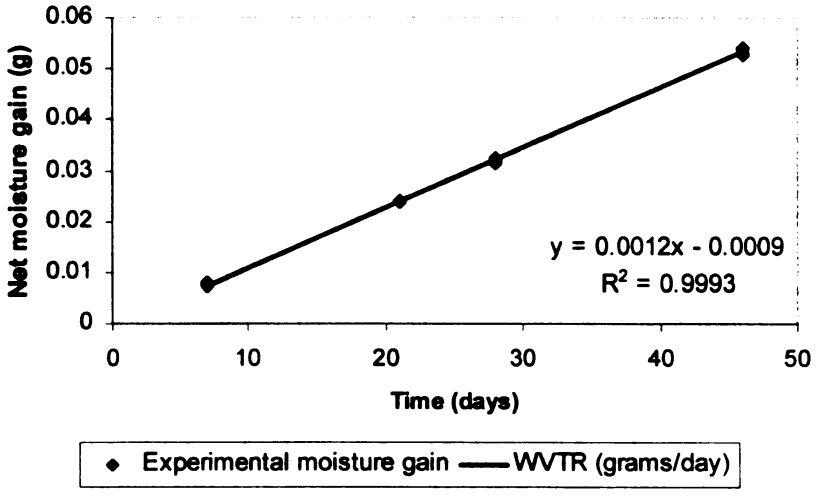


Figure 16 WVTR of HDPE bottles at 40°C/75% RH

Calculation of the permeability of the HDPE bottles

WVTR = 0.0012 grams/day·package

Vapor pressure difference = 75% RH - 0% RH = 75% RH (or 0.75 p_s)

Therefore,

$$Permeability = 0.0012 \frac{g}{day \cdot package} \times \frac{1}{0.75\ p_s} = 0.0016 \frac{g}{day \cdot package \cdot p_s} \quad at\ 40°C$$

2. Moisture content

(1) Initial moisture content

Table 8 shows the experimentally measured initial moisture content of tablets and silica gel, and the calculated equilibrium relative humidity at each initial moisture content. The equilibrium relative humidity can be determined by the moisture sorption isotherm curves or their equations such as GAB or Langmuir equations (see Appendix A 3.(2)(a) GAB equation and (b) Langmuir equation). The equilibrium relative humidities of

tablets were determined by the GAB equation and those of silica gel were determined by the Langmuir equation.

Table 8 Initial moisture content and equilibrium RH of tablets and silica gel

	Uncoated tablets	Coated tablets	Silica gel
M_i	1.93%	2.31%	3.03%
RH at M_i at 25°C	31.72%	40.96%	4.31%
RH at M_i at 40°C	34.23%	42.62%	4.31%

(2) Moisture sorption isotherms

The sigmoid-shaped moisture sorption isotherms of tablets fit well with the GAB equation, and the hyperbolic-shaped moisture sorption isotherms of desiccants such as silica gel fit well with the Langmuir equation over the range of relative humidities between 10% and 90%. The choice of equation depends on the shape of the moisture sorption isotherm. Therefore, the GAB equation was used to describe the relationship between the moisture content of drug X tablets and water activity (a_w) (i.e., p/p_s or %RH/100), and the Langmuir equation was used to describe the relationship between the moisture content of silica gel used in this experiment and a_w (i.e., p/p_s or %RH/100). Table 9 shows the GAB constants of drug X tablets and Langmuir constants of silica gel used in this experiment.

Table 9 GAB constants of tablets and Langmuir constants of silica gel

	GAB constants			Langmuir constants	
	W_m	C_g	K	W_m	C_L
Uncoated tablets at 25°C	0.014118	75.7711	0.919386		
Uncoated tablets at 40°C	0.013392	113.2096	0.933012		
Coated tablets at 25°C	0.014513	297.5468	0.915190		
Coated tablets at 40°C	0.014100	324.3921	0.920041		
Silica gel at 25°C				1.440803	0.498612
Silica gel at 40°C				0.819364	0.924676

(a) Moisture sorption isotherms of drug X tablets (coated and uncoated)

Figure 17 shows the moisture sorption isotherms of coated and uncoated tablets at 25°C and Figure 18 shows the moisture sorption isotherms of coated and uncoated tablets at 40°C. The coated and uncoated tablet isotherms are almost the same, but the moisture sorption isotherm of coated tablets is a little higher because of the coating material (4% of tablet). Tablets were formulated with 63% mannitol and 18% microcrystalline cellulose. If the temperature is increased, the water vapor sorption of mannitol and celluloses decreases at the same pressure (exothermic process).

The moisture sorption isotherms are almost the same as shown in Figure 19. In practice, a single sorption isotherm may be able to be used to describe the water-solid interaction for both coated and uncoated tablets at both 25°C and 40°C in this temperature range as a function of relative humidity.

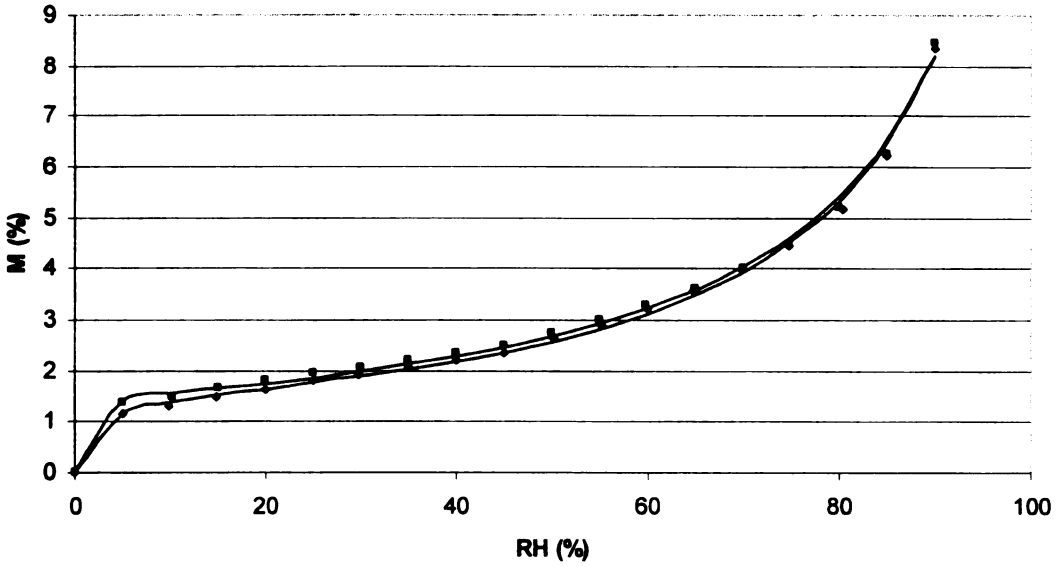


Figure 17 Moisture sorption isotherms of drug X tablets at 25°C

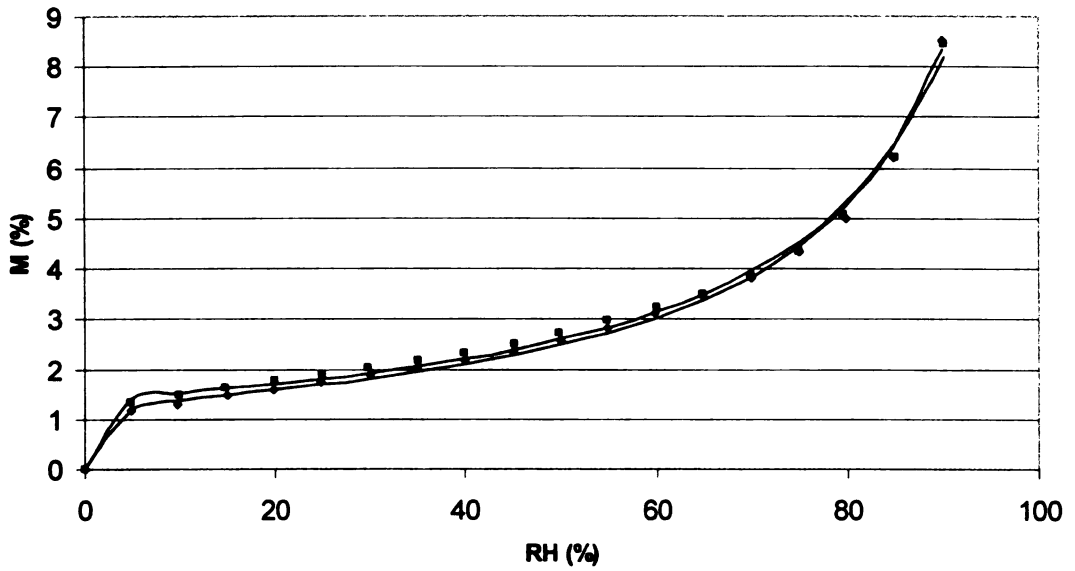


Figure 18 Moisture sorption isotherms of drug X tablets at 40°C

The isotherms in Figure 19 from topmost to lowest are in the order: coated tablets at 25°C, coated tablets at 40°C, uncoated tablets at 25°C, uncoated tablets at 40°C. The difference in moisture content between highest and lowest at 50% RH is 0.18%. This is calculated from the values below:

- M(%) of coated tablets at 25°C/50% RH: 2.67%
- M(%) of coated tablets at 40°C/50% RH: 2.60%
- M(%) of uncoated tablets at 25°C/50% RH: 2.57%
- M(%) of uncoated tablets at 40°C/50% RH: 2.49%

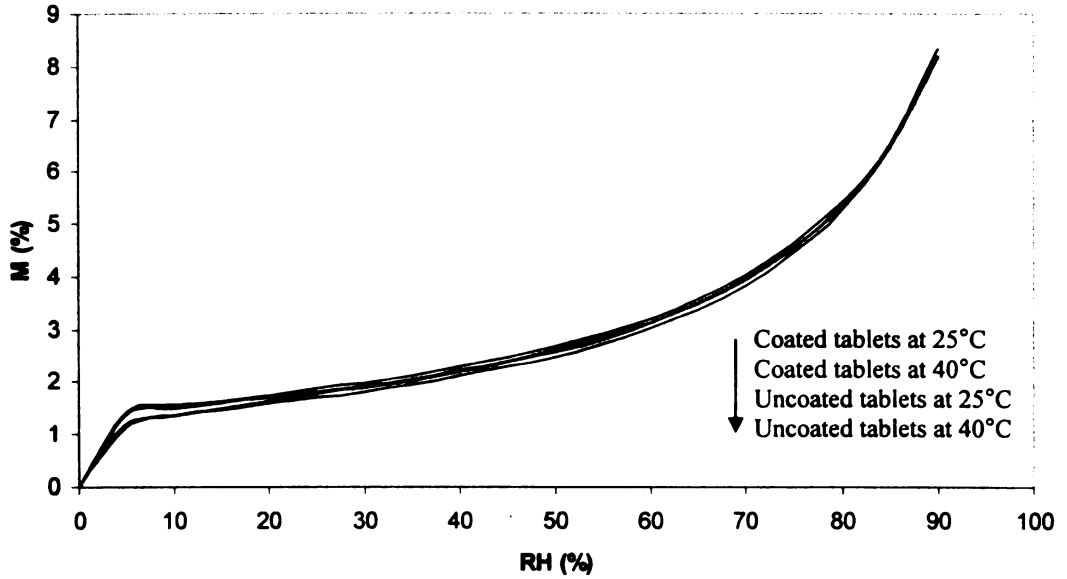


Figure 19 Moisture sorption isotherms calculated by GAB equation for tablets at 25°C and 40°C

(b) Moisture sorption isotherms of silica gel

Figure 20 and Figure 21 show the experimental (dots) and calculated (solid line) moisture sorption isotherms determined by the Langmuir equation. There is fairly good agreement between experimental and calculated moisture sorption isotherm data. Also, the GAB equation was tried to fit moisture sorption isotherms. However, there is little difference between the sorption isotherms calculated from the Langmuir and GAB equations (see Appendix D). Therefore, the simple Langmuir equation was used for silica gel sorption isotherms. The moisture sorption isotherms at 25°C and 40°C are plotted together in Figure 22. Silica gel is an exothermic material. When the material absorbs water, the material gives off heat. At the same *RH* (%), the amount of water that can be absorbed in the material at 40°C is less than that at 25°C. Therefore, if temperature is increased, the water vapor sorption is decreased as shown in Figure 22.

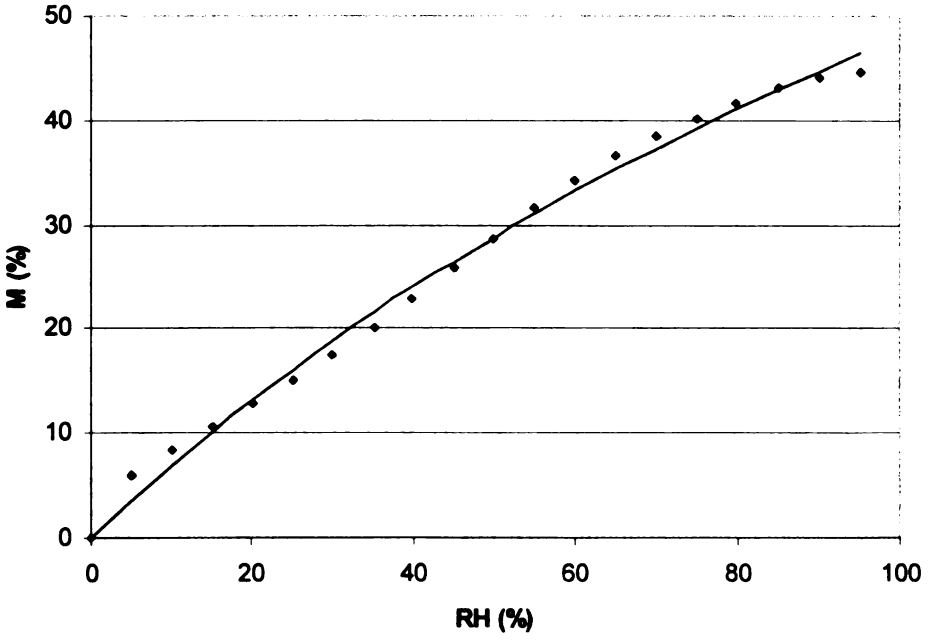
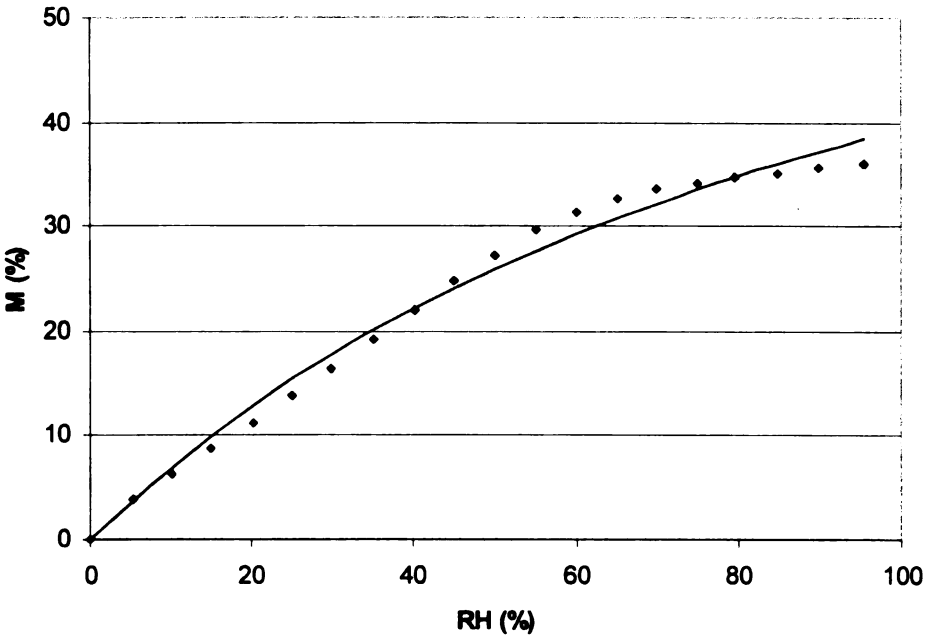


Figure 20 Moisture sorption isotherm of silica gel at 25°C



◆ Experimental M (%) —— Calculated M (%) by Langmuir equation

Figure 21 Moisture sorption isotherm of silica gel at 40°C

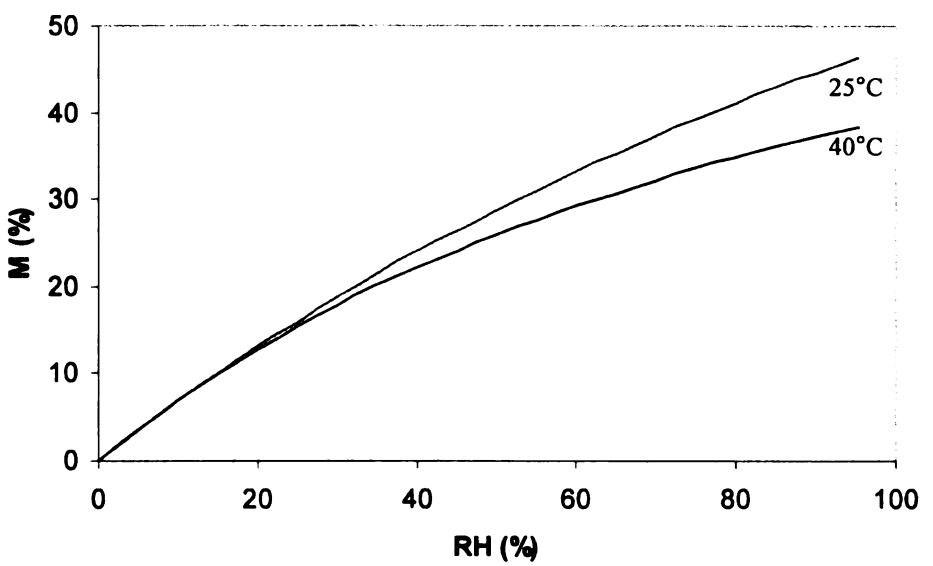


Figure 22 Moisture sorption isotherms calculated by Langmuir equation for silica gel at 25°C and 40°C

3. Dissolution

In this study, the initial tablet is defined as tablets which are inserted into a package. When the initial drug X coated tablet is dropped into the dissolution medium (0.02N HCl), the coating material dissolves quickly in the medium and the croscarmellose sodium (CAS) among granules[g] swell to 4-8 times. This makes tablets rapidly disintegrate to coarse particles. Also, CAS in the granules swells quickly, making coarse particles disintegrate into fine particles of excipients. The dissolution mechanism of drug X uncoated tablet is exactly the same except for dissolving the coating material.

During dissolution testing, it was observed that the time required for tablet wetting and disintegration is very short for the initial tablets. If the first dissolution sample is collected at a 10 minute stirring time, the regions "Mechanical Lag and Wetting", "Disintegration", and "Disaggregation" cannot be obtained. Therefore, the S-shaped dissolution curve of Figure 2 on page 14 can be represented in practice as shown in Figure 23.

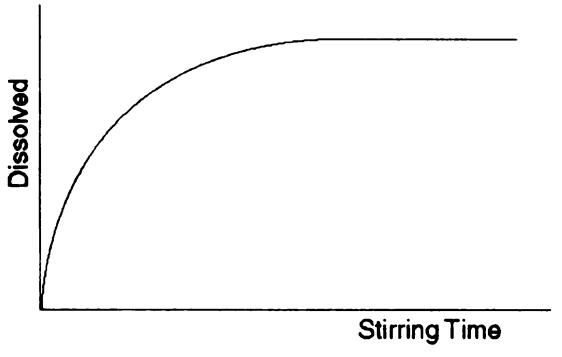


Figure 23 The typical dissolution curve constructed experimentally

Coated tablets aged at 40°C at 50-90% RH require a lot more disintegration time than initial tablets, perhaps because the coating material is degraded physically or

[g] See Appendix C 1. Formulation for the term "granules".

chemically, or excipients are crosslinked to each other above about 50% RH. Uncoated tablets aged at 40°C at 50-90% RH require a lot more disintegration time than initial tablets as well. If an aged tablet is dropped into the dissolution medium, the tablet is wetted and swollen by the medium in the same way as the initial tablet. However, the aged tablet does not disintegrate rapidly but disintegrates slowly. From this, the following can be deduced:

a. The intermolecular forces between excipients and drug may be increased due to the crosslinking of excipients.
b. The hydrophilicity and swelling property of disintegrants may be decreased, so the boundaries between excipients and drug cannot be weakened quickly by uptake of water.
c. The porosity of tablets may be decreased, so the water has difficulty getting into excipients to make them swell, and disintegrate.

(1) Initial dissolution profiles

Table 10 and Figure 24 show the initial dissolution profile for drug X uncoated tablets, and Table 11 and Figure 25 show the initial dissolution profile for drug X coated tablets, illustrating how tablets dissolve over 30 minutes at 100 rpm. At each stirring time, six samples were measured, and the average dissolution is represented by the solid line.

Dissolution for uncoated tablets at the 10 minute stirring time reaches 81%, but dissolution for coated tablets at the 10 minute stirring time reaches only 51%. The dissolution behavior was observed visually. The initial uncoated tablets started to

disintegrate immediately after they were dropped into the medium and the disintegration proceeded quickly. However, the initial coated tablets took a little time to start to disintegrate. That is why the dissolution at the 10 minute stirring time for coated tablets was lower than that for uncoated tablets. However, they reached about the same dissolution at the 30 minute stirring time.

Table 10 Initial dissolution profile data for uncoated tablets

Dissolution Conditions	Time (min)	Apparatus Position						Avg.	SD
		1	2	3	4	5	6		
		Dissolved							
Basket at 100 rpm	0	0%	0%	0%	0%	0%	0%	0%	0.0%
	10	68.2%	81.4%	87.3%	88.8%	84.3%	77.2%	81.2%	7.6%
	20	93.7%	95.4%	94.9%	95.8%	93.8%	95.2%	94.8%	0.9%
	30	95.9%	96.5%	95.9%	97.1%	95.3%	96.7%	96.2%	0.6%

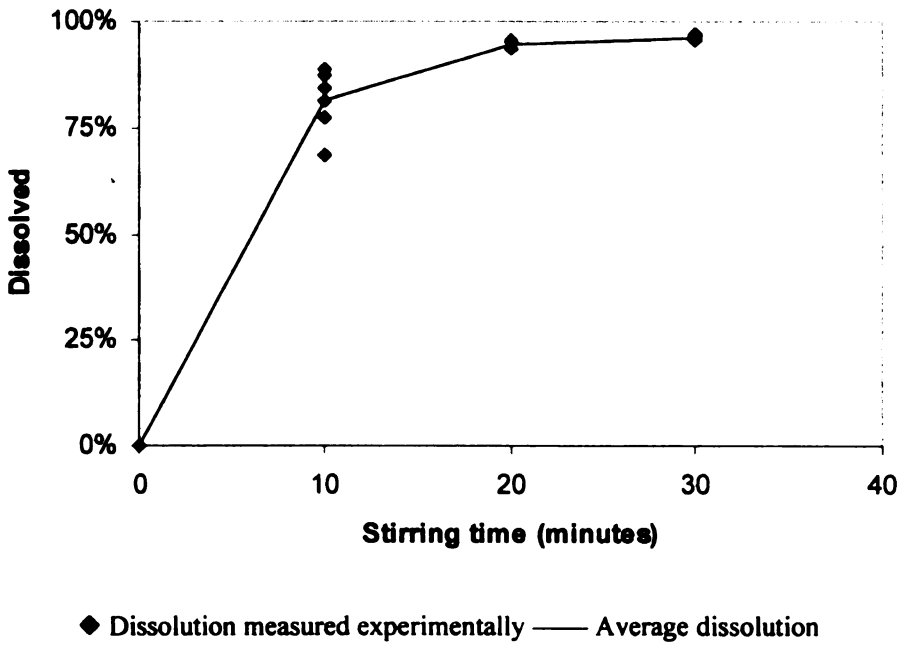


Figure 24 Initial dissolution profile of drug X uncoated tablets

Table 11 Initial dissolution profile data for drug X coated tablets

Dissolution Conditions	Time (min)	Apparatus Position						Avg.	SD
		1	2	3	4	5	6		
		Dissolved							
Basket at 100 rpm	0	0%	0%	0%	0%	0%	0%	0%	0.0%
	10	61.7%	63.0%	32.2%	59.4%	72.9%	16.1%	50.9%	21.8%
	20	95.5%	96.8%	96.6%	95.4%	96.6%	92.9%	95.6%	1.5%
	30	96.5%	97.2%	89.5%	96.7%	97.7%	97.6%	95.9%	3.1%

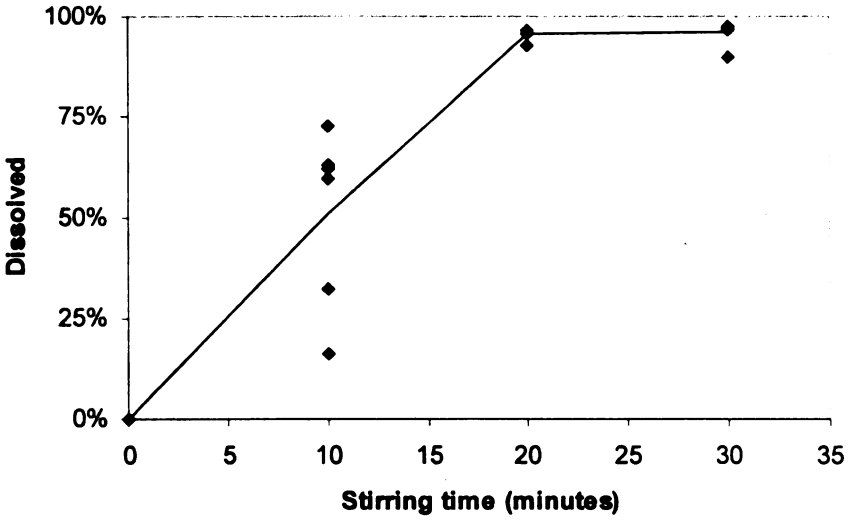


Figure 25 Initial dissolution profile of drug X coated tablets

(2) Dissolution profiles from open dish study

The dissolution of drug X tablets stored in open dishes at 40°C decreased quickly over the 6 month experiment, but the dissolution of drug X tablets stored in open dishes at 25°C did not change over the 6 months. Figures 26-30 show the average dissolution at 10, 20, and 30 minutes stirring time obtained for drug X uncoated tablets stored for 6 months at 40°C/90%, 75%, 65%, 50%, and 0%. They show the trend of dissolution reduction as a function of storage time. Figures 31-35 show the profiles obtained for drug X coated tablets stored for 6 months at 40°C/90%, 75%, 65%, 50%, and 0%. See Appendix E for the dissolution raw data including data variability (standard deviation) and the dissolution profiles of tablets stored for 6 months at 25°C/90%, 75%, 65%, 50%, and 0%.

(a) Drug X uncoated tablets stored in open dishes at 40°C

Figure 26 shows the dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/90% and the decrease in the dissolution profiles as a function of storage time. The solid line represents the dissolution profile of the initial tablets. The 30 minute dissolution of uncoated tablets stored for 6 months is still higher than the 75% dissolution specification limit in USP monograph. In terms of dissolution, uncoated tablets passed the 6 month 40°C/90% testing. However, they failed the hardness testing (see Appendix G. Hardness).

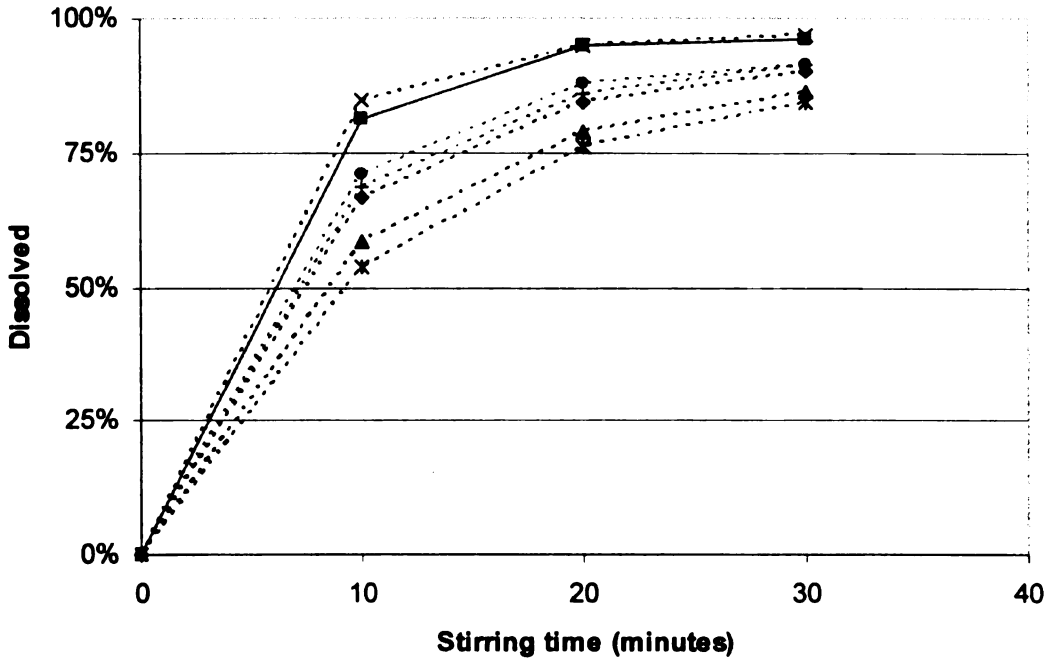


Figure 26 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/90% (each point is average value for 6 tablets)

Dissolution at the 30 minute stirring time for months 0-6 was statistically analyzed using ANOVA. The p-value was 7.0E-11. Statistically, they are significantly different because the p-value is lower than 0.05. Next, dissolution at the 30 minute stirring time for months 0 and 1, 1 and 2, etc., was statistically analyzed using t-tests as shown in Table 12.

Table 12 p-values from t-test using 1 month and 2 month intervals for tablets stored at 40°C/90% RH

Storage time (month)	0 and 1	1 and 2	2 and 3	3 and 4	4 and 5	5 and 6
p-value	1.0E-01	**2.1E-06**	8.6E-01	3.2E-01	**7.5E-03**	1.9E-01
Storage time (month)	0 and 2	1 and 3	2 and 4	3 and 5	4 and 6	
p-value	**3.3E-06**	**2.9E-05**	3.3E-01	**9.5E-04**	**4.9E-04**	

The p-values from t-tests between 1 and 2 months, and between 4 and 5 months are less than 0.05, so they are significantly different. However, the others are not significantly different because the p-values are greater than 0.05. By inspection of Figure 26, it can be seen that average dissolution values decrease as a function of storage time. They decrease within a small range of dissolution change with a large variation. Table 12 shows p-values from t-tests using 2 month intervals are generally less than 0.05. Therefore, it can be concluded that the dissolution decreased as a function of storage time, but the decrease did not occur in a uniform manner.

Figure 27 shows the dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/75%. The dissolution profiles decreased as a function of storage time. The solid line represents the dissolution profile of the initial tablets. The dissolution at 40°C/75% decreased more quickly than at 40°C/90%. There are many proposed reasons such as crosslinking and swelling. See Chapter 4.4. Proposed theory of dissolution retardation as a function of relative humidity for a detailed discussion.

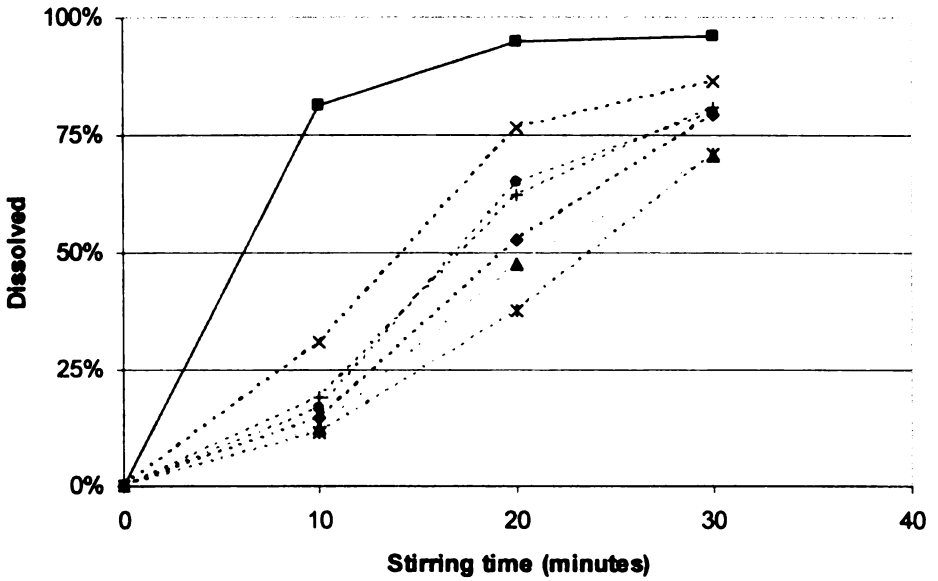


Figure 27 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/75% (each point is average value for 6 tablets)

Dissolution at the 30 minute stirring time for months 0-6 was statistically analyzed using ANOVA. The p-value was 8.6E-08. Statistically, they are significantly different because the p-value is lower than 0.05. Next, dissolution at the 30 minute stirring time for months 0 and 1, 1 and 2, etc., was statistically analyzed using t-tests as shown in Table 13.

Table 13 p-values from t-test using 1 month and 2 month intervals for tablets stored at 40°C/75% RH

Storage time (month)	0 and 1	1 and 2	2 and 3	3 and 4	4 and 5	5 and 6
p-value	**3.5E-05**	**2.4E-03**	6.7E-01	6.6E-01	1.1E-01	9.4E-01
Storage time (month)	0 and 2	1 and 3	2 and 4	3 and 5	4 and 6	
p-value	**3.0E-08**	**3.3E-02**	8.6E-01	5.3E-02	**4.0E-02**	

The p-values from t-tests between 0 and 1 month, and between 1 and 2 months are less than 0.05, so they are significantly different. However, the others are not significantly different because the p-values are greater than 0.05. From inspection of Figure 27, it can be seen that average dissolution values decrease as a function of storage time. They decrease within a small range of dissolution change with a large variation. Table 13 shows p-values from t-tests using 2 month intervals are generally less than 0.05 and close to 0.05. Therefore, it can be concluded that the dissolution decreased as a function of storage time.

Figure 28 shows the dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/65%. The dissolution profiles decreased as a function of storage time. The solid line represents the dissolution profile of the initial tablets.

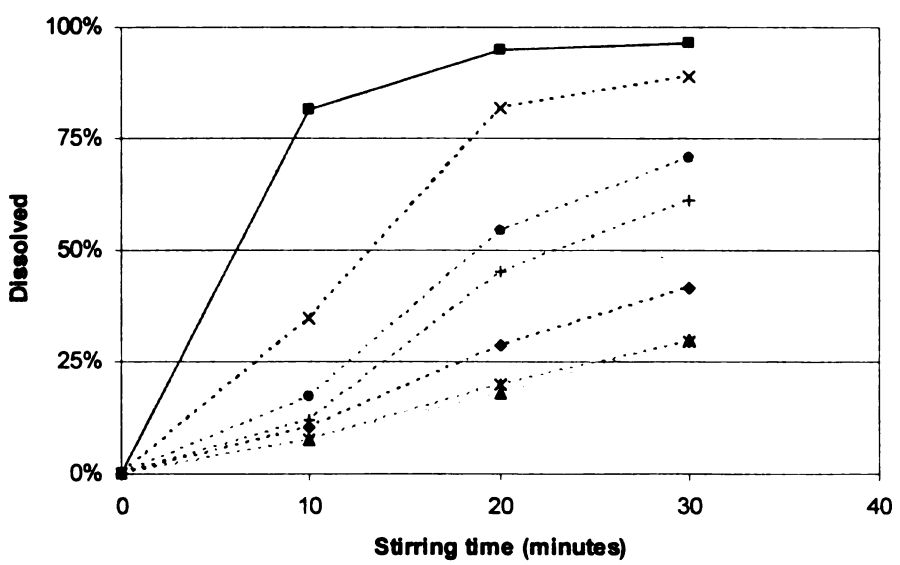


Figure 28 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/65% (each point is average value for 6 tablets)

Dissolution at the 30 minute stirring time for months 0-6 was statistically analyzed using ANOVA. The p-value was 8.3E-08. Statistically, they are significantly different because the p-value is lower than 0.05. Next, dissolution at the 30 minute stirring time for months 0 and 1, 1 and 2, etc., was statistically analyzed using t-tests as shown in Table 14.

Table 14 p-values from t-test using 1 month and 2 month intervals for tablets stored at 40°C/65% RH

Storage time (month)	0 and 1	1 and 2	2 and 3	3 and 4	4 and 5	5 and 6
p-value	**1.4E-06**	**9.9E-04**	2.3E-01	5.9E-02	1.2E-01	9.7E-01
Storage time (month)	0 and 2	1 and 3	2 and 4	3 and 5	4 and 6	
p-value	**6.7E-05**	**1.7E-03**	**2.9E-03**	**1.4E-03**	1.5E-01	

The p-values from t-tests between 0 and 1 month, and between 1 and 2 months are less than 0.05, so they are significantly different. However, the others are not significantly different because the p-values are greater than 0.05. From inspection of Figure 28, it can be seen that average dissolution values decrease as a function of storage time. They decrease with a large variation. Table 14 shows p-values from t-tests using 2 month intervals are generally less than 0.05 and close to 0.05. Therefore, it can be concluded that the dissolution decreased as a function of storage time.

Figure 29 shows the dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/50%. The dissolution profiles decreased as a function of storage time. The solid line represents the dissolution profile of the initial tablets.

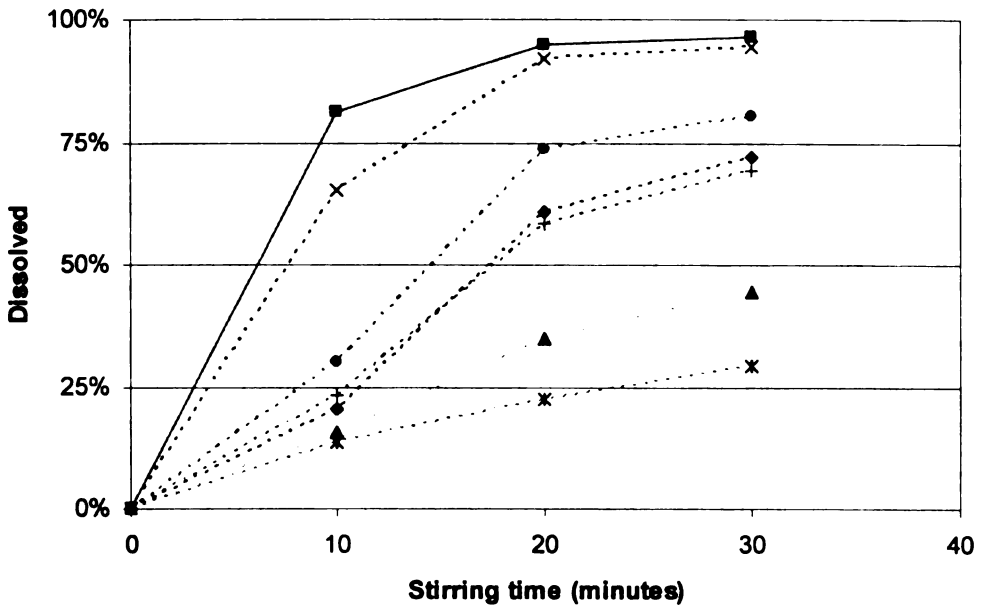


Figure 29 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/50% (each point is average value for 6 tablets)

Dissolution at the 30 minute stirring time for months 0-6 was statistically analyzed using ANOVA. The p-value was 1.0E-10. Statistically, they are significantly different because the p-value is lower than 0.05. Next, dissolution at the 30 minute stirring time for months 0 and 1, 1 and 2, etc., was statistically analyzed using t-tests as shown in Table 15.

Table 15 p-values from t-test using 1 month and 2 month intervals for tablets stored at 40°C/50% RH

Storage time (month)	0 and 1	1 and 2	2 and 3	3 and 4	4 and 5	5 and 6
p-value	**2.2E-02**	**5.9E-07**	1.8E-01	7.7E-01	**7.9E-03**	1.4E-01
Storage time (month)	0 and 2	1 and 3	2 and 4	3 and 5	4 and 6	
p-value	**7.4E-08**	**7.8E-03**	**1.9E-02**	**4.4E-02**	**2.4E-05**	

The p-values from t-tests between 0 and 1 month, between 1 and 2 months, and between 4 and 5 months are less than 0.05, so they are significantly different. However, the others are not significantly different because the p-values are greater than 0.05. From inspection of Figure 29, it can be seen that average dissolution values decrease as a function of storage time. They decrease with a large variation. Table 15 shows all p-values from t-tests using 2 month intervals are generally less than 0.05. Therefore, it can be concluded that the dissolution decreased as a function of storage time.

Figure 30 shows the dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/0%. The dissolution profiles do not change as a function of storage time. The solid line represents the dissolution profile of the initial tablets. Dried tablets may exhibit little hydrogen bonding (no physical interaction among excipients). Therefore, uncoated tablets stored in open dishes at 40°C/0% RH were not affected by temperature and storage time, so they disintegrated rapidly. There is little moisture in the tablets, so it is assumed there is no physical reaction among excipients induced by moisture.

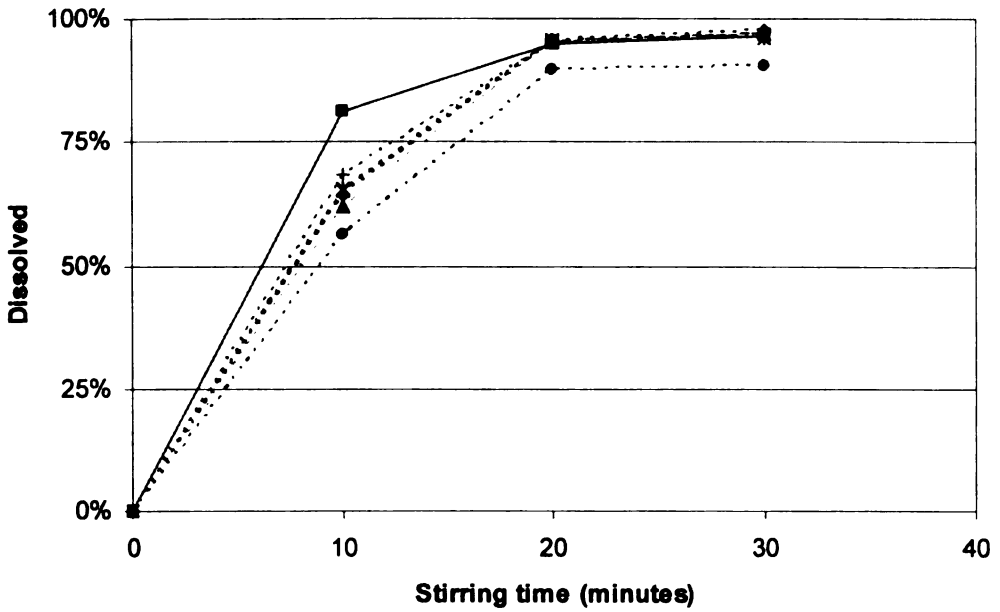


Figure 30 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 40°C/0% (each point is average value for 6 tablets)

(b) Drug X coated tablets stored in open dishes at 40°C

The dissolution of drug X coated tablets stored in open dishes at 40°C behaved very differently compared with drug X uncoated tablets. The coated tablets did not follow the dissolution theory (S-shaped dissolution change as a function of stirring time), so the dissolution at the 30 minute stirring time did not change regularly as a function of storage time.

Figure 31 shows the dissolution of 1 month and 2 month aged coated tablets stored at 90% RH at the 10 minute stirring time are greater than the dissolution of the initial coated tablets at the 10 minute stirring time.

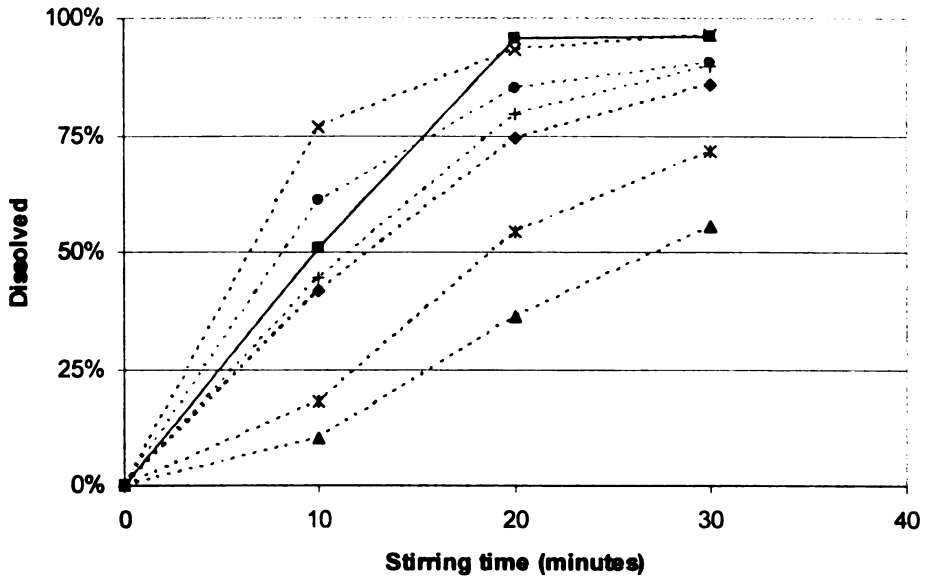


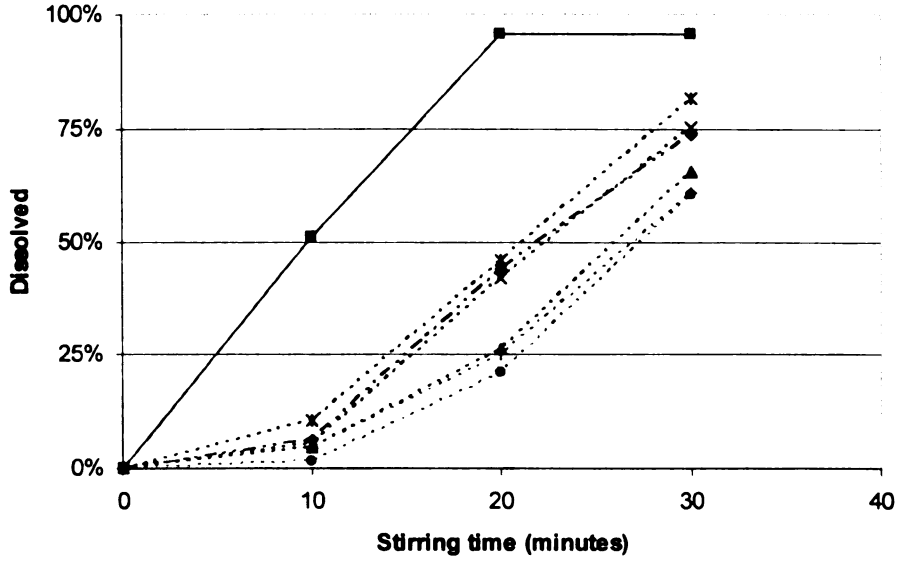
Figure 31 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 40°C/90% (each point is average value for 6 tablets)

When coated and uncoated tablets were stored at 40°C/90%, they both swelled by absorbing moisture. The swelling of excipients can make boundaries among excipients weak. That was why the tablets disintegrated rapidly. It caused the high dissolution value at the 10 minute stirring time. After 3 months, the dissolution of coated tablets at the 10 minute stirring time was lower than that of the initial coated tablets even if they still swelled. Dissolution and disintegration are generally directly proportional, if the tablet disintegrates slowly, dissolution is low. A logical reason for increased disintegration time is the following:

The properties of the coating material (color mix yellow) might be degraded. It is soluble in water, so the initial coated tablets started to disintegrate rapidly after being dropped into the medium. However, aged coated tablets did not disintegrate rapidly. They took a longer time to start to disintegrate. They swelled without any disintegration.

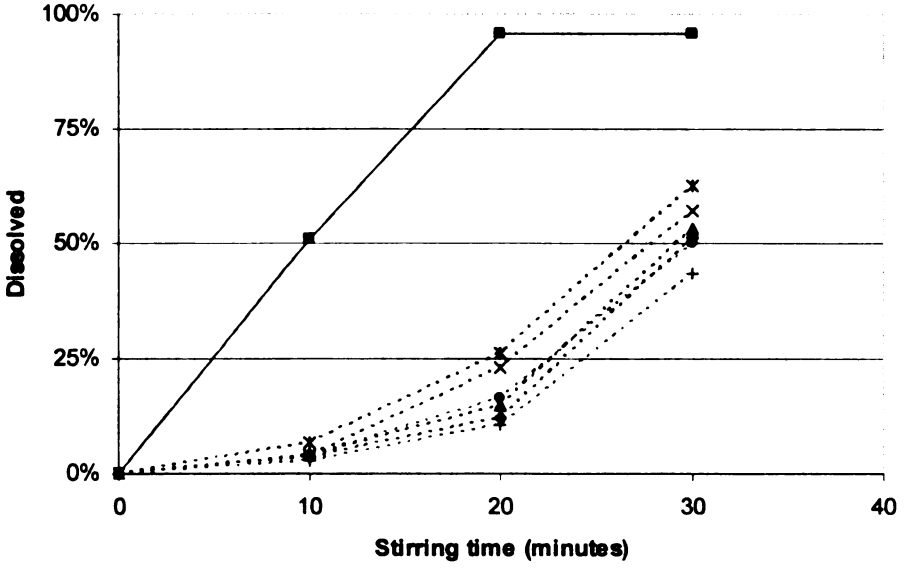
The coating material was observed to behave like a plastic film. This means the coating material was degraded either chemically or physically. When aged coated tablets started to disintegrate, the coating material was broken out suddenly. After that, aged coated tablets disintegrated rapidly. Therefore, the disintegration of aged coated tablets happened suddenly, not gradually. For the dissolution of aged coated tablets, the disintegration starting point was very important.

Figures 32-34 show very low dissolution of aged coated tablets at the 10 minute stirring time. The aged coated tablets did not disintegrate at all for about 6-8 minutes of stirring time, and then started to disintegrate suddenly. The profiles do not show a general decrease in dissolution as a function of storage time. The aged coated tablets did not dissolve according to the dissolution theory. The dissolution is very much dependent on the disintegration starting point.



■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 32 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 40°C/75% (each point is average value for 6 tablets)



■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 33 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 40°C/65% (each point is average value for 6 tablets)

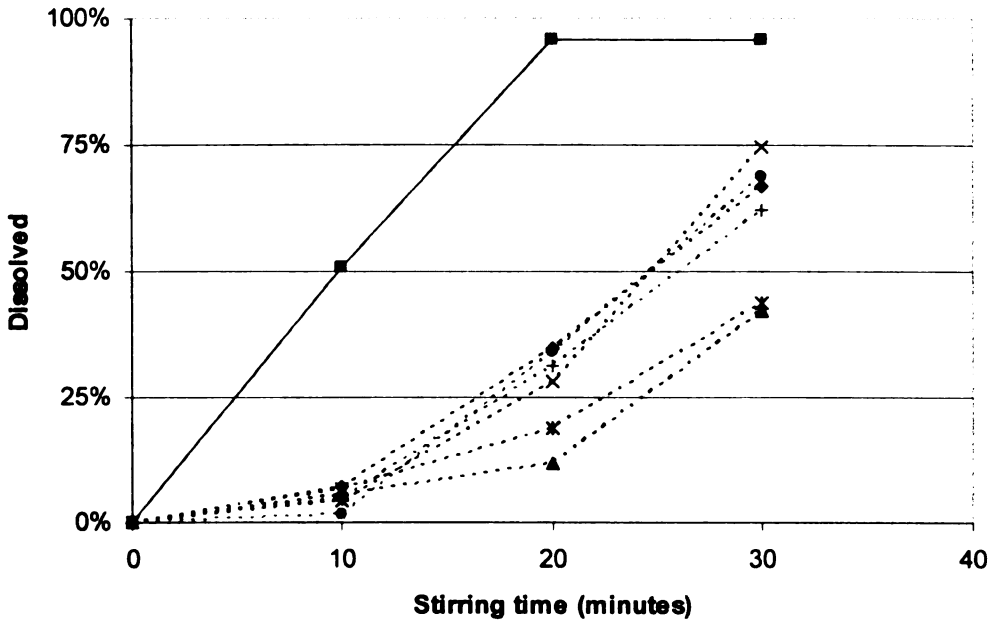


Figure 34 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 40°C/50% (each point is average value for 6 tablets)

The dissolution for the aged coated tablets stored at 40°C/90% RH is high at the 10 minute stirring time. The coating material may be cracked by the tablet swelling, so it does not behave like a plastic film. The dissolution for the aged coated tablets stored at 40°C/75%, 65%, and 50% RH is low at the 10 minute stirring time; the swelling at those conditions is not enough to crack the coating material. This low dissolution value can occur due to a degradation of the coating material and physical interaction among excipients.

Figure 35 shows the dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 40°C/0%. They did not swell and they lost moisture. Dried tablets exhibit little hydrogen bonding (no physical interaction among excipients). Therefore,

tablets disintegrated rapidly. From Figure 35, it can be explained that the coating material may be degraded physically or chemically. Dissolution at the 20 and 30 minute stirring time is almost the same between the initial and aged tablets. However, dissolution at the 10 minute stirring time is different between initial/1 month aged tablets and 2-6 month aged tablets. This shows clearly the dissolution difference caused by the coating material. There is little moisture in the tablets, so it is assumed there is no physical reaction among excipients affected by moisture. That is why the dissolution of aged tablets at the 20 and 30 minute stirring time is close to that of the initial tablets. The reason can be explained why the dissolution of aged coated tablets at the 10 minute stirring time decreases as a function of storage time. That is because the coating material is degraded by a high temperature (40°C), so the disintegration starting point took a longer time.

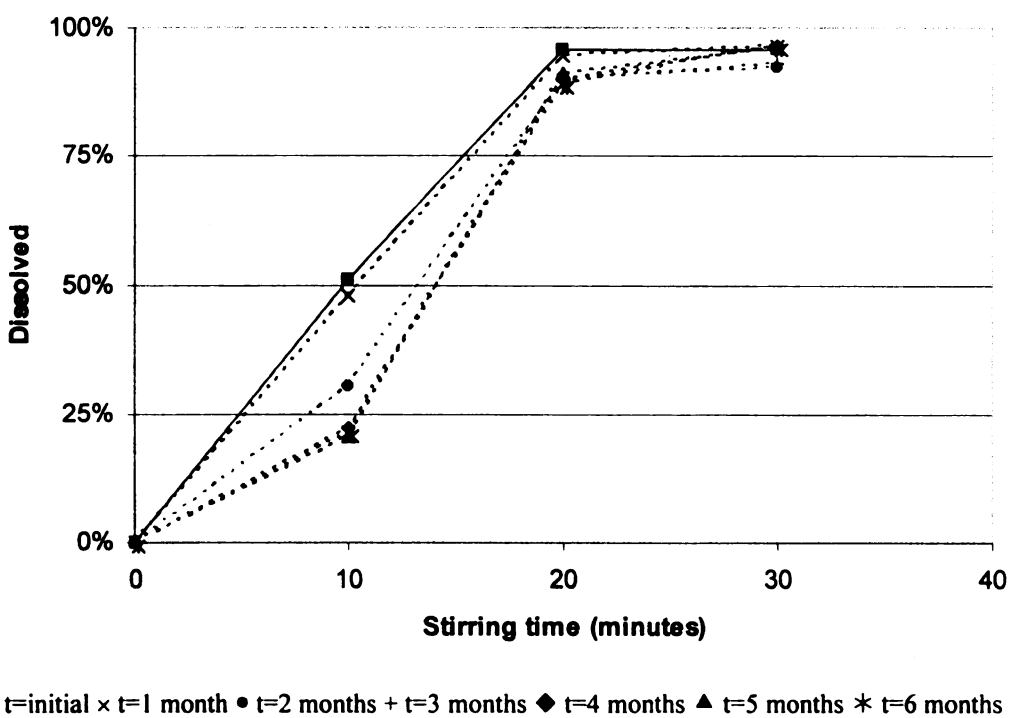


Figure 35 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 40°C/0% (each point is average value for 6 tablets)

(3) Summary of dissolution behavior

Drug X coated and uncoated tablets dissolve differently in the medium depending on the storage conditions. In comparison with the initial tablets, tablets stored at 40°C/90% and 0% RH dissolve similarly. Tablets stored at 40°C/75%, 65% and 50% RH dissolve differently in the medium from those stored at 40°C/90% and 0% RH. They do dissolve similarly to each other (see Figures 24 - 35 for the initial tablets, uncoated tablets, and coated tablets).

For uncoated tablets, dissolution profiles for initial, 90%, and 0% RH (Figures 24, 26, 30) look similar to each other. They show the dissolution is still high at 6 months storage time. And, dissolution profiles for 75%, 65%, and 50% RH (Figures 27, 28, 29) look similar to each other. They show that dissolution decreased rapidly as a function of storage time for 6 months. So, dissolution profiles obtained from initial, 90%, and 0% RH (Figures 24, 26, 30) look different in comparison with dissolution profiles obtained from 75%, 65%, and 50% RH (Figures 27, 28, 29). Coated tablets show the same behavior.

For both coated and uncoated initial tablets, there may be no change in physical interactions among excipients because they have been stored at ambient conditions. So, dissolution at the 30 minute stirring time is high (96% for both coated and uncoated tablets). And, for both coated and uncoated tablets stored at 0% RH, there may be no physical interactions among excipients because there is little moisture in tablets. So, tablets stored at 0% RH behaves like the initial tablets. Finally, for both coated and uncoated tablets stored at 90% RH, there may be physical interactions such as crosslinking. However, the swelling may counteract crosslinking among excipients.

Also, the swelling may be able to crack the coating material, so aged coated tablets disintegrate rapidly to reach high dissolution. Therefore, the dissolution of the initial tablets, and tablets stored at 0% and 90% RH behaves similarly.

For tablets stored at 75%, 65%, and 50% RH, there may be physical interactions such as crosslinking, so dissolution decreases rapidly as a function of storage time. Therefore, dissolution of tablets stored at 75%, 65% and 50% RH behaves similarly. See Chapter 4.4. Proposed theory of dissolution retardation as a function of relative humidity for more information.

CHAPTER 4

DISSOLUTION PREDICTION PROGRAMMING AND VERIFICATION

The dissolution is affected by the following five major factors (Abdou, 1989):

a. Formulation

b. Manufacturing process

c. Packaging and storage conditions

d. Dissolution apparatus

e. Test parameters

The final dosage form, the tablet, is considered in this study, so the factors *a* and *b* can be removed because the same formulation and manufacturing process are used for all tablets. Also, if the same dissolution method is used consistently, the factors *d* and *e* are assumed to be constant, so they can be removed. Therefore, the effect of aging on in-vitro dissolution is assumed to depend only on packaging and storage conditions such as moisture, temperature, oxygen, light and storage time. In this study, the product is moisture sensitive. The packages such as plastic bags or bottles cannot protect against temperature, but they can protect against light by using amber color or opaque walls. Therefore, if the relationship among dissolution, moisture, and storage time is found, the in-vitro dissolution of products in a package can be predicted at a specific temperature.

1. Technical review of Nakabayashi's method

As explained in Chapter 1, Nakabayashi's dissolution reduction rate (K) represents the log ratio of dissolution rates [$ln(k_f/k_i)$] as a function of storage time. If the

relationship between dissolution reduction rate (K) and RH (or M) is determined, the dissolution at any storage RH for any storage time can be calculated. Nakabayashi and coworkers used a multiple regression method to determine the relationship between the dissolution reduction rate, moisture, and temperature.

Nakabayashi and coworkers determined the dissolution rate (k) by plotting data $ln[C_t/(C_i - C_m)]$ versus stirring time. They presented dissolution determinations resulting from samples of three tablets taken every 2 minutes stirring time from about 2 minutes to 16 minutes. From this, they presented straight line plots of $ln[C_t/(C_i - C_m)]$ versus stirring time. There is very little variation indicated in the data even if they used the rotating basket model for the dissolution method. The basket dissolution method has poor mixing system, so it is hard to reproduce data (Ross and Rasis, 1988). Nakabayashi et al. made no statement of variation at all. Many of the points (average of 3) fall exactly on the trend lines. However, the variation in dissolution is known to be large, especially at stirring times of less than 30 minutes.

In this study, six tablets were taken every 10 minutes for a total of 30 minutes stirring time. Variation in this study is high, especially at the 10 minute stirring time for short term aged tablets, and at the 20 and 30 minute stirring time for long term aged tablets as shown in Table 16. Short term (Initial-1 month aged) tablets disintegrate quickly, so the short term aged tablets at the 10 minute stirring time are very active, causing a large variation at that stirring time. However, tablets at the 30 minute stirring time disintegrate completely, and reach almost the maximum dissolution value, so, have little variation. Long term (2 months-6 months aged) tablets disintegrate slowly. The long term aged tablets before the 10 minutes stirring time are inactive, so dissolution at

that stirring time is low, and variation is small. Tablets beyond 10 minutes stirring time are very active. They rapidly disintegrate into small particles, and the drug in the particles dissolves into the medium. During this process, the dissolution value for each tablet is variable.

Table 16 Variation of dissolution for drug X uncoated tablets stored at 40°C (coefficient of variance greater than 0.1 is bold-faced.)

Stirring time (minutes)		Drug X uncoated tablets stored at 40°C/90% RH						
		Initial	1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.
10	SD	7.6	3	7.2	5.2	5.6	5.7	3.6
	Mean	81.2	84.9	71	68.6	66.7	58.3	53.7
	Coef. of variation	0.094	0.035	**0.101**	0.076	0.084	0.098	0.067
20	SD	0.9	1.6	2.4	2.8	3	3.2	2.4
	Mean	94.8	94.66	87.7	86	84.5	78.7	75.9
	Coef. of variation	0.009	0.017	0.027	0.033	0.036	0.041	0.032
30	SD	0.6	0.9	1.1	1.7	2	2.2	2
	Mean	96.2	96.88	91.3	91.5	90.4	86.2	84.5
	Coef. of variation	0.006	0.009	0.012	0.019	0.022	0.026	0.024
		Drug X uncoated tablets stored at 40°C/75% RH						
		Initial	1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.
10	SD	7.6	12.1	3.7	5.2	4	1.9	3.2
	Mean	81.2	31	16.8	19.2	14.8	12.3	11.3
	Coef. of variation	0.094	**0.390**	**0.220**	**0.271**	**0.270**	**0.154**	**0.283**
20	SD	0.9	7.2	4.7	11.8	18.4	11.3	11.3
	Mean	94.8	767	65.2	62.4	52.8	47.5	37.8
	Coef. of variation	0.009	0.009	0.072	**0.189**	**0.348**	**0.238**	**0.299**
30	SD	0.6	3.3	2.5	4.7	6.6	10.4	5.7
	Mean	96.2	86.7	79.9	80.9	79.4	70.6	71
	Coef. of variation	0.006	0.038	0.031	0.058	0.083	**0.147**	0.080

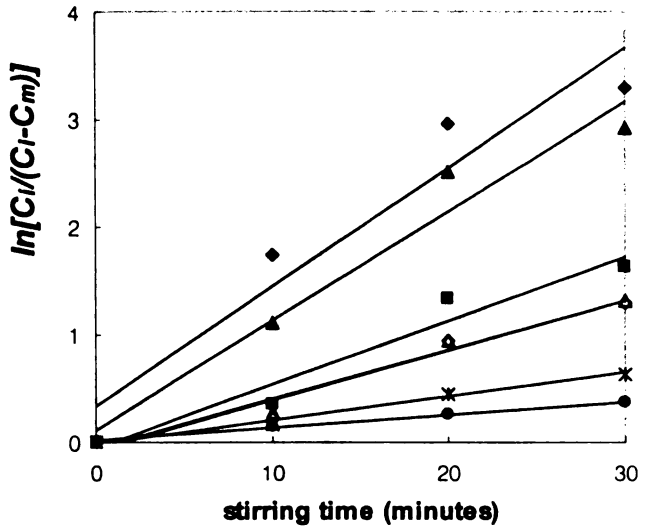
Table 16 Variation of dissolution for drug X uncoated tablets stored at 40°C (coefficient of variance greater than 0.1 is bold-faced.) (Continued)

		Drug X uncoated tablets stored at 40°C/65% RH						
		1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.	1 mo.
10	SD	7.6	5.2	2.7	0.8	1.4	1.4	0.7
	Mean	81.2	34.5	17.3	11.9	10.4	7.5	7.63
	Coef. of variation	0.094	**0.151**	**0.156**	0.067	**0.135**	**0.187**	0.092
20	SD	0.9	2	13	14	12.7	5.1	8.4
	Mean	94.8	81.9	54	45	28.5	17.9	19.8
	Coef. of variation	0.009	0.024	**0.241**	**0.311**	**0.446**	**0.285**	**0.424**
30	SD	0.6	1.7	9.6	16	15.3	7.1	11.3
	Mean	96.2	88.9	70.5	60.9	41.6	29.8	29.6
	Coef. of variation	0.006	0.019	**0.136**	**0.263**	**0.368**	**0.238**	**0.382**
		Drug X uncoated tablets stored at 40°C/50% RH						
		1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.	1 mo.
10	SD	7.6	10	5.4	9.3	3.2	3.3	2
	Mean	81.2	65.3	30	23.1	20.5	15.7	13.6
	Coef. of variation	0.094	**0.153**	**0.180**	**0.403**	**0.156**	**0.210**	**0.147**
20	SD	0.9	1.7	3	17.2	7.1	14.3	9.4
	Mean	94.8	91.8	73.7	58.4	60.8	34.8	22.6
	Coef. of variation	0.009	0.019	0.041	**0.295**	**0.117**	**0.411**	**0.416**
30	SD	0.6	1.5	2.7	18.5	6.9	19.2	12.3
	Mean	96.2	94.5	80.3	69.4	71.8	44.2	29.4
	Coef. of variation	0.006	0.016	0.034	**0.267**	0.096	**0.434**	**0.418**
		Drug X uncoated tablets stored at 40°C/0% RH						
		1 mo.	2 mo.	3 mo.	4 mo.	5 mo.	6 mo.	1 mo.
10	SD	7.6	5.5	2.9	7.5	7.4	5.6	3.7
	Mean	81.2	65.2	56.3	68.4	64.1	61.9	65.5
	Coef. of variation	0.094	0.084	0.052	**0.110**	**0.115**	0.090	0.056
20	SD	0.9	1.3	0.9	0.8	1.1	1	0.8
	Mean	94.8	95.3	89.6	95.4	95.5	95.1	95.8
	Coef. of variation	0.009	0.014	0.010	0.008	0.012	0.011	0.008
30	SD	0.6	0.9	0.9	0.3	0.7	0.8	1.6
	Mean	96.2	96.9	90.4	97	97.5	96.9	96.1
	Coef. of variation	0.006	0.009	0.010	0.003	0.007	0.008	0.017

SD: standard deviation from six dissolution (%) values
Mean: Mean of six dissolution (%) values
Coef. of variation: coefficient of variation (SD/Mean)

As shown in Table 16, there is a large variation in dissolution using the basket method (average coefficient of variation: 0.041 at 90%, 0.157 at 75%, 0.192 at 65%, 0.187 at 50%, 0.035 at 0%). The average coefficients of variation for 40°C at 75%, 65%, and 50% RH are four times higher than those of variation for 40°C at 90% and 0% RH. If the coefficient of variation in Table 16 is higher than 0.1, the value is in bold. There are many more bold-faced values at 75%, 65%, and 50% RH than at 90% and 0% RH. The coefficient values at intermediate relative humidities (50, 65, and 75% RH) are higher than at either 0% or 90% RH. Therefore, it is hard to determine the dissolution rate (k) with $ln[C_t/(C_i - C_m)]$ and stirring time for tablets stored at 40°C at 75%, 65%, and 50% RH (lack of fit).

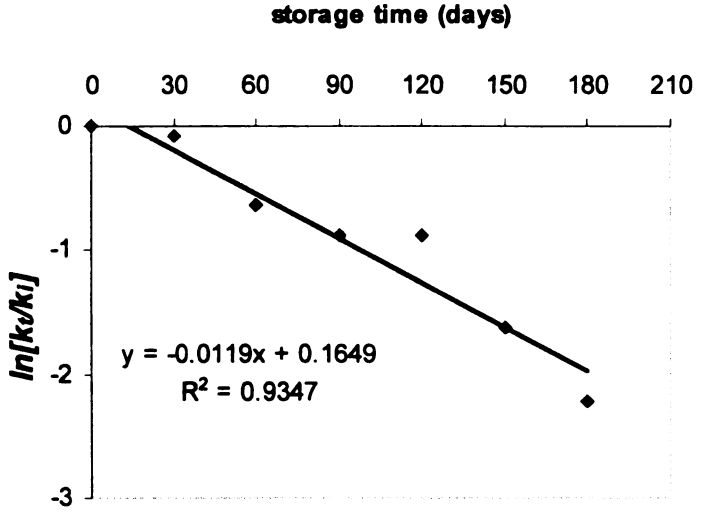
Figure 36 shows an example of the relationship between $ln[C_t/(C_i - C_m)]$ and stirring time obtained from drug X uncoated tablets stored for 6 months at 40°C/50% RH. There was a poor relationship between $ln[C_t/(C_i - C_m)]$ and stirring time, and dissolution rates (k) did not change regularly as a function of storage time.



◆ (t = initial) ▲ (t = 1 month) ■ (t = 2months)△ (t = 3 months) ◇ (t = 4 months) ∗ (t = 5 months) ● (t = 6 months) — (dissolution rate)

Figure 36 Dissolution rates (*k*) of uncoated tablets stored in open dishes for 6 months at 40°C/50% RH

The log ratio of dissolution rates ($ln[k_t/k_i]$) was plotted as a function of storage time to determine the dissolution reduction rate (*K*) as shown in Figure 37.



◆ Calculated $ln[k_t/k_i]$ — Dissolution reduction rate

Figure 37 Dissolution reduction rate (*K*) of uncoated tablets stored at 40°C/50% RH

Next, dissolution reduction rates (K) were plotted as a function of relative humidity giving the relationship shown in Figure 38.

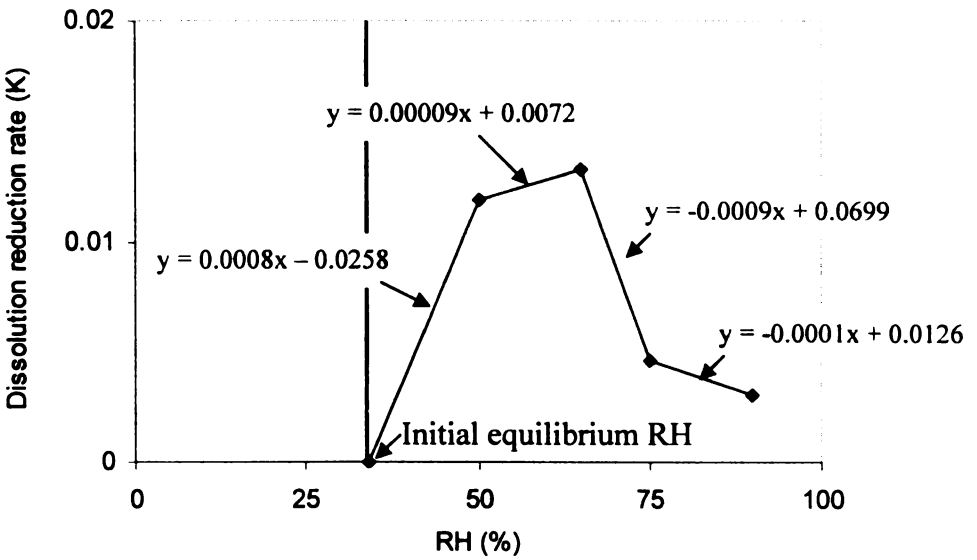


Figure 38 Dissolution reduction rate as a function of RH (%)

By using the relationship in Figure 38, the dissolution of tablets in a package is to be calculated as a function of storage time. The linear relationship between dissolution reduction rate and relative humidity can be expressed as Equation 14.

$$K = a \cdot RH(\%) + b \tag{14}$$

Substitute Equation 14 into Equation 10:

$$k_t = k_i \cdot e^{-(a \cdot RH(\%)+b) \cdot t} \tag{15}$$

Substitute Equation 15 into Equation 8:

$$C_m = C_i - C_i \cdot e^{-[k_i \cdot e^{-(a \cdot RH(\%)+b) \cdot t}] \cdot 30} \tag{16}$$

Equation 16 was used to calculate the dissolution at 30 minutes stirring time for a time interval (t) in the dissolution prediction program.

Example calculation: 15 tablets in HDPE bottle stored at 40℃/90% RH

Initial dissolution rate (k_i): 0.111

At storage time 0, the dissolution at 30 minutes stirring time is:

$C_m = 1 - 1 \times e^{-[0.111] \times 30} = 0.9642$ (96.42% dissolution)

After 1 day, the relative humidity of HDPE bottle headspace is 34.63%.

$C_m = 1 - 1 \times e^{-[0.111 \times e^{-(0.0008 \times 34.63 - 0.0258) \times 1}] \times 30} = 0.964$ (96.4% dissolution)

So, the dissolution of tablets at 34.63% RH is changed to 96.4% for 1 day. The dissolution decreased by 0.02% from the initial dissolution.

After 2 days, the relative humidity of HDPE bottle headspace is 35.44%.

$C_m = 1 - 1 \times e^{-[0.111 \times e^{-(0.0008 \times 35.44 - 0.0258) \times 1}] \times 30} = 0.9639$

So, the dissolution of tablets at 35.44% RH is changed to 96.39 for 1 day. The dissolution decreased by 0.03% from the initial dissolution, and so on.

For 6 days, the accumulated dissolution change is 0.19% (0.02% + 0.03% + 0.04% + 0.05% + 0.05% + 0.06%). Therefore, the dissolution decreased to 96.23% from 96.42%.

Dissolution results using Nakabayashi's method with this data show poor agreement between calculated and experimental results, as shown in Figure 39. This is an illustration of results (tablets in LDPE bags without silica gel, tablets in LDPE bags with 0.5 g, 1 g, 2 g silica gel, tablets in HDPE bottles without silica gel, and tablets in HDPE bottles with 0.5 g silica gel).

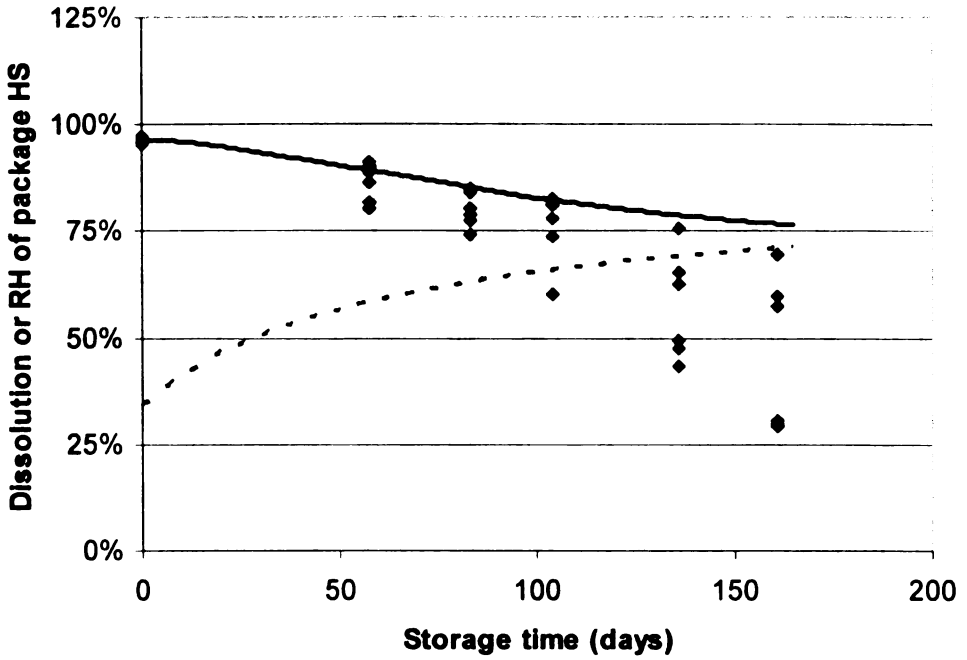


Figure 39 Dissolution of tablets in HDPE bottles stored at 40°C/90% RH as a function of storage time – Nakabayashi method

Therefore, in this study, the method for prediction of dissolution of tablets in a package was approached differently by using the dissolution retardation rate (R).

2. Dissolution retardation rate (R)

Dissolution is dependent on moisture as well as storage time, so a rate representing dissolution change as a function of storage time must be determined. The theory of the dissolution change as a function of storage time has not been explained clearly in the literature, so the rate must be determined experimentally at various relative humidities to determine the relationship between the rate and relative humidity.

As explained in Chapter 3.3 (2) Dissolution profiles from open dish study, the 30 minute dissolution of drug X, both coated and uncoated tablets, stored in open dishes at 25°C did not change over the 6 month period, but it did change at 40°C except for 40°C/0% RH. For the coated tablets stored at 40°C, it was hard to determine the relationship between the 30 minute dissolution and storage time because the coated tablets dissolved suddenly, not gradually. They did not follow the dissolution theory. However, uncoated tablets stored at 40°C did follow the dissolution theory. Figures 40-44 show 30 minute dissolution values of uncoated tablets stored at 40°C as a function of storage time.

Based on empirical data fitting methods, it must be determined how the 30 minute dissolution changes as a function of storage time. A polynomial equation can be applied to determine the relationship between the 30 minute dissolution and storage time. A better fit can be made by using the polynomial equation. However, there is no method to compare the relationships obtained from a variety of relative humidities (50, 65, 75, and 90% RH). The relationship between the 30 minute dissolution and storage time can be assumed to follow zero order kinetics (linear relationship) or first order kinetics (exponential relationship). The dissolution prediction model using first order kinetics can make better results for drug X uncoated tablets. So, the first order kinetic was chosen to treat the relationship. The average initial 30 minute dissolution (D_i) of uncoated tablets is 96.23%.

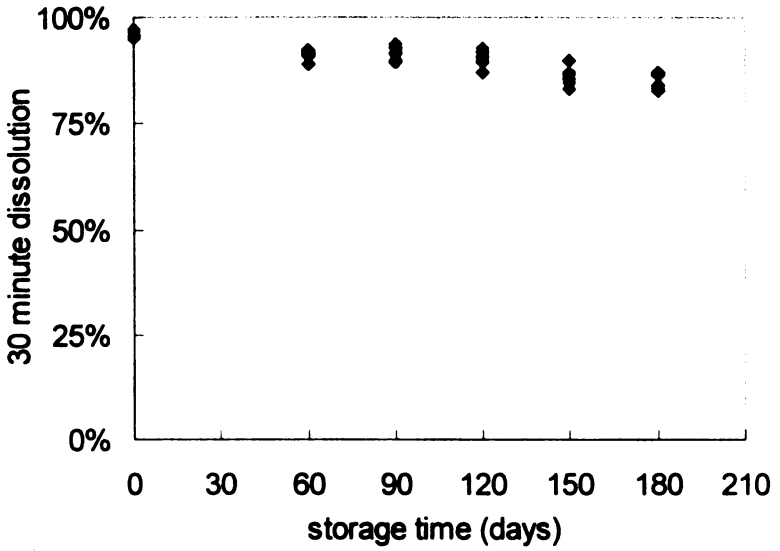


Figure 40 30 minute dissolution of drug X uncoated tablets stored in open dishes for 6 months at 40°C/90% (each month has 6 dissolution values)

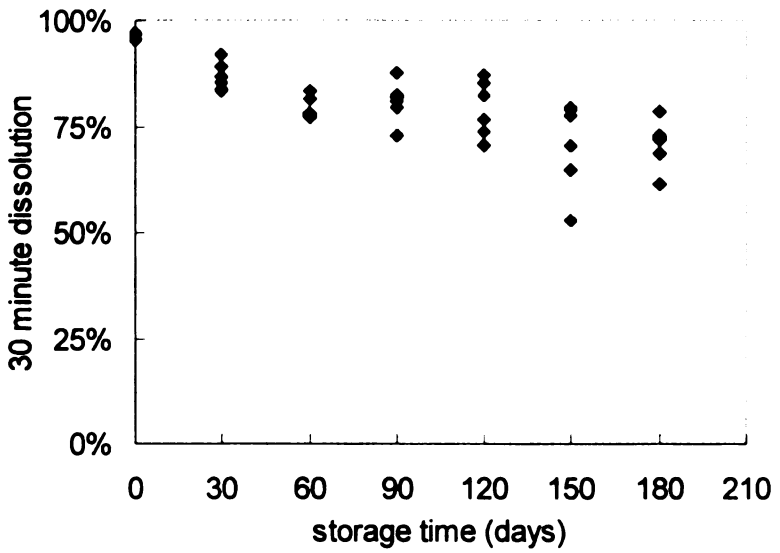


Figure 41 30 minute dissolution of drug X uncoated tablets stored in open dishes for 6 months at 40°C/75% (each month has 6 dissolution values)

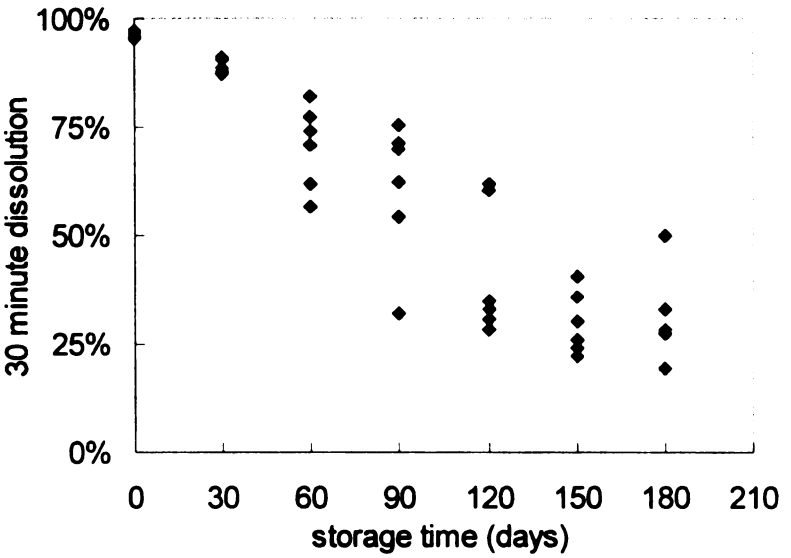


Figure 42 30 minute dissolution of drug X uncoated tablets stored in open dishes for 6 months at 40°C/65% (each month has 6 dissolution values)

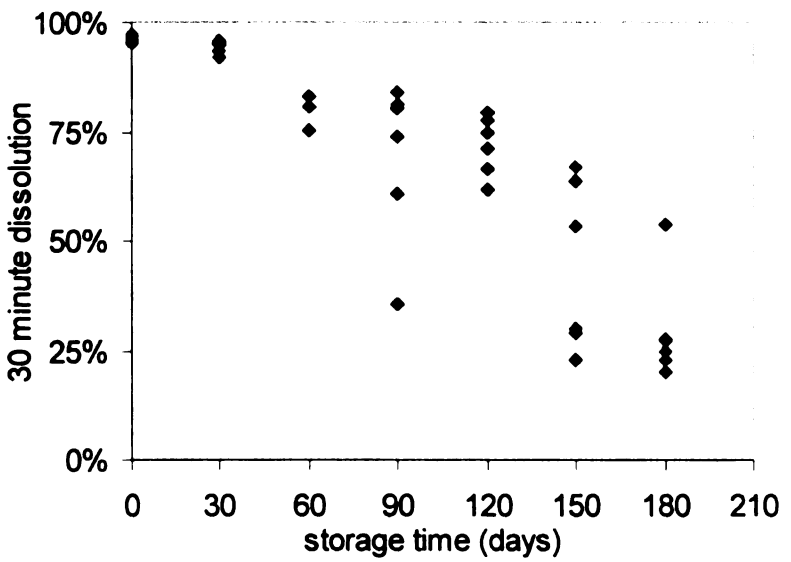


Figure 43 30 minute dissolution of drug X uncoated tablets stored in open dishes for 6 months at 40°C/50% (each month has 6 dissolution values)

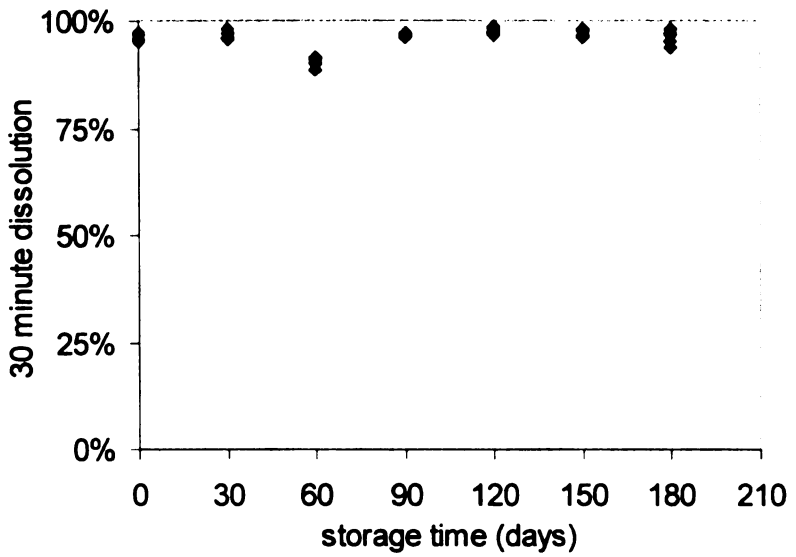


Figure 44 30 minute dissolution of drug X uncoated tablets stored in open dishes for 6 months at 40°C/0% (each month has 6 dissolution values)

As can be seen in Figures 40-44, the variability of 30 minute dissolutions is large, especially for 40°C/75%, 65%, and 50% RH. This large variability can make it hard to determine the relationship between the 30 minute dissolution and storage time.

In order to make the relationship, an exponential equation can be applied. Figure 45 shows a general exponential graph ($y = -e^x$). If plotted function moves up the y-axis as much as $1+D_i$ (initial dissolution value), an equation ($y = -e^x + D_i + 1$) can be obtained as shown in Figure 46.

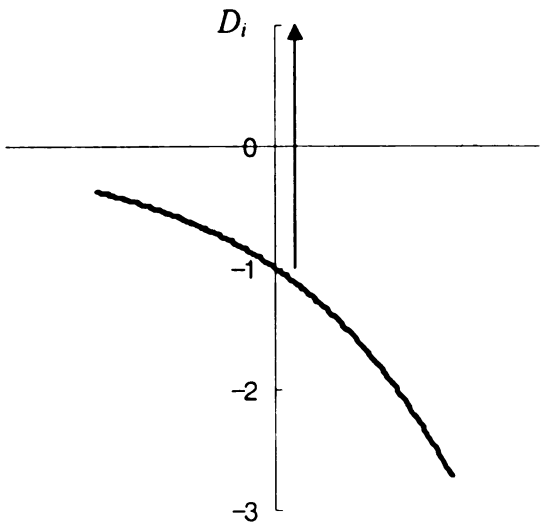


Figure 45 Graph of $y = -e^x$

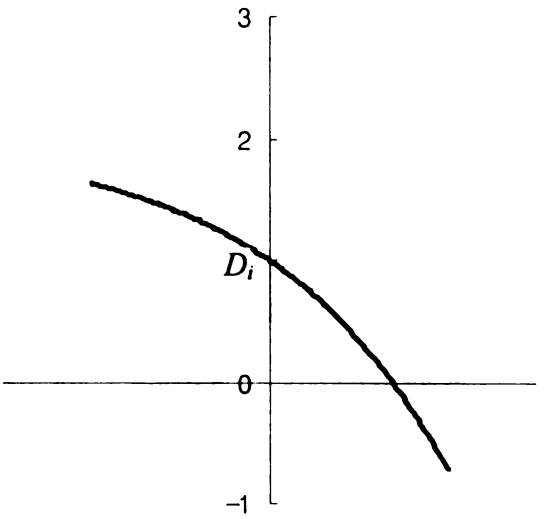


Figure 46 Graph of $y = -e^x + (D_i+1)$

The equation shown in Figure 46 can be applied to make the relationship between the 30 minute dissolution and storage time. Figure 47 shows a typical graph for dissolution change as a function of storage time.

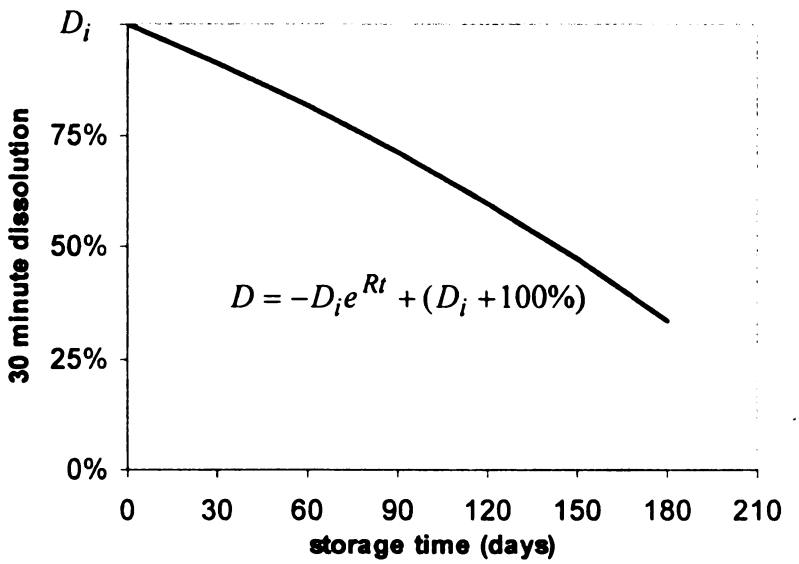


Figure 47 A typical graph for 30 minute dissolution change as a function of storage time

Equation 17 represents the relationship between the 30 minute dissolution and storage time. R denotes the dissolution retardation rate. R must be determined at each relative humidity.

$$D = -D_i e^{Rt} + (D_i + 100\%) \tag{17}$$

In order to get the dissolution retardation rate (R), Equation 17 is rearranged. Plots of the 30 minute dissolution on a logarithmic scale, against storage time on the abscissa with a linear scale, yield a straight line.

$$\ln\left[\frac{D_i}{D_i - D + 100\%}\right] = -Rt \tag{18}$$

By plotting $ln[D_i/(D_i\text{-}D+100\%)]$ versus storage time (t), the dissolution retardation rate (R) can be determined using a trend line as shown in Figure 48.

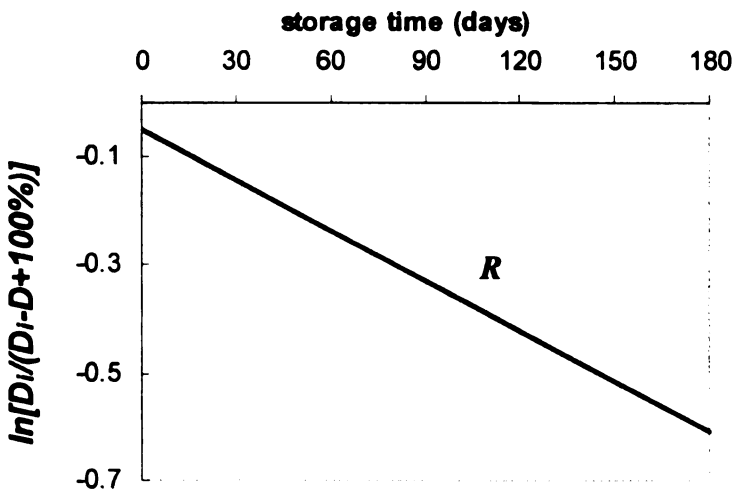


Figure 48 Dissolution retardation rate (R)

Figure 49 shows dissolution retardation rates determined at various relative humidities at 40°C. The dissolution retardation rate at 40°C/65% is greatest. It means that the dissolution of tablets stored at that condition decreases most quickly as a function

of storage time. And, the dissolution retardation rate at 40°C/90% is lowest. See 4. Proposed theory of dissolution retardation as a function of relative humidity for more information. This result is different from previous research at the School of Packaging in Michigan State University, and from Nakabayashi (1980) and Kadir (1986). They concluded that the dissolution decreased more rapidly if tablets are stored at a high temperature and high relative humidity. See Chapter 1. Background and literature review for more information.

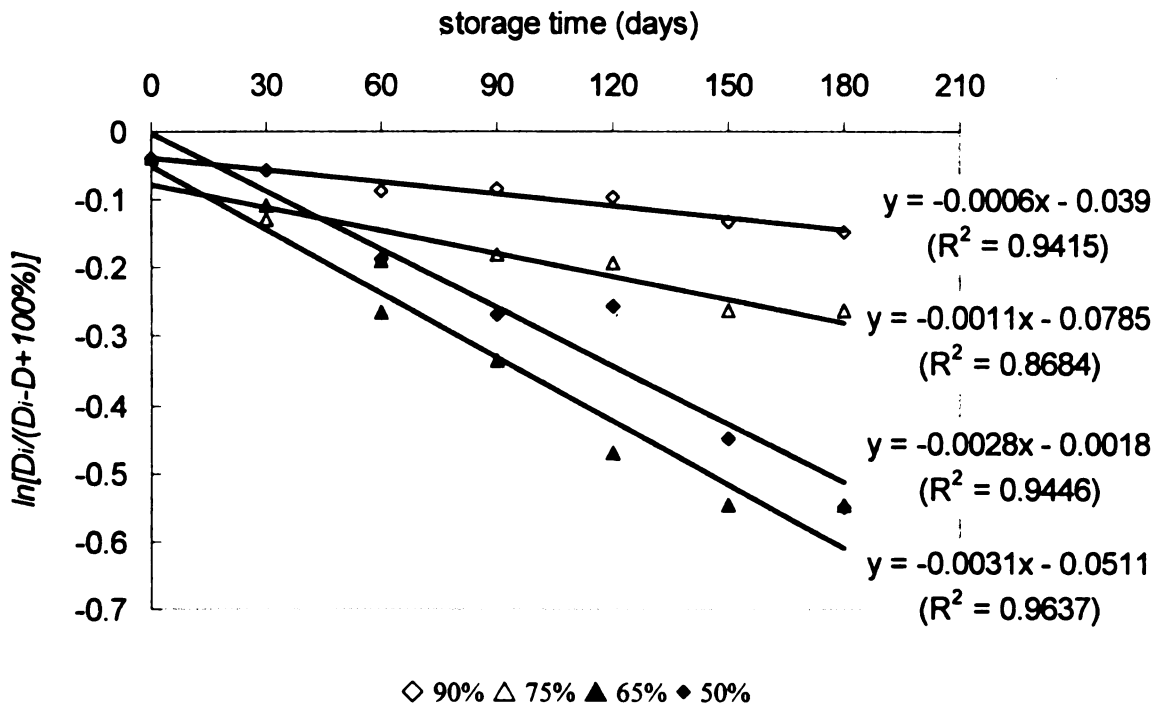


Figure 49 Dissolution retardation rate of drug X uncoated tablets at various relative humidities at 40°C

Table 17 shows dissolution retardation rates (R, % dissolution change/day) at 40°C.

Table 17 Dissolution retardation rates (R) of drug X uncoated tablets stored in open dishes at 40°C

RH	0%	50%	65%	75%	90%
Dissolution retardation rate (% dissolution change/day)	0	0.0028	0.0031	0.0011	0.0006

To predict the dissolution of tablets in a package, the dissolution retardation rate (% dissolution change/storage time) as a function of relative humidity must be determined.

Figure 50 shows the relationship between the dissolution retardation rate and relative humidity. Based on 6 month experimental results, it is assumed that the dissolution of tablets stored below the initial equilibrium relative humidity does not change. Dissolution when stored in open dishes at 40°C/0% did not change for 6 months (see Figure 30). The tablets in the HDPE bottle containing 0.5 g silica gel did not reach the initial equilibrium RH for 3 months, and the dissolution did not change below that initial equilibrium RH (34.23%) (see Figure 57). Even though there is no 6 month dissolution data between 0% RH and initial RH (34.23%), it is assumed in this study that the dissolution of drug X uncoated tablets stored below initial conditions does not change for 6 months at 40°C. So, a zero value of the dissolution retardation rate is applied to calculate the dissolution of tablets between 0% RH and initial equilibrium RH (34.23% RH). The piecewise equations shown in Figure 50 are used to calculate the dissolution retardation rate at any RH according to Equation 19.

$$R = a \cdot RH(\%) + b \tag{19}$$

where a and b = constants of the equation between R and RH (%)

Substitute Equation 19 into 17.

$$\%\,Dissolution\,(D) = -D_i \cdot e^{[a \cdot RH(\%)+b] \cdot t} + D_i + 100\% \tag{20}$$

Equation 20 can be used to calculate the 30 minute dissolution at any RH.

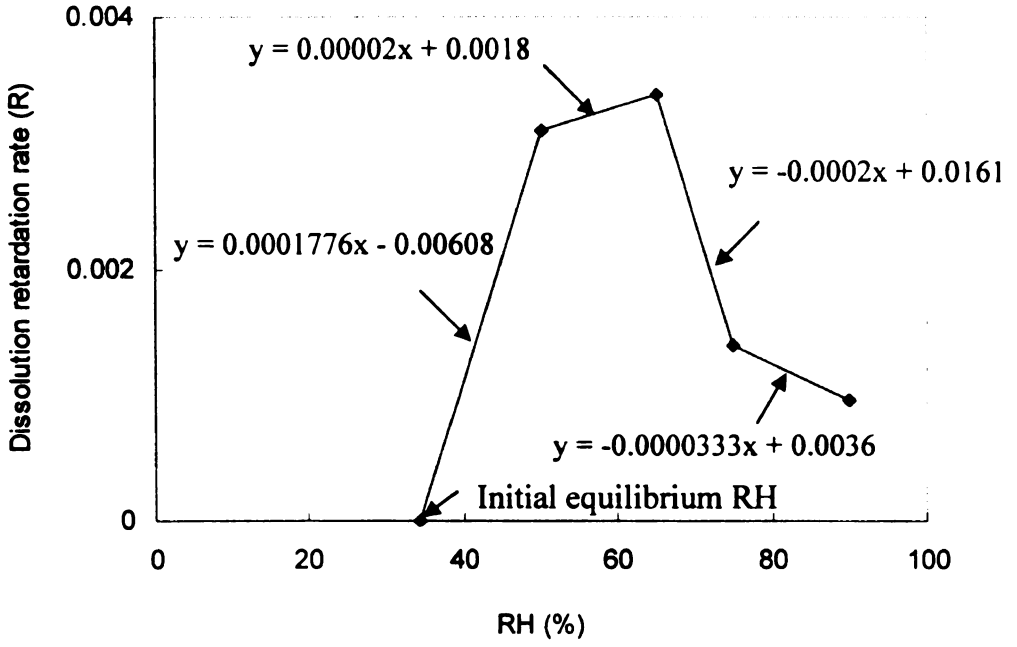


Figure 50 Dissolution retardation rate (R) as a function of relative humidity at 40°C

Example Calculation

The following shows how to calculate the dissolution using the dissolution retardation rate at 40°C/50% RH for 30 days.

$$D(\%) = -96.23\% \cdot e^{[0.0001776 \times 50 - 0.00608] \cdot 30} + 96.23\% + 100\% = 91.57\%$$

The dissolution prediction program works with the moisture prediction program. At each time interval, the tablets in a package have a different moisture content associated with the equilibrium headspace RH (%) at that time interval. So, the dissolution prediction program calculates the dissolution of tablets at each equilibrium $RH(\%)$ (or $(p/p_s)_{in}$) determined by the moisture prediction program at each time interval j. Figure 51 shows the algorithm used to calculate the dissolution at various relative humidities. The dissolution changes for a time interval at various RHs are summed for a

storage time, and then the accumulated dissolution change is subtracted from the initial dissolution to calculate the dissolution of tablets stored for storage time t.

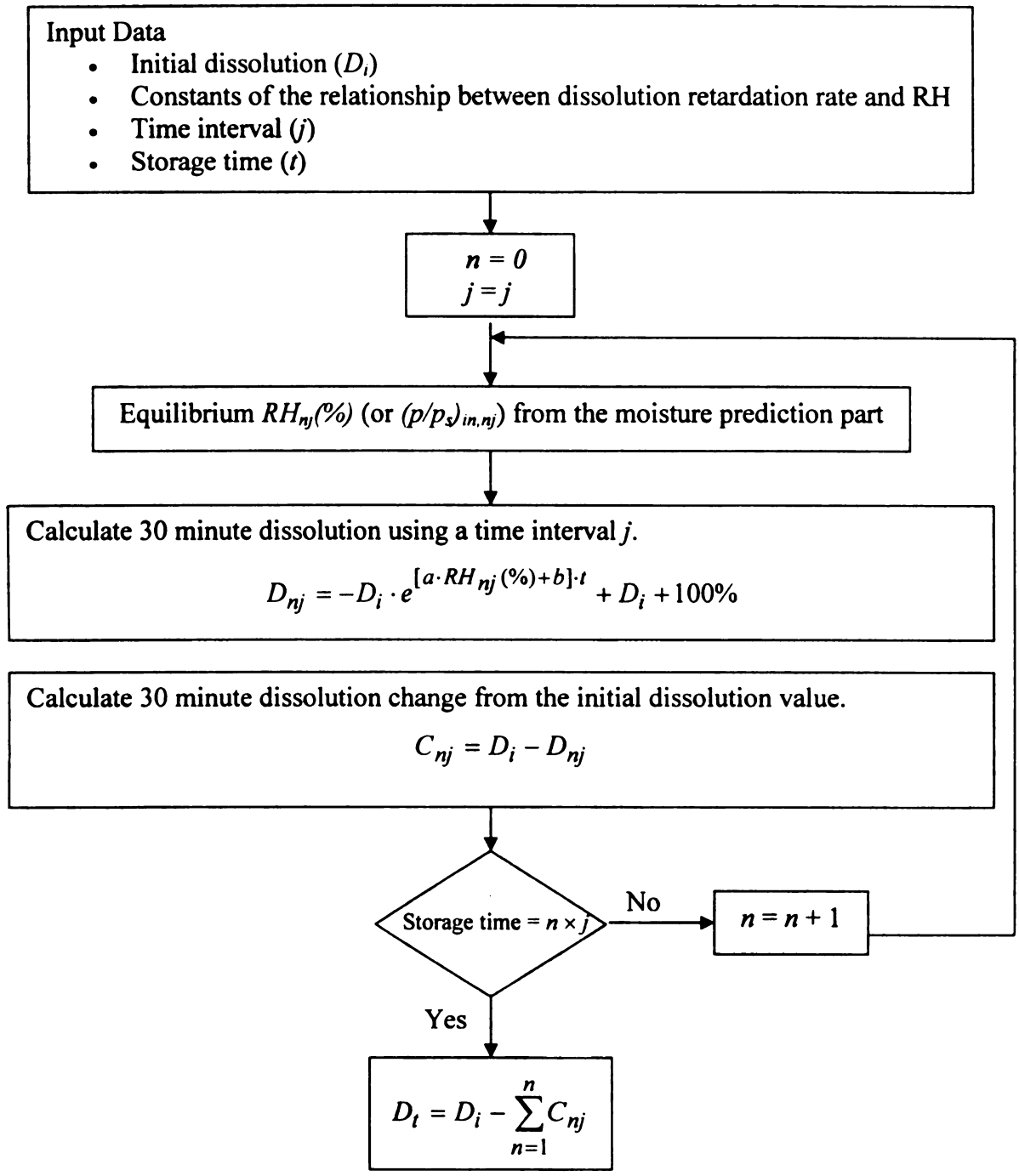


Figure 51 Algorithm used to calculate the dissolution at various relative humidities

3. Verification of dissolution prediction program

The stepwise storage conditions and continuous storage conditions were used to verify the dissolution prediction model.

(1) Stepwise storage conditions (open dish study)

In order to verify that dissolution is dependent on moisture content as well as storage time, stepwise storage conditions can be used. In addition to that, results from stepwise storage conditions at 40°C were used to verify the dissolution prediction program. Table 18 shows the stepwise storage conditions, dissolution obtained experimentally and the dissolution calculated by use of the dissolution prediction program. The experimental dissolution was measured when tablets were transferred to another condition.

Table 18 Comparison of the results from experimental and predicted dissolution stored at stepwise conditions (at 40°C)

No.	Storage time (months)	Experimental Dissolution (avg.)	Predicted Dissolution	Storage Conditions
1	1	93%	87.8%	50%(1 month)
2	2	77%	78.4%	50%(1 month), 65%(1 month)
3	3	69%	74.7%	50%(1 month), 65%(1 month), 75%(1 month)
4	4	63%	70.9%	50%(1 month), 65%(1 month), 75%(2 months)
5	4	61%	73.0%	50%(1 month), 65%(1 month), 75%(1 month), 90%(1 month)
6	5	42%	66.9%	50%(1 month), 65%(1 month), 75%(3 month)
7	5	26%	71.2%	50%(1 month), 65%(1 month), 75%(1 month), 90%(2 month)

Stepwise (I): 1, 2, 3, 4, and 6 (Results are plotted in Figure 52)
Stepwise (II): 1, 2, 3, 5, and 7 (Results are plotted in Figure 53)

Example calculation

Table 19 shows the predicted dissolution changes from the initial dissolution value, and they are calculated by the dissolution prediction program at each RH for a given storage time.

Table 19 The predicted dissolution change from the initial dissolution value calculated by the dissolution prediction program at each RH for a given storage time

Storage time	1 month	2 months	3 months	4 months
90%	1.7%	3.5%	5.3%	7.2%
75%	3.7%	7.5%	11.5%	15.6%
65%	9.4%	19.7%	31.0%	43.4%
50%	8.4%	17.6%	27.6%	38.4%

The following shows an example calculation using value in Table 19 of the dissolution of tablets stored at 50% for 1 month 65% for 1 month and 75% for 2 months.

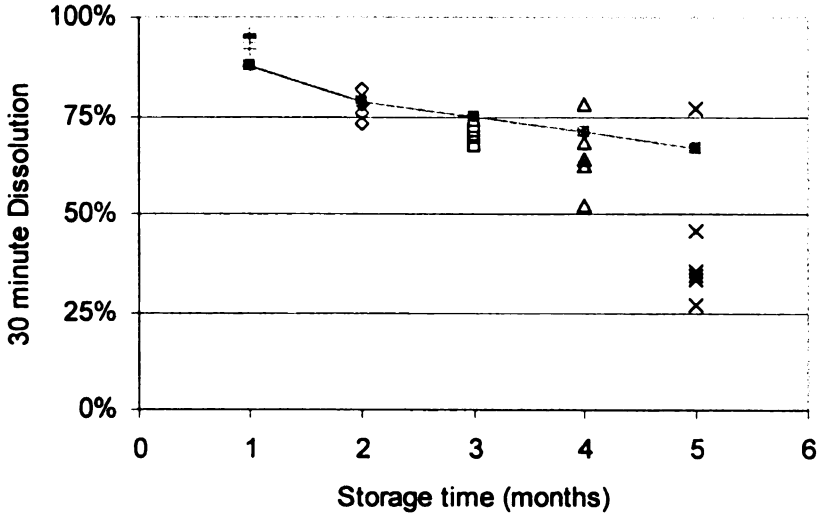
[96.23% (initial dissolution) – 8.4% change for 1 month at 50% – 9.4% change for 1 month at 65% – 7.5% change for 2 months at 75%] = 70.93%

The dissolution decreases to 70.93% from 96.23%.

Table 18 also shows the effect of storage time. Compare rows 3, 4 and 6. In all three rows, the tablets were stored in open dish at 50% and 65% RH for 1 month each. But they were stored at 75% RH for 1, 2 and 3 months respectively. The tablets reached equilibrium with 75% RH within 2-3 days. They remained at equilibrium for 1, 2 and 3 months. The increased time at 75% equilibrium resulted in progressively lower dissolution: 69%, 63%, 42%. This is strong evidence that the dissolution is time dependent and that this dependence is not linear. Similarly, rows 5 and 7 of Table 18

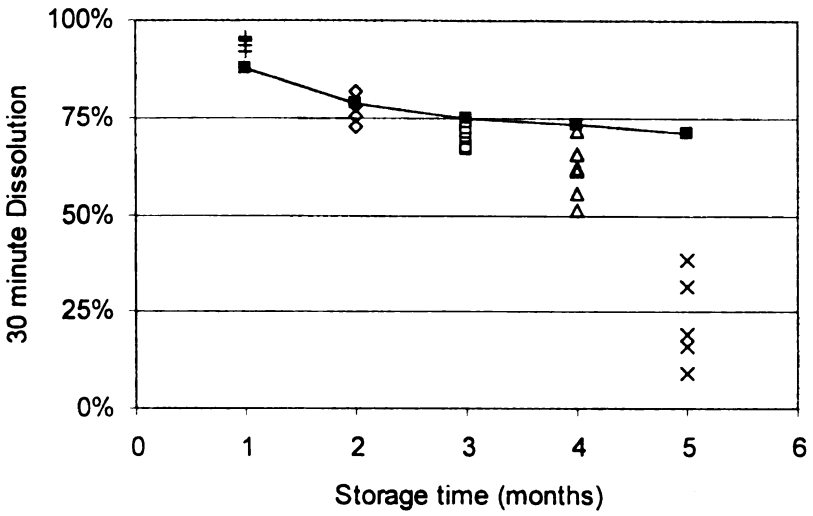
show the effect of time at equilibrium at another relative humidity (90%). Here dissolution changed from 61% after 1 month to only 26% after 2 months at 90%.

Figure 52 and Figure 53 show the experimental and predicted dissolution. They show there is fairly good agreement until 4 months. However, beginning at 4 months storage time, the experimental and predicted results diverge sharply. At that time, high moisture absorption may accelerate the physical interaction such as crosslinking among excipients. Perhaps there is a threshold level of interaction between time and moisture content. This mechanism must be explained in the future.



+ dissolution stored at 50% for 1 month, ◇ dissolution stored at 50% for 1 month and 65% for 1 month, □ dissolution stored at 50% for 1 month, 65% for 1 month, and 75% for 1 month, △ dissolution stored at 50% for 1 month 65% for 1 month and 75% for 2 months, × dissolution stored at 50% for 1 month, 65% for 1 month, and 75% for 3 months, —■— dissolution calculated by the dissolution prediction program

Figure 52 Dissolution of tablets stored at stepwise conditions (I) at 40°C



+ dissolution stored at 50% for 1 month, ◇ dissolution stored at 50% for 1 month and 65% for 1 month, □ dissolution stored at 50% for 1 month, 65% for 1 month, and 75% for 1 month, △ dissolution stored at 50% for 1 month, 65% for 1 month, 75% for 1 month, and 90% for 1 month, × dissolution stored at 50% for 1 month, 65% for 1 month, 75% for 1 month, and 90% for 2 months, —■— dissolution calculated by the dissolution prediction program

Figure 53 Dissolution of tablets stored at stepwise conditions (II) at 40°C

Open dish storage at 40°C with stepwise transition from one humidity to the next higher one reveals an interaction among moisture content, relative humidity and time that has not yet been fully explained. The prediction methods developed in this work do not account for this unexplained mechanism. However, when the product is packaged in a container closure system, and stored at a single temperature and humidity, for example 40°C, 75% RH, the resulting dissolution can be predicted fairly well using the technique described here. The following section on continuous storage conditions explains this.

(2) Continuous storage conditions

Uncoated tablets stored in LDPE bags and HDPE bottles at 40°C/90% RH were also used to verify the dissolution prediction program. The relative humidity of the package headspace in the LDPE bags and HDPE bottles changed quickly, so one day time intervals were used to calculate the dissolution at those relative humidities. The dissolution calculated using the dissolution retardation rate (R) shows fairly good agreement with experimentally measured trends in dissolution as shown in Figures 54-59. Table 20 shows dissolution differences between experimentally measured dissolution and predicted dissolution. They may occur from the 30 minute dissolution variability. The dissolution of aged uncoated tablets at 40°C/75%, 65%, and 50% RH has a large variation (see Figures 40-43). So, dissolution retardation rates determined from that data can cause error.

Table 20 Dissolution differences between experimentally measured average dissolution and predicted dissolution of tablets in package stored at 40°C/90% RH

		Storage time (days)					
		44	58	83	104	136	161
Tablets in LDPE bags without desiccant	D_{exp}	75.7%	80.0%	77.3%			
	D_{calc}	90.8%	89.8%	88.1%			
	$D_{difference}$	15.1%	9.8%	10.8%			
	% $D_{difference}$	19.9%	12.3%	14.0%			
Tablets in LDPE bags with 0.5 g desiccant	D_{exp}		80.3%	71.7%			
	D_{calc}		88.1%	86.1%			
	$D_{difference}$		7.8%	14.4%			
	% $D_{difference}$		9.7%	20.1%			
Tablets in LDPE bags with 1 g desiccant	D_{exp}		78.5%	72.8%			
	D_{calc}		87.5%	84.7%			
	$D_{difference}$		9.0%	11.9%			
	% $D_{difference}$		11.5%	16.3%			
Tablets in LDPE bags with 2 g desiccant	D_{exp}		86.3%	70.0%			
	D_{calc}		87.5%	84.7%			
	$D_{difference}$		1.2%	14.7%			
	% $D_{difference}$		1.4%	21.0%			
Tablets in HDPE bottles without desiccant	D_{exp}		86.4%	80.0%	76.6%	57.2%	46.0%
	D_{calc}		83.9%	76.6%	70.4%	62.5%	57.6%
	$D_{difference}$		-2.5%	-3.4%	-6.2%	5.3%	11.6%
	% $D_{difference}$		-2.9%	-4.3%	-8.1%	9.3%	25.2%
Tablets in HDPE bottles with 0.5 g desiccant	D_{exp}		96.2%	96.7%	96.4%	93.2%	91.2%
	D_{calc}		96.2%	96.1%	94.5%	88.5%	81.8%
	$D_{difference}$		0%	-0.6%	-1.9%	-4.7%	-9.4%
	% $D_{difference}$		0%	-0.6%	-2.0%	-5.0%	-10.3%

D_{exp}: Experimentally measured average dissolution
D_{calc}: Predicted dissolution
$D_{difference}$: Difference in dissolution between D_{exp} and D_{calc} (D_{calc} - D_{exp})
% $D_{difference}$: % Dissolution difference from experimentally measured average dissolution ($D_{difference}/D_{exp} \times 100$)

The moisture content of tablets increased as a function of storage time, and dissolution decreased as a function of the moisture content of tablets and storage time. Figures 54-59 show relative humidity (dotted line) of the package headspace, experimentally measured dissolution (dots), and predicted dissolution (solid line) of

tablets in LDPE bags and HDPE bottles. The following shows an example dissolution calculation using the dissolution retardation rate determined at each relative humidity.

Example calculation: 15 tablets in LDPE bags stored at 40℃/90% RH

At storage time 0, the dissolution at 30 minutes stirring time is:

$$D(\%) = -96.23\% \cdot e^{0} + 96.23\% + 100\% = 100\%$$

After 1 day, the relative humidity of the LDPE package headspace is 45.61%. So, the dissolution at that RH (%) is changed to 99.81% for 1 day. The dissolution decreases by 0.19% from the initial dissolution.

$$D(\%) = -96.23\% \cdot e^{[0.0001776 \times 45.61 - 0.00608] \cdot 1} + 96.23\% + 100\% = 99.81\%$$

After 2 days, the relative humidity of the LDPE package headspace is 52.57%. So, the dissolution at that RH (%) is changed to 99.73% for 1 day. The dissolution decreases by 0.27% from the initial dissolution, and so on.

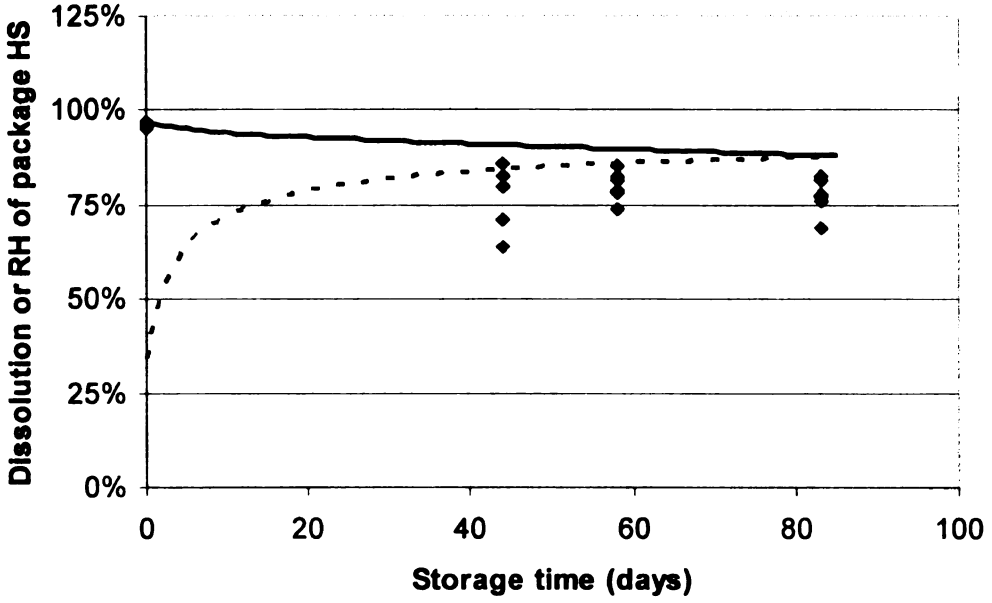
$$D(\%) = -96.23\% \cdot e^{[0.00002 \times 52.57 + 0.0018] \cdot 1} + 96.23\% + 100\% = 99.73\%$$

After 3, 4, 5, and 6 days, the relative humidities of the LDPE package headspace are 57.35%, 60.89%, 63.65%, and 65.88%. The dissolution decreases by 0.28%, 0.29%, 0.30%, and 0.30% at each relative humidity.

For 6 days, the accumulated dissolution change is 1.63% (0.19% + 0.27% + 0.28% + 0.29 + 0.30% + 0.30%). Therefore, the dissolution decreases to 94.60% from 96.23%.

(a) Tablets in LDPE bags without silica gel and tablets with silica gel (0.5 g, 1 g, and 2 g) stored in LDPE bags at 40°C/90% RH

Figure 54 shows results from LDPE bags without silica gel. The predicted relative humidity of the package headspace changed quickly. Tablets reach 75% RH in 13 days. Table 21 shows experimentally measured and predicted dissolution of tablets at the 30 minute stirring time, and relative humidity of the package headspace.



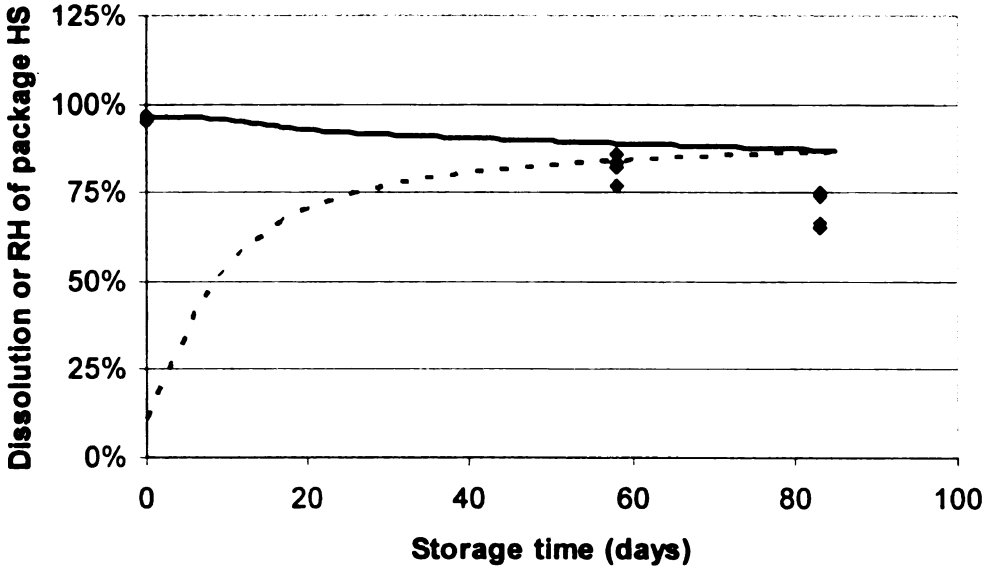
◆ Experimentally measured dissolution ----- Relative humidity of the package headspace ━ Predicted dissolution using the dissolution retardation rate (*R*)

Figure 54 Dissolution of tablets in LDPE bags stored at 40°C/90% RH as a function of storage time

Table 21 Experimentally measured and predicted dissolution of tablets at 30 minutes stirring time as a function of storage time (tablets stored in LDPE bag without desiccant)

Storage time (days)	Experimental Dissolution (%)							Predicted Dissolution (%)	Predicted RH (%)
	1	2	3	4	5	6	Avg.		
44	79.9	70.9	63.6	86.1	71.0	82.8	75.7	90.8	84.5
58	85.1	78.3	81.8	82.4	73.7	78.7	80.0	89.8	86.0
83	81.4	82.7	76.1	77.1	69.1	77.8	77.4	88.1	87.6

Figure 55 shows results from LDPE bags with 0.5 g silica gel. Tablets desorbed moisture initially, and again reached the initial moisture content after 5 days. The dissolution is assumed not to change for 5 days. When the dissolution prediction program was run, the dissolution for the first 5 days was calculated as equal to the initial dissolution. Table 22 shows experimentally measured and predicted dissolution of tablets at the 30 minute stirring time, along with the relative humidity of the package headspace.



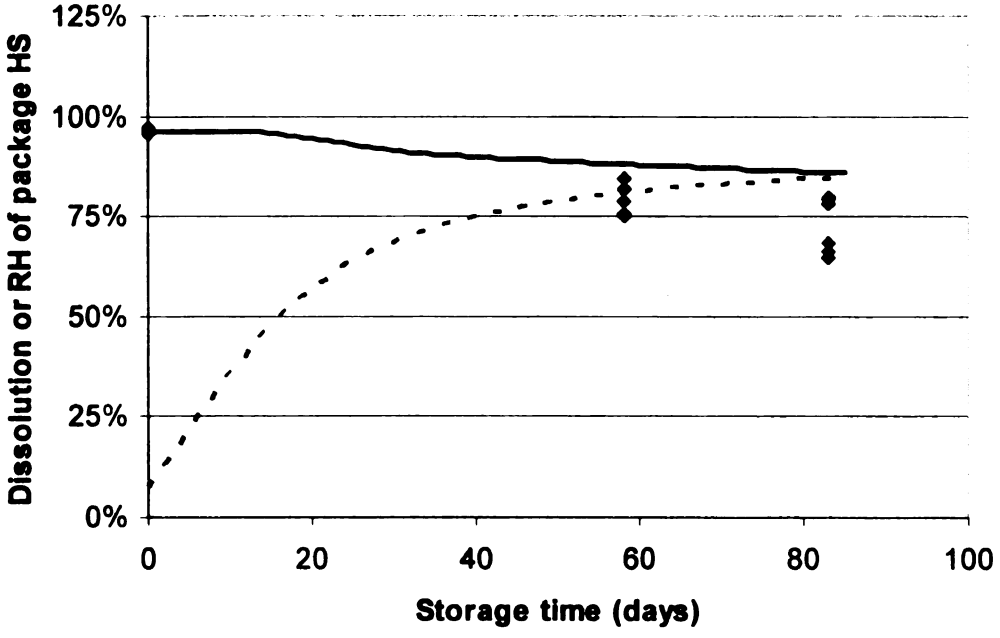
◆ Experimentally measured dissolution ----- Relative humidity of the package headspace ━ Predicted dissolution using the dissolution retardation rate (*R*)

Figure 55 Dissolution of tablets in LDPE bags containing 0.5 g silica gel stored at 40°C/90% RH as a function of storage time

Table 22 Experimentally measured and predicted dissolution of tablets at 30 minutes stirring time as a function of storage time (tablets in LDPE bag containing 0.5 g silica gel)

Storage time (days)	Experimental Dissolution (%)							Predicted Dissolution (%)	Predicted RH (%)
	1	2	3	4	5	6	Avg.		
58	82.2	77.0	85.6	77.1	83.3	76.8	80.3	88.9	84.1
83	74.0	65.4	74.2	74.9	75.3	66.6	71.7	87.1	86.5

Figure 56 shows results from LDPE bags with 1 g silica gel. Tablets desorbed moisture initially, and again reached the initial moisture content after 10 days. The dissolution is assumed not to change for 10 days. When dissolution prediction program was run, the dissolution for the first 10 days was calculated as equal to the initial dissolution. Table 23 shows experimentally measured and predicted dissolution of tablets at the 30 minute stirring time, along with the relative humidity of the package headspace.



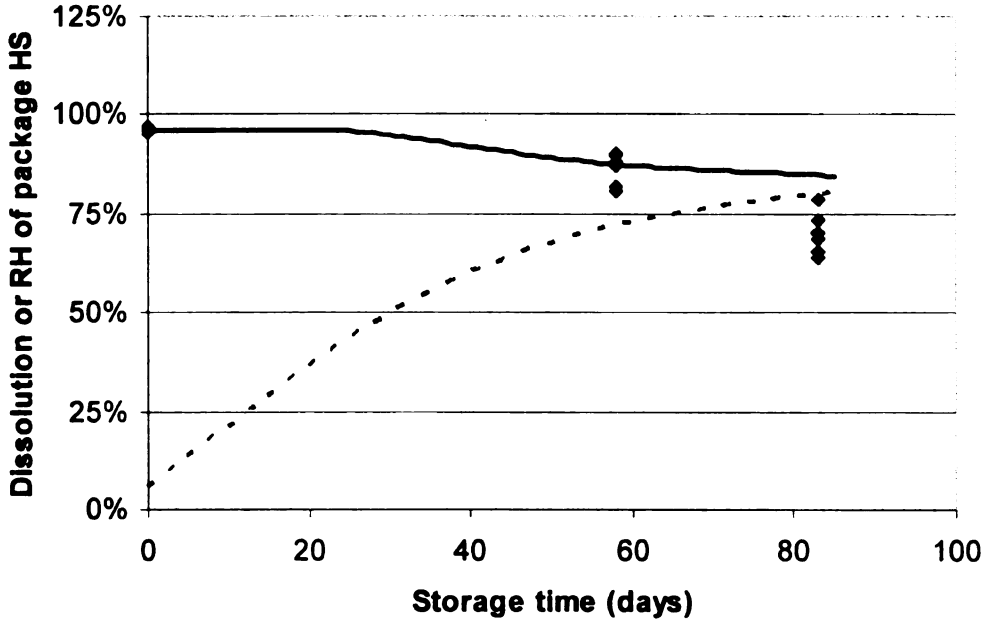
◆ Experimentally measured dissolution ----- Relative humidity of the package headspace ━ Predicted dissolution using the dissolution retardation rate (*R*)

Figure 56 Dissolution of tablets in LDPE bags containing 1 g silica gel stored at 40°C/90% RH as a function of storage time

Table 23 Experimentally measured and predicted dissolution of tablets at 30 minutes stirring time as a function of storage time (tablets in LDPE bag containing 1 g silica gel)

Storage time (days)	Experimental Dissolution (%)							Predicted Dissolution (%)	Predicted RH (%)
	1	2	3	4	5	6	Avg.		
58	78.6	75.3	81.8	84.6	75.4	75.1	78.5	88.1	81.0
83	66.2	80.1	64.6	68.4	79.4	78.0	72.8	86.1	84.8

Figure 57 shows results from LDPE bags with 2 g silica gel. Tablets desorbed moisture initially, and again reached the initial moisture content after 19 days. The dissolution is assumed not to change for 19 days. When dissolution prediction program was run, the dissolution for the first 19 days was calculated as equal to the initial dissolution. Table 24 shows experimentally measured and predicted dissolution of tablets at the 30 minute stirring time, along with the relative humidity of the package headspace.



◆ Experimentally measured dissolution ----- Relative humidity of the package headspace ━ Predicted dissolution using the dissolution retardation rate (*R*)

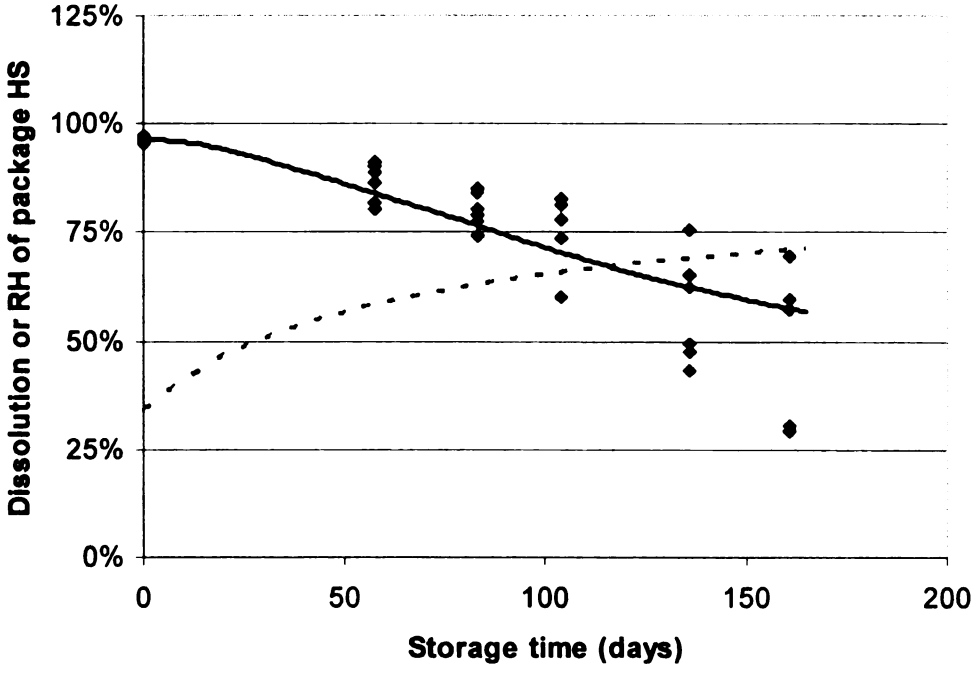
Figure 57 Dissolution of tablets in LDPE bags containing 2 g silica gel stored at 40°C/90% RH as a function of storage time.

Table 24 Experimentally measured and predicted dissolution of tablets at 30 minutes stirring time as a function of storage time (tablets in LDPE bag containing 2 g silica gel)

Storage time (days)	Experimental Dissolution (%)							Predicted Dissolution (%)	Predicted RH (%)
	1	2	3	4	5	6	Avg.		
58	88.2	80.9	90.1	89.6	81.9	87.0	86.3	87.5	72.1
83	78.7	63.6	73.4	70.1	68.5	65.5	70.0	84.7	80.1

(b) Tablets in HDPE bottles without silica gel and tablets with 0.5 g silica gel stored in HDPE bottles at 40°C/90% RH

Even if tablets were packaged in relatively high barrier HDPE bottles, the dissolution decreased a lot in 160 days. Figure 58 shows the predicted relative humidity of the package headspace as a function of storage time. Predicted dissolution using the dissolution retardation rate is in the range of experimentally measured dissolution of tablets in HDPE bottles without silica gel. Table 25 shows measured and predicted dissolution of tablets at the 30 minute stirring time.



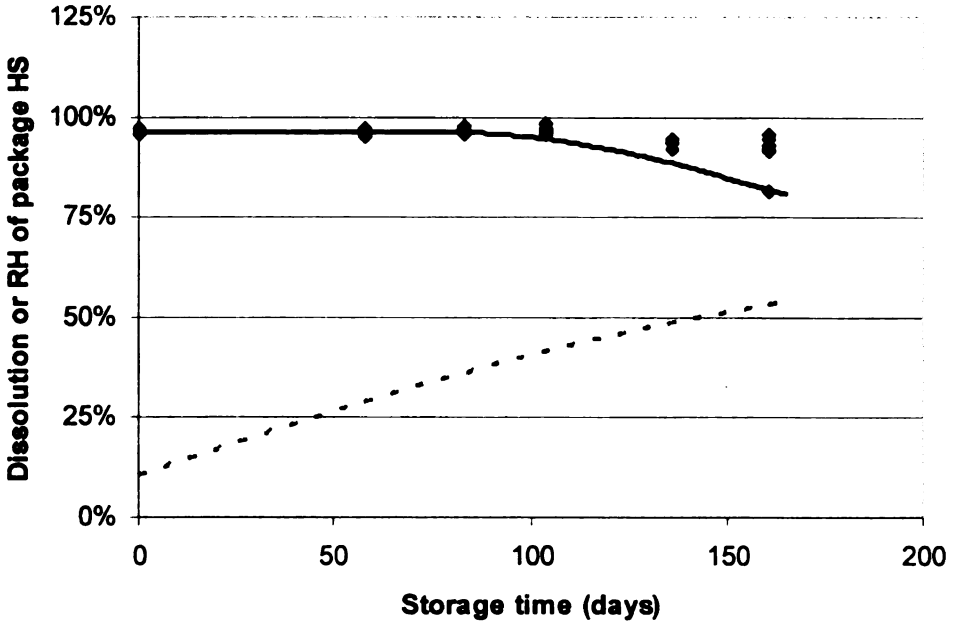
◆ Experimentally measured dissolution ----- Relative humidity of the package headspace ━ Predicted dissolution using the dissolution retardation rate (R)

Figure 58 Dissolution of tablets in HDPE bottles stored at 40°C/90% RH as a function of storage time.

Table 25 Experimentally measured and predicted dissolution of tablets at 30 minutes stirring time as a function of storage time (tablets in HDPE bottle without desiccant)

Storage time (days)	Experimental Dissolution (%)							Predicted Dissolution (%)	Predicted RH (%)
	1	2	3	4	5	6	Avg.		
58	81.5	91.2	90.2	88.7	80.3	86.5	86.4	83.9	58.5
83	74.2	78.9	77.8	80.2	84.0	84.9	80.0	76.6	63.1
104	78.2	60.3	82.9	81.2	74.0	82.8	76.6	70.4	65.9
136	62.3	75.7	65.3	49.4	43.3	47.4	57.2	62.5	69.2
161	29.4	59.7	57.4	30.5	69.6	29.6	46.0	57.6	71.2

Figure 59 shows results from HDPE bottles with 0.5g silica gel. Tablets desorbed moisture initially, and again reached the initial moisture content at 75 days. The dissolution is assumed not to change for 75 days. Figure 59 shows dissolution changes using the dissolution retardation rate are a little over estimated for tablets in HDPE bottle containing 0.5 g silica gel. Table 26 shows experimentally measured and predicted dissolution of tablets at the 30 minute stirring time.



◆ Experimentally measured dissolution ----- Relative humidity of the package headspace ━ Predicted dissolution using the dissolution retardation rate (*R*)

Figure 59 Dissolution of tablets in HDPE bottles containing 0.5 g silica gel stored at 40°C/90% RH as a function of storage time.

Table 26 Experimentally measured and predicted dissolution of tablets at 30 minutes stirring time as a function of storage time (tablets in HDPE bottle containing 0.5 g silica gel)

Storage time (days)	Experimental Dissolution (%)							Predicted Dissolution (%)	Predicted RH (%)
	1	2	3	4	5	6	Avg.		
58	97.2	96.5	96.4	96.7	95.4	95.3	96.2	96.2	29.1
83	97.1	97.1	96.2	96.2	95.7	97.7	96.7	96.1	36.2
104	95.5	96.9	95.9	96.5	95.7	98.1	96.4	94.5	41.6
136	94.4	93.5	92.0	93.7	93.4	92.2	93.2	88.5	48.6
161	91.4	92.8	91.7	81.4	95.6	94.3	91.2	81.8	53.2

4. Proposed theory of dissolution retardation as a function of relative humidity

The phenomenon of dissolution change as a function of RH and storage time is better understood if we develop a model for dissolution retardation. The mechanism of tablets aging as a function of storage time at a certain amount of moisture content has not been understood in terms of physical interactions among excipients. In this section, a theory of drug X dissolution retardation as a function of relative humidity is proposed.

Drug X tablets consist of 63% mannitol and 18% microcrystalline cellulose (MCC). Mannitol is a saccharide derivative. Mannitol may be crosslinked by absorbing moisture. Sugars are generally hydrophilic and therefore interact readily with water. The physical form of the sugar affects the interaction of the saccharide with water (Derbyshire et al., 2001).

Tablet crosslinking may affect tablet hardness and dissolution. In this experiment, the dissolution of tablets stored above 50% RH at 40°C decreased as a function of storage time. The reason for the dissolution reduction may be that the structure inside the tablets was changed. Tablets might be crosslinked above 50% RH at 40°C. The crosslinking occurs through increase of intermolecular forces among excipients, and these may become stronger as a function of storage time.

The dissolution did not decrease for tablets stored at 25°C at 0, 50, 65, 75, and 90% RH. Based on the above explanation, tablets may be crosslinked above 50% RH at 25°C, but the intermolecular forces of tablets stored at 25°C may not be as strong as those of tablets stored at 40°C. In fact, they may be not strong enough to affect crosslinking and dissolution during the 6 months time of this experiment. The interaction of

temperature and moisture may accelerate the crosslinking of tablets, then it may increase intermolecular forces.

Also, cellulose can form a large aggregate structure held together by hydrogen bonding (Nakai, 1977). This may increase the intermolecular forces among excipients. Figure 60 shows hardness as a function of relative humidity and Figure 61 shows the 30 minute dissolution as a function of relative humidity. Together, they show the dissolution of harder tablets is low. The hardness may increase if intermolecular forces are increased. Tablets having strong intermolecular forces are disintegrated slowly, so the dissolution at the 30 minute stirring time is low. As intermolecular forces decrease at even higher RH, the tablet softens and dissolution increases. Thus, there is peak in intermolecular forces around 45-65% RH at 40°C. At the same conditions, the hardness reaches a maximum and dissolution reaches a minimum.

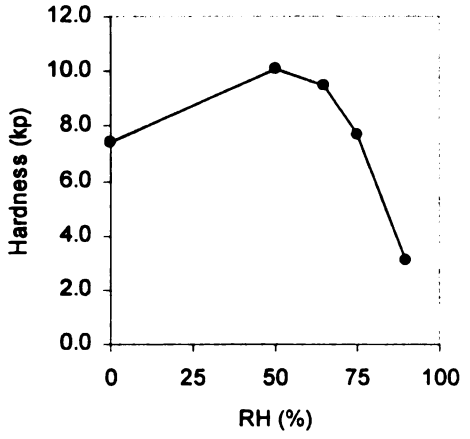


Figure 60 The hardness of uncoated tablets stored for 6 months at 40°C as a function of relative humidity

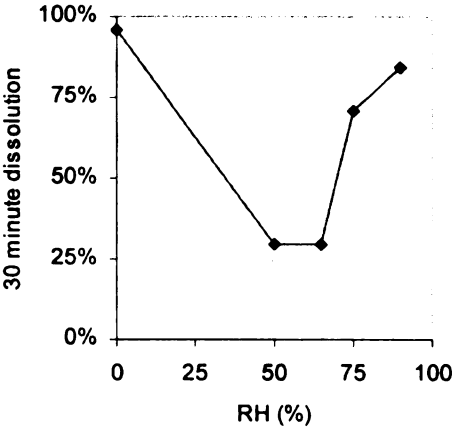


Figure 61 30 minute dissolution of uncoated tablets stored for 6 months at 40°C as a function of relative humidity

Also, drug X tablets swell above 50% RH as described in Appendix F (see Figure 96 and Figure 99). Drug X tablets are formulated with a hygroscopic swellable material (croscarmellose sodium (CAS)).

Tablets stored in the range of 50-65% RH at 40°C have the greatest hardness value as shown in Figure 60, and water in tablets may be bound directly to polymer units. While tablets stored in the range of 75-90% RH at 40°C have the smallest hardness value, they contain much more water that may be used for hydrogen bonding (water-water and water-polymer). Therefore, they may be crosslinked much more than tablets stored in the range of 50-65% RH. However, they can also swell much more than tablets stored in the range of 50-65% RH. The swelling may counteract crosslinking among excipients. Therefore, it may offset intermolecular forces in tablets stored at 75-90% RH.

If excipients in the tablet are crosslinked with each other, intermolecular forces among excipients may increase, then tablets are hard to disintegrate into the medium. However, when CAS in the tablet swells, intermolecular forces among excipients may decrease, finally tablets disintegrate readily into the medium. It may be that the dissolution of tablets stored at 40°C/65% RH decreased most rapidly as a function of storage time because excipients were crosslinked but they did not swell much (1.5% swelling). On the other hand, the dissolution of tablets stored at 40°C/90% RH decreased less even if tablets may be crosslinked much more than those stored at 40°C/65% RH because they swelled a lot (by 4.2% of the thickness of tablets).

CHAPTER 5

PACKAGE DESIGN

Based on the open dish study, it was found that the dissolution of drug X, both coated and coated tablets, was very sensitive to temperature and moisture. The dissolution of both uncoated and coated tablets at the 30 minute stirring time did not change at all at 25°C at 0, 50, 65, 75, and 90% RH for 6 months, but it declined at 40°C 50, 65, 75, and 90% RH for 6 months. The dissolution of both coated and uncoated tablets was not reduced when stored at 40°C, 0% RH for 6 months.

Uncoated tablets in the HDPE bottle containing 0.5 g silica gel did not reach initial equilibrium RH for 3 months, and the dissolution was not reduced below the initial equilibrium RH (34.23%) (see Figure 59). Even though there is no 6 month dissolution data from the open dish study between 0% RH and initial RH (34.23%), it is assumed that the dissolution of drug X uncoated tablets stored below initial conditions does not change for 6 months at 40°C in this study. So, a zero value of the dissolution retardation rate is applied to calculate the dissolution of tablets between 0% RH and the initial equilibrium RH (34% RH).

The dissolution of tablets in open dishes stored at 25°C at 0, 50, 65, 75, and 90% RH did not change significantly for 6 months, so dissolution retardation rates could not be determined. The 6 month accelerated testing is used as an indication of the 24 month long-term testing.

Assume a company wants to select a package for NDA registration stability testing. They want drug X tablets to be safe for 6 months at accelerated testing (40°C±2°C/75% RH±5%) and 24 months at long-term testing (25°C±2°C/60% RH±5%).

available packages are Aclar blister, and 50 mL HDPE bottles, with 0.5 g, 1 g, or 2 g
gel canisters.

Aclar blister (PVC/2 mil PE/0.6 mil Aclar, P = 0.00058404 g/day·cavity·p_s at 40°C)

The permeability of this Aclar blister was obtained from previous work at the
ool of Packaging. The first example assumes that one tablet (W_d = 250 mg) is
erted into one blister cavity. For the blister package, it is impossible to use silica gel
siccant, so the relative humidity of Aclar blister headspace will increase from the initial
uilibrium relative humidity as shown in Figure 62. The tablet reaches equilibrium with
e environmental condition (40°C/75%) in 180 days based on the moisture prediction
rogram. The relative humidity inside the package is changed from initial to equilibrium
RH as a function of storage time. Dissolution at each relative humidity between initial
and equilibrium RH is calculated by the dissolution prediction program using 1 day time
interval iterations. The tablet is predicted to reach the specification limit 75% dissolution
in 50 days. Therefore, the Aclar blister is predicted to not be a suitable package for drug
X tablets.

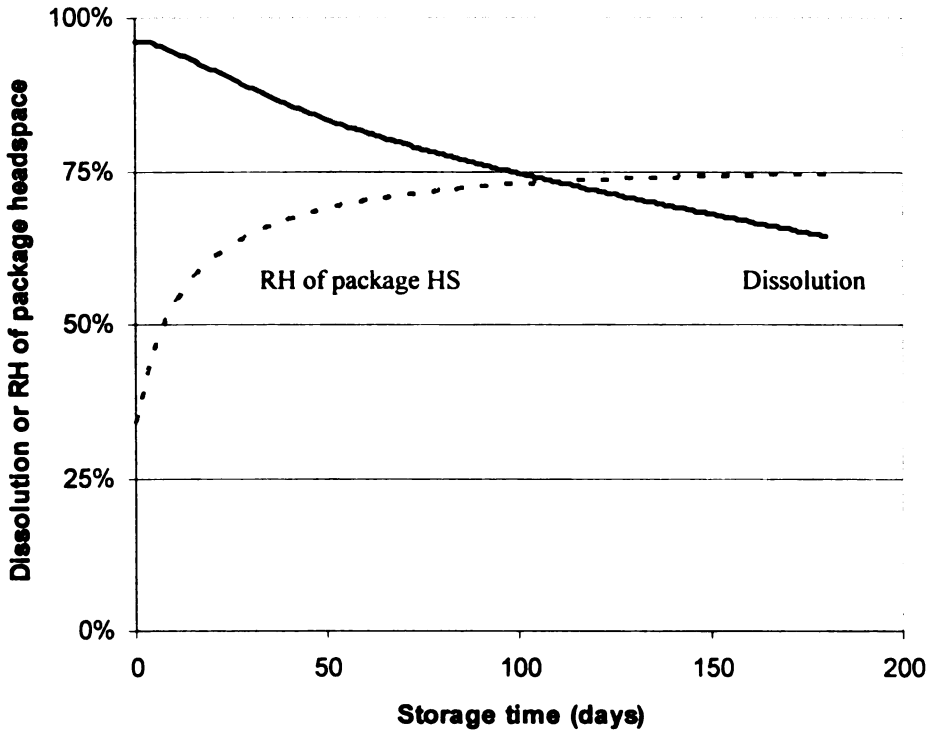


Figure 62 RH of Aclar blister headspace calculated by the moisture prediction program and 30 minute dissolution calculated by the dissolution prediction program as a function of storage time.

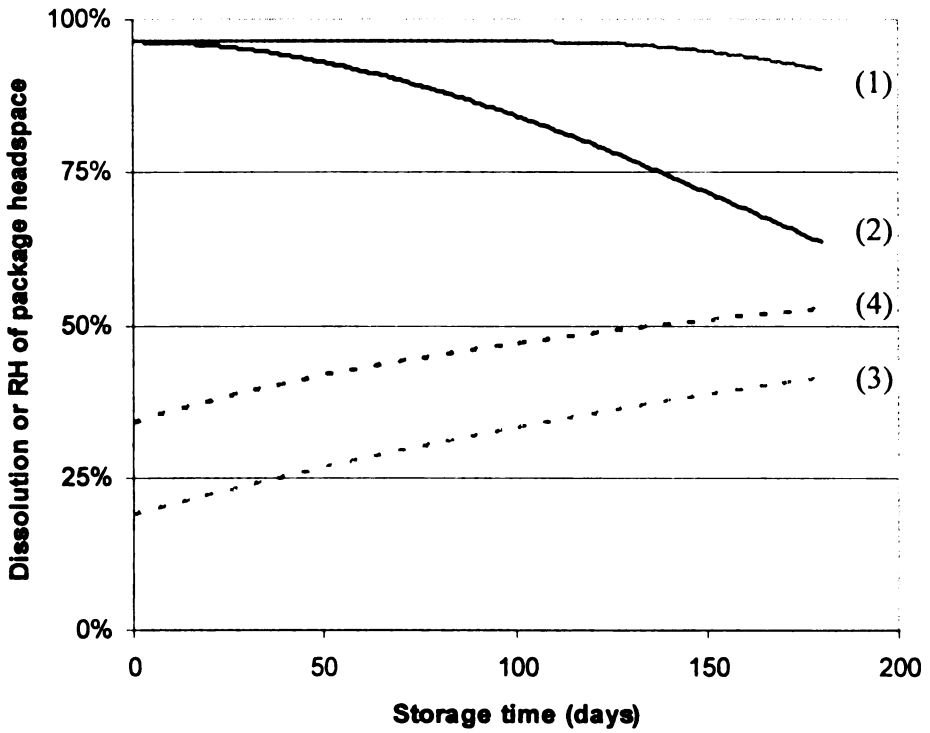
2. HDPE bottle (50 mL, P = 0.0016 g/day·pkg·p_s at 40°C)

First, assume that 50 tablets (W_d = 12.5 g) are inserted into the HDPE bottle without desiccant. The relative humidity of the package headspace reaches 52.7% equilibrium RH in 6 months based on the moisture prediction program. Dissolution behavior at various moisture contents is calculated by the dissolution prediction program using 1 day time interval iterations. The prediction is that dissolution significantly changes for 6 months (see Figure 63), so the HDPE bottle without any amount of desiccant is not a suitable package for drug X tablets.

Second, it is assumed that 0.5 g silica gel is inserted into HDPE bottles containing 50 tablets (W_d = 12.5 g). The RH of the package headspace reaches 41.30% at 6 months

based on the moisture prediction program, and the dissolution reaches 79.54% at 6 months based on the dissolution prediction program (see Figure 63).

Based on the above trials, the package for drug X tablets can be designed. If a 0.5 g silica gel canister is inserted into HDPE bottle containing 50 tablets, tablets are predicted to be safe in terms of dissolution at the accelerated testing condition (40°C/75%) for 6 months.



Curves (1) and (2) represent the 30 minute dissolution: (1) 12.5g tablets in HDPE bottle with 0.5 g silica gel (2) 12.5g tablets in HDPE bottle without silica gel
Curves (3) and (4) represent the RH of the package headspace: (3) 12.5g tablets in HDPE bottle with 0.5 g silica gel (4) 12.5g tablets in HDPE bottle without silica gel

Figure 63 RH of the HDPE bottle headspace calculated by the moisture prediction program and 30 minute dissolution calculated by the dissolution prediction program as a function of storage time

3. Permeability calculation

The package permeability required to maintain dissolution above the 75% specification for drug X tablets stored for 6 months at 40°C/75% RH can be determined. To do so, calculate the required permeability by trial and error using the moisture and dissolution prediction programs.

Parameters used to calculate the permeability using moisture and dissolution prediction programs

- Solids
  - Dry weight: 12.5 g (tablets)
  - Initial moisture content: 1.9312% (tablets)
  - Sorption isotherm equations: GAB constants (W_m: 0.013392, C_g: 113.2096, K: 0.933012) for tablets
- Package
  - Volume: 0.05 L
- Storage condition
  - Temperature at packaging line: 25°C
  - Relative humidity at packaging line: 40%
  - Temperature at storage: 40°C
  - Relative humidity at storage: 75%
  - Storage time: 180 days

If a package permeability of 0.0004 g/day·pkg·p_s is used for drug X tablets, the package can maintain the dissolution of tablets above 75% for 6 months at 40°C/75% RH. Figure 64 shows the dissolution and relative humidity of the package headspace change for 6 months.

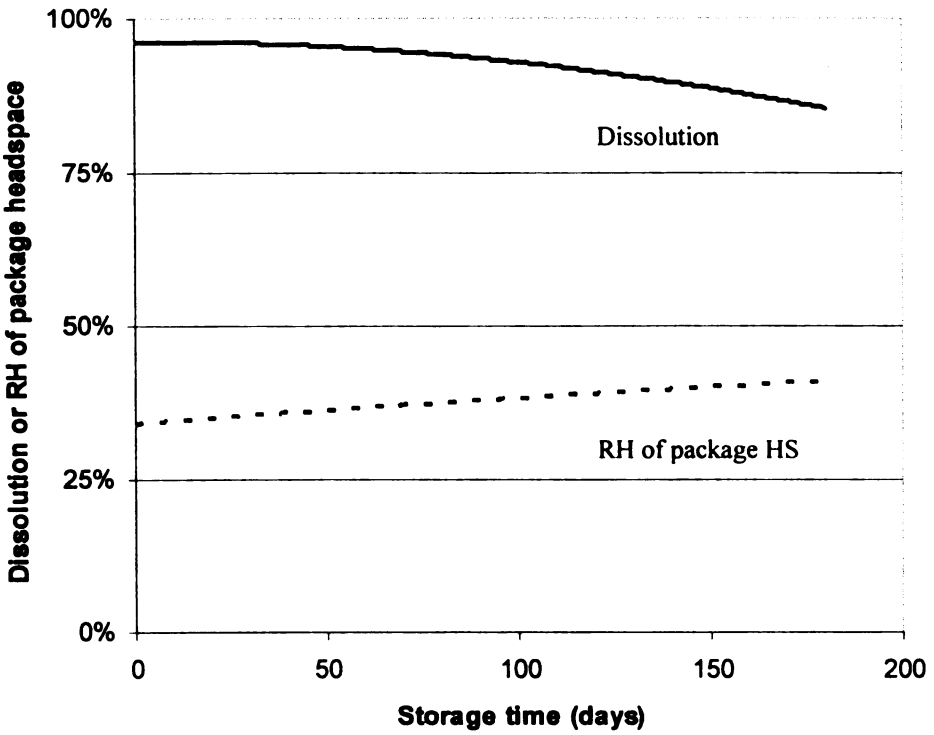


Figure 64 RH of a package (P=0.0004 g/day·pkg·p_s) headspace calculated by the moisture prediction program and 30 minute dissolution calculated by the dissolution prediction program as a function of storage time

The calculated package permeation (0.0004 g/day·pkg·p_s) required is about four times lower than 50 mL HDPE bottle permeability (0.0016 g/day·pkg·p_s). This barrier package may be very costly, so it may be not a good choice to package drug X tablets. In this case, HDPE bottle with 0.5 g silica gel may be a better choice.

CHAPTER 6

CONCLUSIONS AND FUTURE WORK

By using an open dish study in this experiment, it was found that coated and uncoated tablets dissolve differently as a function of storage RH. Dissolution of coated and uncoated tablets stored at 40°C/90% and 0% RH is still high at 6 months storage time because tablets swell at 90% RH and there may be no physical interactions at 0% RH. However, dissolution of coated and uncoated tablets stored at 40°C at 75%, 65%, and 50% RH decreases rapidly during 6 months of storage time because they may be degraded physically such as crosslinking among excipients.

Also, the dissolution variability from six dissolution values of uncoated tablets stored at 40°C at 90% and 0% RH is small, but the dissolution variability at 40°C at 75%, 65%, and 50% RH is very large (see Table 16 on page 78). Apparently, high temperature dissolution behavior can be grouped in two different patterns. One group (40°C at 75%, 65% and 50% RH) has rapid dissolution change during a 6 month period, so these are not good conditions for storage of tablets. The other group (40°C at 90% and 0%) can maintain tablets at a high dissolution value for 6 months but tablets stored at 90% RH are failed with hardness. Uncoated tablets stored below the initial RH at 40°C show no dissolution change for 3 months (see Figure 59 on page 107). Therefore, it can be concluded that drug X coated and uncoated tablets would best be maintained below the initial RH at the 40°C storage condition.

The dissolution of drug X coated tablets stored in open dishes at 40°C behaved very differently in comparison with that of drug X uncoated tablets. The coated tablets

did not follow the dissolution theory (S-shaped dissolution change as a function of stirring time). Aged coated tablets did not disintegrate rapidly. They took some longer time to start to disintegrate. They swelled without any disintegration. The coating material was observed to behave like a plastic film. This means the coating material may be degraded either chemically or physically. When aged coated tablets started to disintegrate, the coating material broke open suddenly. After that, aged coated tablets disintegrated rapidly. Therefore, the dissolution of coated tablets at the 30 minute stirring time did not change regularly as a function of storage time.

By using the open dish study in this experiment, the relationships between RH (or moisture) and tablets' physical properties such as dissolution and hardness were determined more quickly than doing stability testing. It was found that the dissolution of drug X tablets was dependent on temperature, moisture content, and storage time. In order to determine the relationship between moisture and dissolution, Nakabayashi's method was tried, but his model did not work well for drug X tablets because of dissolution variability.

A different approach was developed by using the dissolution retardation rate (R). The 30 minute dissolution was plotted as a function of storage time at each relative humidity. Based on empirical data fitting using a first order kinetic method, dissolution retardation rates were determined at each relative humidity. Dissolution retardation rates were plotted with RH, and then a dissolution prediction model (Equation 20) was developed based on that relationship. The dissolution can be calculated simply at any RH and storage time by using Equation 20. The relative humidity of the package headspace changes during the unsteady state, so the dissolution of tablets stored at that condition is

ard to calculate. Therefore, the dissolution prediction computer program was developed sing the Visual Basic program language.

Dissolution retardation rates for drug X coated tablets could not be determined in his study because they did not behave according to the dissolution theory.

Dissolution results from the dissolution prediction program were compared with the experimental results to verify the program. There is fairly good agreement between experimental and predicted dissolution. However, the dissolution prediction program still needs more verification with other products.

As a necessary tool for the dissolution prediction program, a mathematical model calculating the time required to reach final moisture content was also developed. The model was developed using piecewise linear equations, which could work for any number of components in a package. And, the simple approach calculating the moisture content of components (any number of components) as a function of storage time was developed. Based on the new mathematical models, moisture and shelf life prediction computer programs were developed using the Visual Basic program language (see Appendix B). The moisture content and the time required to reach final moisture content of drug X tablets were predicted by using the moisture and shelf life prediction programs. These programs were verified based on the experimental data. The prediction programs worked well for both one component and two components in packages such as LDPE bags and HDPE bottles, and they should work for even more than two components in a package.

In this study, a small amount of tablets (15 tablets, 3.75g) was used to verify the moisture and shelf life prediction programs. In the future, it should be verified for bulk

packages (e.g., 100,000 tablets, 25kg) too. The moisture and shelf life prediction programs should work for bulk packages but the bulk package must be represented by some assumptions (see Appendix B for several major assumptions). The equilibrium between moisture and the solid component inside the package should be reached quickly. In other words, there should be no gradient of water vapor in the solid component. If this assumption is satisfied, the moisture and shelf life prediction programs can be used for bulk package too.

By using the moisture and dissolution prediction programs, a package for NDA stability testing can be designed as explained in Chapter 5. Package design. An open dish study was done for 6 months to determine the relationship between dissolution and moisture content of tablets, and it was used to design a package to make drug X tablets survive at 40°C/75% RH for 6 months. It seems this is not a useful method because 6 months time was spent to design a package for 6 months accelerated testing. However, this still can be very useful to select a package without any trial and error approach for stability testing, and also many situations can be simulated using different permeabilities and storage conditions. Until now, there were no good models to select a package for the registration stability testing in terms of dissolution. Now, the correct barrier package can be selected with greater confidence. The prediction programs cannot be an absolute tool yet, but they can be useful when further refined to determine a package prior to the registration stability testing.

It is recommended that the open dish study work be done during drug development and well before the time when stability tests must be started. Then the calculation of required barrier can be made in a timely manner. Furthermore, if the open

dish data are available when a change in packaging is required for marketing, the choice of package barrier can be done quickly.

In the future, if a protocol for open dish study is established for every new product, a barrier package can be selected confidently based on parameters already established during product development. Also, if the mechanism of tablet aging as a function of RH and storage time is explained, it will be very helpful in understanding the relationship between the dissolution retardation rate (R) and RH. The mechanism by which the disintegration time is increased as a function of storage time must be explained based on the physical interaction between moisture and ingredients (drug and excipients). In order to develop that mechanism, the following research is suggested.

1. The properties of each ingredient should be understood as a function of temperature, RH, moisture sorption rate, and storage time.
2. The physical structure change inside tablets should be explained as a function of temperature, RH, moisture sorption rate, and storage time.
3. If the dissolution testing is improved to have good reproducibility, a better relationship between dissolution and moisture content of tablets can be made. This can result in better dissolution prediction results.

Appendix A

Background and Literature Review
(Moisture and Shelf life Prediction Models)

The moisture content of solid oral dosage forms such as tablets and capsules in a package has been the subject of research for a long time because it plays an important role in properties such as dissolution and hardness of solid dosage forms. Before the 1990s, the moisture content of product in a package was predicted using a simple linear relationship between initial and final points of the moisture sorption isotherm. Van Den Berg and Bruin (1981) stressed the advantages of using the GAB equation obtained from Guggenheim-Anderson-De Boer. This is a nonlinear equation for moisture sorption isotherms (Bizot, 1983). Since then, nonlinear equations have been applied to develop shelf life and moisture prediction models for one component in a package and for two components in a package.

Three concepts (moisture content equations, psychrometric equations, moisture sorption isotherm equations) together are necessary to develop moisture and shelf life prediction programs.

1. Moisture content equations

Models predicting the shelf life and moisture content of solids are normally calculated based on the dry weight. When solids change weight during moisture sorption and desorption, an equation that can be used to calculate the dry-weight-based moisture content using initial and final wet weight is needed. Equation 23 is the simplest such equation available. It is used in the PKG 815 Shelf Life class at the School of Packaging, Michigan State University. The following discussion shows how Equation 23 is derived from basic principles. Equations 21-31 are regularly used in shelf life calculations.

Equations 32 and 33 are added as clarifying equation developing steps to improve understanding.

The moisture content [*M(%)*] based on the dry weight of solids can be calculated by Equation 21:

$$M(\%) = \frac{m_e}{W_d} \times 100 \tag{21}$$

where m_e = the mass of moisture at equilibrium, W_d = the dry weight of solid

The moisture content based on the wet weight of solids can be calculated by Equation 22.

$$M_w(\%) = \frac{m_e}{W} \times 100 \tag{22}$$

If solids absorb or desorb moisture as a function of relative humidity, the moisture content can be determined by Equation 23.

$$M(\%) = \left[\frac{W_f \cdot (M_i + 1)}{W_i} - 1 \right] \times 100 \tag{23}$$

Equation 23 is derived from Equation 21. Equation 21 looks simple, but m_e and W_d need to be calculated. So, the following shows how to derive Equation 23 from Equation 21. There are two parts. One is to calculate the numerator (m_e) and the other is to calculate the denominator (W_d) in Equation 21.

(1) Calculation of m_e, the mass of moisture at equilibrium

Equation 24 can be used to calculate the mass of moisture at equilibrium (m_e).

$$m_e = m_i + moisture\ gain/loss = m_i + (W_f - W_i) \tag{24}$$

To calculate the mass of moisture at initial time (m_i) using the initial weight of product (W_i) and initial moisture content (M_{wi}) based on the wet weight of product, Equation 25 can be used.

$$m_i = M_{wi} \times W_i \tag{25}$$

If the initial moisture content is calculated based on the dry weight of product,

$$M_i = \frac{m_i}{W_d} \tag{26}$$

Then, M_{wi}, the initial moisture content based on the wet weight of product, can be represented as Equation 27.

$$M_{wi} = \frac{m_i}{W_i} = \frac{m_i}{W_d + m_i} \tag{27}$$

From Equation 26 and Equation 27,

$$\frac{1}{M_{wi}} = \frac{W_d + m_i}{m_i} = \frac{W_d}{m_i} + 1 = \frac{1}{M_i} + 1$$

Therefore,

$$M_{wi} = \frac{M_i}{1 + M_i} \tag{28}$$

Substitute Equation 28 into Equation 25.

$$m_i = \frac{M_i}{1 + M_i} \times W_i \tag{29}$$

Substitute Equation 29 into Equation 24.

$$m_e = \frac{M_i}{1 + M_i} \times W_i + (W_f - W_i) \tag{30}$$

(2) Calculation of W_d, the dry weight of solid

Equation 31 can be used to calculate the dry weight of product (W_d).

$$W_d = W_i - m_i \tag{31}$$

Substitute Equation 29 into Equation 31,

$$W_d = W_i - \frac{M_i}{1+M_i} \times W_i \tag{32}$$

Now, m_e (Equation 30) and W_d (Equation 32) are derived, so substitute them into Equation 21.

$$M(\%) = \frac{\frac{M_i}{1+M_i} \times W_i + (W_f - W_i)}{W_i - \frac{M_i}{1+M_i} \times W_i} \times 100 \tag{33}$$

By simplifying the Equation 33, Equation 23 is obtained.

2. Psychrometric equations

The psychrometric equations and chart are a very useful tool to determine the relationship between air and the moisture it contains. ASAE (American Society of Agricultural Engineers) publishes equations of saturation vapor pressure, vapor pressure, and absolute humidity. They were used to develop the moisture simulation computer program. Below are three useful psychrometric equations:

(1) Saturation vapor pressure (p_s, Pascal)

At a given temperature T, saturation vapor pressure (p_s) can be calculated by Equation 34 which is designed for the unit "pascal" value.

$$ln(p_s/R) = \frac{A + BT + CT^2 + DT^3 + ET^4}{FT - GT^2} \quad (273.16 \le T \le 533.16) \qquad (34)$$

where, R = 22,105,649.25 A = -27,405.526 B = 97.5413 C = -0.146244
$D = 0.12558\times10^{-3}$ $E = -0.48502\times10^{-7}$ F = 4.34903 $G = 0.39381\times10^{-2}$
T = the absolute temperature (°K = °C + 273.16)

(2) Vapor pressure (p)

At a given relative humidity [RH (%)], vapor pressure (p) can be calculated by Equation 35.

$$p = p_s \times \frac{RH(\%)}{100} \qquad (35)$$

(3) Absolute humidity (g H_2O/g dry air) (AH)

At a given water vapor pressure (p) and atmospheric pressure (p_{atm}), absolute humidity (AH) (or water vapor concentration) can be calculated by Equation 36. AH is given in grams of water per gram of dry air.

$$AH = \frac{0.6219\, p}{p_{atm} - p} \quad (255.38 \le T \le 533.16,\ p < p_{atm}) \qquad (36)$$

Another Equation 37 for the saturation vapor pressure was published by ASHRAE (American Society of Heating, Refrigeration and Air Conditioning Engineers). It is designed for the unit "psia" value.

$$ln(p_s) = \frac{C_1}{T} + C_2 + C_3T + C_4T^2 + C_5T^3 + C_6\, ln(T) \quad (32°F \le T \le 392°F) \qquad (37)$$

where C_1 = -1.044039E+04 C_2 = -1.1294650E+01 C_3 = -2.7022355E-02
C_4 = 1.2890360E-05 C_5 = -2.4780681E-09 C_6 = 6.5459673
T = the absolute temperature, °R = °F + 459.67

Also, the saturation vapor pressure (p_s) can be calculated by using Equation 38 which is used in calculations developed by Downes (1989) at the School of Packaging, Michigan State University.

$$p_s(mmHg) = 1132570000 * e^{\frac{-5269}{T}} \tag{38}$$

where T = the absolute temperature (°K = °C + 273.16)

He obtained the constants (-5269 and 1132570000) used in Equation 38 from an empirical fit to the known data based on the theoretical model 39. This is an Arrhenius type of expression.

$$p_s = A \cdot e^{\frac{Activation\ Energy}{Temperature}} \tag{39}$$

where A = a constant

The simple Equation 38 was used to develop the moisture simulation computer program. The equations (saturation vapor pressure Equations 34, 37, 38 and absolute humidity Equation 36) given above yield results that agree closely with existing psychrometric charts.

3. Moisture sorption isotherm equations

A moisture sorption isotherm is a tool for describing the relationship between equilibrium moisture content (M) and the moisture in the air surrounding a product (a_w), which is necessary to develop the shelf life and moisture prediction programs. It can be

determined by storing the products at several humidities over the range 5-95 percent. In order to represent that relationship mathematically, linear and non-linear equations can be used.

In this study, the initial point of an isotherm is defined as the intersection of the initial moisture content and initial equilibrium a_w on the sorption isotherm curve, and the final point of an isotherm is defined as the intersection of the final moisture content and final equilibrium a_w on the sorption isotherm curve. The final equilibrium a_w can be chosen to be equal to or below the external ambient condition. It will never be higher than ambient. Figure 65 shows a graphical representation of linear and nonlinear relationships between M and a_w. The slope (β) shows the linear relationship and the sorption isotherm curve itself shows the nonlinear relationship.

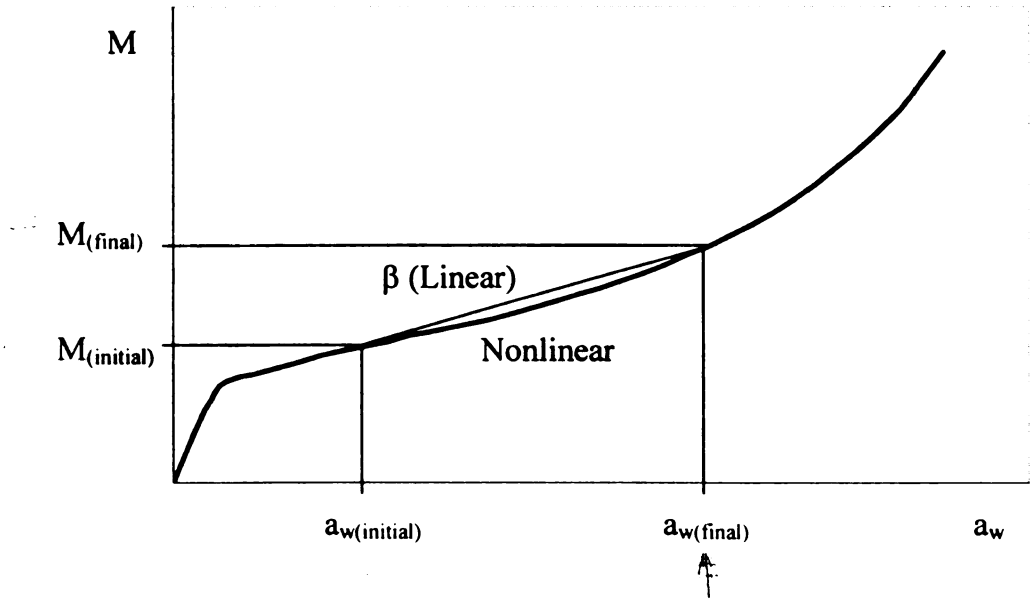


Figure 65 Graphical representation of linear and nonlinear relationships between M and a_w

(1) Linear equation

The sorption relationship between the initial and final points on the sorption isotherm curve sometimes can be simplified with a linear equation as shown in Equation 40. When the curvature of the isotherm is small, the linear equation can be a useful approximation. In this relationship, moisture content is a variable dependent upon water activity (a_w). a_w is used interchangeably with equilibrium relative humidity [*RH(%)/100*] or relative vapor pressure (p/p_s).

$$M = \beta \cdot a_w + C \tag{40}$$

where $\beta = \dfrac{M_{(final)} - M_{(initial)}}{a_{w(final)} - a_{w(initial)}}$

(2) Nonlinear equations

In order to represent the real path between the initial and final points on the sorption isotherm curve, nonlinear equations such as GAB and Langmuir equations can be used (Bell, 2000 and Bizot, 1983).

(a) GAB equation

The GAB equation can be used to describe the relationship between the moisture content of solids (e.g. tablets) and a_w as shown in Equation 41. The GAB equation often fits sigmoid-shaped moisture isotherm data very well over the range of relative humidities between 10% and 90% (Bizot, 1983).

$$M = \frac{W_m \cdot C_g \cdot K \cdot a_w}{[1 - K \cdot a_w] \times [1 - K \cdot a_w + C_g K \cdot a_w]} \tag{41}$$

where W_m, C_g, K = GAB constants

Equation 41 can be solved for the constants by rearranging it into a polynomial form of the GAB equation:

$$\frac{a_w}{M} = \frac{K}{W_m}\left(\frac{1}{C_g} - 1\right)a_w^2 + \frac{1}{W_m}\left(1 - \frac{2}{C_g}\right)a_w + \frac{1}{W_m K C_g} \tag{42}$$

So, if the moisture sorption or desorption data are plotted as $\frac{a_w}{M}$ vs a_w, the plot can be represented by a polynomial equation. Then the GAB constants can be calculated from the polynomial constants:

$$\frac{a_w}{M} = A \cdot a_w^2 + B \cdot a_w + C \tag{43}$$

where $A = \frac{K}{W_m}\left(\frac{1}{C_g} - 1\right)$, $B = \frac{1}{W_m}\left(1 - \frac{2}{C_g}\right)$, $C = \frac{1}{W_m K C_g}$

Rearranging and substituting into the above polynomial constants, one ultimately arrives at the following solutions for the GAB constants:

$$K = \frac{\sqrt{B^2 - 4AC} - B}{2C} \qquad C_g = \frac{B}{C \cdot K} + 2 \qquad W_m = \frac{1}{C \cdot K \cdot C_g} \tag{44}$$

(b) Langmuir equation

The Langmuir equation can also be used to describe the relationship between moisture content of solids (e.g. desiccant) and a_w as shown in Equation 45 (Zografi, 1988). The Langmuir equation often fits hyperbolic-shaped moisture isotherm data very well over the range of relative humidities between 10% and 90%.

$$M = \frac{W_m \cdot C_L \cdot a_w}{1 + C_L \cdot a_w} \tag{45}$$

where W_m[h] and C_L = Langmuir constants.

Equation 45 can be solved for the constants by rearranging it into a polynomial form of the Langmuir equation:

$$\frac{1}{M} = \frac{1}{W_m} + \frac{1}{W_m \cdot C_L} \cdot \frac{1}{a_w} \tag{46}$$

So, if the moisture sorption or desorption data are plotted as $\frac{1}{M}$ vs $\frac{1}{a_w}$, the plot can be represented by a linear equation. Then the Langmuir constants can be calculated from the polynomial constants:

$$\frac{1}{M} = B \cdot \frac{1}{a_w} + C \tag{47}$$

where $B = \frac{1}{W_m \cdot C_L}$, $C = \frac{1}{W_m}$

Rearranging and substituting into the above polynomial constants, one ultimately arrives at the following solutions for the Langmuir constants:

$$C_L = \frac{C}{B} \qquad W_m = \frac{1}{C} \tag{48}$$

The GAB and Langmuir constants also can be determined by computer fitting the isotherm data to the GAB or Langmuir equations with a statistical program such as the

[h] W_m is the moisture content of the monolayer. W_m used in GAB and Langmuir equations is the same concept.

nonlinear regression Solver function in Microsoft Excel. The solver algorithm used in Microsoft Excel is not available to see, so a simple algorithm to help the reader understand how Solver works is explained in detail in Appendix B Moisture and Shelf Life Prediction Programming, and Verification.

4. Shelf life prediction models

Shelf life prediction models have been developed by various researchers using the linear equation for one or two solids in a package and using the GAB non-linear equation for one solid in a package.

The basic equations (Equations 49 and 50) for moisture transfer through a permeable package were derived from Fick's law in combination with Henry's law (Labuza et al., 1972). Either one can be used to develop the shelf life prediction models.

$$\frac{dw}{dt} = \frac{P \cdot A \cdot p_s}{\ell}\left[a_{w(out)} - a_{w(in)}\right] \tag{49}$$

or

$$\frac{dM}{dt} = \frac{P \cdot A}{\ell \cdot W_d} \cdot (p_{out} - p_{in}) \tag{50}$$

Equation 49 and Equation 50 provide the same information in terms convenient for different uses. If the focus is on the mass of moisture change permeating into the package (dw) in developing the shelf life prediction model, Equation 49 can be used. And, if the focus is on the moisture content change of a component (dM) in developing the shelf life prediction model, Equation 50 can be used. When Downes et al. (1989) and Pocas (1995) developed shelf life prediction models using the linear equation, Equation

49 was used. And, when Diosady (1996) developed the shelf life prediction model using the GAB non-linear equation, Equation 50 was used. By using Equation 49 and 50, the time required to reach the final moisture content from the initial moisture content can be calculated based on the unsteady state vapor pressure difference between the outside and inside of the package. The outside vapor pressure is assumed to be constant, so the inside vapor pressure should be determined as a function of storage time. Linear and non-linear equations can be used to calculate the vapor pressure of the package headspace.

(1) Linear equation

Downes et al. (1989) at the School of Packaging in Michigan State University developed a DOS based shelf life prediction program using the linear Equation 51 to determine the inside air water activity values ($a_{w(in)}$) used in Equation 49. Equation 51 provides water activity values for known moisture contents. In order to calculate the water activity of air inside the package ($a_{w(in)}$) simply, a_w moves to the y-axis and M moves to the x-axis in contrast to Equation 40 that represents a typical relationship between M and a_w, with M as the dependent variable.

$$a_{w(in)} = C + \beta \cdot M \tag{51}$$

where $\beta = \dfrac{a_{w(final)} - a_{w(initial)}}{M_{(final)} - M_{(initial)}}$

Substitute Equation 51 into Equation 49.

$$\frac{dw}{dt} = \frac{P \cdot A \cdot p_s}{\ell}\left[a_{w(out)} - C - \beta \cdot M\right] \tag{52}$$

Assume the contents in a package absorb the permeated moisture immediately. Then:

$$M = \frac{w}{W_d} \tag{53}$$

Differentiate Equation 53.

$$dM = \frac{1}{W_d} dw \tag{54}$$

Divide by dt on both sides, then rearrange.

$$\frac{dw}{dt} = \frac{dM}{dt} W_d \tag{55}$$

Substitute Equation 55 into Equation 52.

$$\frac{dM}{dt} W_d = \frac{P \cdot A \cdot p_s}{\ell} \left[a_{w(out)} - C - \beta \cdot M \right] \tag{56}$$

Rearrange equation 56 to integrate.

$$\frac{dM}{a_{w(out)} - C - \beta \cdot M} = \frac{P \cdot A \cdot p_s}{\ell \cdot W_d} dt \tag{57}$$

Integrating from M_i to M_f ($t = 0$ to $t = t$).

$$\int_{M_i}^{M_f} \frac{dM}{a_{w(out)} - C - \beta \cdot M} = \frac{P \cdot A \cdot p_s}{\ell \cdot W_d} \int_0^t dt \tag{58}$$

For integration, let $u = a_{w(out)} - C - \beta M$

$du = -\beta \, dM$

$dM = -\frac{1}{\beta} du$

$$M_i \text{ at } u = \left[a_{w(out)} - a_{w(in)}\right] \text{at time} = 0$$
$$M_f \text{ at } u = \left[a_{w(out)} - a_{w(in)}\right] \text{at time} = t$$

Substitute u into Equation 58.

$$-\frac{1}{\beta}\left[\int_{\left[a_{w(out)}-a_{w(in)}\right]_{t=0}}^{\left[a_{w(out)}-a_{w(in)}\right]_{t=t}} \frac{du}{u}\right] = \frac{P \cdot A \cdot p_s}{\ell \cdot W_d}\int_0^t dt \tag{59}$$

Integrate Equation 59.

$$-\frac{1}{\beta}\ln\left[\frac{(a_{w(out)} - a_{w(in)})_{t=t}}{(a_{w(out)} - a_{w(in)})_{t=0}}\right] = \frac{P \cdot A \cdot p_s}{\ell \cdot W_d} t \tag{60}$$

Solving 60 for t yields the shelf life equation 61 using the linear equation.

$$t = \frac{-W_d \cdot \ell}{\beta \cdot P \cdot A \cdot p_s}\ln\left[\frac{(a_{w(out)} - a_{w(in)})_{t=t}}{(a_{w(out)} - a_{w(in)})_{t=0}}\right] \tag{61}$$

If the numerator and denominator in the logarithm are switched, the minus sign can be removed:

$$t = \frac{W_d \cdot \ell}{\beta \cdot P \cdot A \cdot p_s}\ln\left[\frac{(a_{w(out)} - a_{w(in)})_{t=0}}{(a_{w(out)} - a_{w(in)})_{t=t}}\right] \tag{62}$$

Equation 61 or Equation 62 can be used to calculate the shelf life of one component in a package by using a simple linear relationship between M and a_w.

Pocas (1995) developed a mathematical model to predict the shelf life of two solids in a package by using linear sorption isotherms. She said that when two solids A and B are packaged together, the total amount of moisture dw permeating through the package is equal to the moisture change in solid A plus the moisture change in solid B:

$$dw = W_{dA} dM_A + W_{dB} dM_B \tag{63}$$

Substitute Equation 63 into Equation 49, then rearrange:

$$W_{dA} dM_A + W_{dB} dM_B = \frac{P \cdot A \cdot p_s}{\ell} \left[a_{w(out)} - a_{w(in)} \right] dt \tag{64}$$

The moisture sorption isotherms of the solids can be represented by linear equations:

$$M_A = C_A + \beta_A \cdot a_w \quad \left(\frac{dM_A}{da_w} = \beta_A \right) \tag{65}$$

$$M_B = C_B + \beta_B \cdot a_w \quad \left(\frac{dM_B}{da_w} = \beta_B \right) \tag{66}$$

where $C_A, \beta_A, C_B, \beta_B$ are the coefficients of each linear equation.

Then, dM_A can be expressed as a function of dM_B and vice versa:

$$dM_A = dM_B \frac{\beta_A}{\beta_B} \tag{67}$$

$$dM_B = dM_A \frac{\beta_B}{\beta_A} \tag{68}$$

Substitute Equation 68 into Equation 64, then rearrange:

$$dM_A (W_{dA} + W_{dB} \frac{\beta_B}{\beta_A}) = \frac{P \cdot A \cdot p_s}{\ell} \left[a_{w(out)} - a_{w(in)} \right] dt \tag{69}$$

Rearrange Equation 69 for *dt*.

$$dt = \frac{\ell}{P \cdot A \cdot p_s} (W_{dA} + W_{dB} \frac{\beta_B}{\beta_A}) \left[\frac{dM_A}{a_{w(out)} - a_{w(in)}} \right] \tag{70}$$

Integrate Equation 70.

$$t = \frac{\ell}{P \cdot A \cdot p_s}\left(W_{dA} + W_{dB}\frac{\beta_B}{\beta_A}\right)\int_{M_{Ai}}^{M_{Af}} \frac{dM_A}{a_{w(out)} - a_{w(in)}} \tag{71}$$

The analytical integration of Equation 71 gives Equation 72 (see Equations 58-60 for more information about integrating).

$$t = \frac{\ell}{P \cdot A \cdot p_s}(W_{dA}\beta_A + W_{dB}\beta_B)\ln\left[\frac{(a_{w(out)} - a_{w(in)})_{t=0}}{(a_{w(out)} - a_{w(in)})_{t=t}}\right] \tag{72}$$

Equation 72 will be used to calculate the shelf life of two solid contents (e.g., tablets and desiccant) in a package by using a simple linear relationship between M and a_w.

(2) Nonlinear equation

When the linear equation is too simple to represent real relationships, the use of a nonlinear equation needs to be considered. Diosady (1996) incorporated the nonlinear GAB equation into the basic equation for the rate of moisture transfer into a permeable package, thus obtaining a shelf life prediction model. Equations 75-83, 85, and 89 are rearranged from Diosady's (1996) paper, and Equations 73, 74, 84, 86, 87, and 88 are added by this author as clarifying intermediate steps to improve understanding.

Equation 43 is rearranged as shown in Equation 73.

$$A \cdot M \cdot a_w^2 + (B \cdot M - 1)a_w + C \cdot M = 0 \tag{73}$$

Equation 73 is modified to the following equation by the quadratic formula:

$$a_w = \frac{-(B \cdot M - 1) - \sqrt{(B \cdot M - 1)^2 - 4 \cdot A \cdot C \cdot M^2}}{2 \cdot A \cdot M} \tag{74}$$

The polynomial constants *A*, *B*, and *C* are substituted into Equation 74:

$$a_w = \frac{2 + (W_m/M - 1)\cdot C_g - \sqrt{[2 + (W_m/M - 1)\cdot C_g]^2 - 4 + 4\cdot C_g}}{2\cdot K\cdot(1 - C_g)} \tag{75}$$

From $a_{w(in)} = \frac{p_{in}}{p_s}$ and $a_{w(out)} = \frac{p_{out}}{p_s}$ in combination with 75:

$$p_{in} = p_s \cdot \frac{2 + (W_m/M - 1)\cdot C_g - \sqrt{[2 + (W_m/M - 1)\cdot C_g]^2 - 4 + 4C_g}}{2\cdot K\cdot(1 - C_g)} \tag{76}$$

and

$$p_{out} = p_s \cdot \frac{2 + (W_m/M_e - 1)\cdot C_g - \sqrt{[2 + (W_m/M_e - 1)\cdot C_g]^2 - 4 + 4C_g}}{2\cdot K\cdot(1 - C_g)} \tag{77}$$

where M_e = the equilibrium moisture content of solids exposed to the package outside RH (g H_2O/g dry weight of solids)

Substitute 76 and 77 into 50:

$$\begin{aligned}\frac{dM}{dt} = \frac{P\cdot A\cdot p_s}{W_d\cdot \ell\cdot(2)\cdot K\cdot(1 - C_g)}\{&(W_m/M_e)\cdot C_g \\ &- \sqrt{[2 + (W_m/M_e)\cdot C_g - C_g]^2 - 4 + 4C_g} - (W_m/M)\cdot C_g \\ &+ \sqrt{[2 + (W_m/M)\cdot C_g - C_g]^2 - 4 + 4C_g}\}\end{aligned} \tag{78}$$

Assuming constant temperature and external relative humidity, let

$$\frac{P\cdot A\cdot p_s}{W_d\cdot \ell\cdot(2)\cdot K\cdot(1 - C_g)} = constant = \Phi \tag{79}$$

and

$$(W_m/M_e)\cdot C_g - \sqrt{[2+(W_m/M_e)\cdot C_g - C_g]^2 - 4 + 4C_g} = constant = \Pi \qquad (80)$$

Substitute 79 and 80 into 78, and integrate from $t = 0$ to $t = t$ and M_i to M_f:

$$\int_{M_i}^{M_f} \frac{dM}{\Pi - (W_m/M)\cdot C_g + \sqrt{[2+(W_m/M)\cdot C_g - C_g]^2 - 4 + 4C_g}} = \Phi t \qquad (81)$$

Expanding the square in the denominator and simplifying:

$$\int_{M_i}^{M_f} \frac{dM}{\Pi - (W_m/M)\cdot C_g + \sqrt{1/M(4W_mC_g - 2W_mC_g^2) + (W_m/M)^2\cdot C_g^2 + C_g^2}} = \Phi t \qquad (82)$$

Diosady (1996) said that Equation 82 can be integrated only by numerical methods. However, if C_g is large so that $4W_mC_g << 2W_mC_g^2$, or $C_g >> 2$[i] then Equation 82 can be written as:

$$\int_{M_i}^{M_f} \frac{dM}{\Pi - (W_m/M)\cdot C_g + \sqrt{1/M(-2W_mC_g^{\,2}) + (W_m/M)^2\cdot C_g^{\,2} + C_g^{\,2}}} = \Phi t \qquad (83)$$

In order to simplify the denominator, multiply numerator and denominator by M. Then, rearrange.

$$\int_{M_i}^{M_f} \frac{M\cdot dM}{\Pi M - W_mC_g + C_g\sqrt{M^2 - 2W_mM + W_m^2}} = \Phi t \qquad (84)$$

But $M^2 - 2W_mM + W_m^2 = (M - W_m)^2$

Therefore, Equation 84 simplifies to

[i] Diosady wrote $C_g >> 2$ at that statement but he wrote $C_g >> 20$ in text. If C_g is much greater than 2, $4W_mC_g << 2W_mC_g^2$ can be obtained. So, 2 is correct.

$$\int_{M_i}^{M_f} \frac{M \cdot dM}{M(\Pi + C_g) - 2W_m \cdot C_g} = \Phi t \qquad (85)$$

For integration,

Let $\xi = M(\Pi + C_g) - 2W_m C_g$

$d\xi = dM(\Pi + C_g)$

$$dM = \frac{d\xi}{(\Pi + C_g)}, \quad M = \frac{\xi + 2W_m C_g}{(\Pi + C_g)}$$

M_f *at* $\xi = M_f(\Pi + C_g) - 2W_m C_g$ *at time* $= t$

M_i *at* $\xi = M_i(\Pi + C_g) - 2W_m C_g$ *at time* $= 0$

Substitute ξ into Equation 85.

$$\int_{M_i(\Pi + C_g) - 2W_m C_g}^{M_f(\Pi + C_g) - 2W_m C_g} \frac{(\xi + 2W_m C_g)/(\Pi + C_g)}{\xi} \frac{d\xi}{(\Pi + C_g)} = \Phi t \qquad (86)$$

Rearrange, and split.

$$\Phi t = \int_{M_i(\Pi + C_g) - 2W_m C_g}^{M_f(\Pi + C_g) - 2W_m C_g} \frac{1}{(\Pi + C_g)^2} d\xi + \int_{M_i(\Pi + C_g) - 2W_m C_g}^{M_f(\Pi + C_g) - 2W_m C_g} \frac{2W_m C_g}{(\Pi + C_g)^2 \xi} d\xi \qquad (87)$$

Integrate Equation 87.

$$\Phi t = \frac{1}{(\Pi + C_g)^2} \cdot \xi \Big|_{M_i(\Pi + C_g) - 2WmC_g}^{M_f(\Pi + C_g) - 2WmC_g} + \frac{2W_m C_g}{(\Pi + C_g)^2} ln|\xi| \Big|_{M_i(\Pi + C_g) - 2WmC_g}^{M_f(\Pi + C_g) - 2WmC_g} \qquad (88)$$

Therefore, a shelf life equation using the GAB non-linear equation can be derived as shown in Equation 89.

$$t = \frac{1}{(\Pi + C_g)\Phi}\left[M_f - M_i + \frac{2W_m C_g}{(\Pi + C_g)} ln[\frac{(\Pi + C_g)M_f - 2W_m C_g}{(\Pi + C_g)M_i - 2W_m C_g}] \right] \quad (89)$$

Equation 89 was used by Diosady to calculate the time to reach the final moisture content from the initial moisture content in a package at a given storage condition by using the non-linear GAB sorption equation. He said this model is limited to C_g values greater than about 2 and it can be applied to only one component in a package as shown. It is very complicated to develop a shelf life prediction model analytically using the GAB nonlinear equation. If one more component is added into the package to develop the shelf life prediction model, it will be very complicated, or it might be impossible to develop a shelf life prediction model using the nonlinear equations.

5. Moisture prediction models

Zografi et al. (1988) developed a mathematical model to predict the final relative water vapor pressure in a closed system for a multicomponent mixture of solids knowing the initial water content for each component. The mathematical model for a closed system is useful for calculating the initial equilibrium water vapor pressure of components that have different water vapor pressures.

Zografi et al. put micro crystalline cellulose (MCC) and corn starch in a glass bottle and they assumed that the bottle was closed completely, there was no moisture permeation through the bottle. The packaging line was conditioned at 23 °C/65% RH, so the initial relative humidity of the package headspace was 65% RH. Before MCC and corn starch were inserted into the bottle, their initial moisture contents were measured as shown in Table 27.

Table 27 Initial moisture content of MCC and corn starch

	M_i (%)	Equilibrium *RH (%)*
MCC	18.1%	96% RH based on Moisture Desorption Isotherm
Corn Starch	0	0% RH based on Moisture Sorption Isotherm

MCC has a higher equilibrium vapor pressure than the package head space and corn starch has a lower one, so water in the MCC will be desorbed into the package headspace and the corn starch will absorb water from the package head space. Therefore, the moisture desorption isotherm of MCC and the moisture sorption isotherm of corn starch must be used to predict the final RH of the package headspace. Figures 66 and 67 help to explain Zografi et al.'s model more clearly.

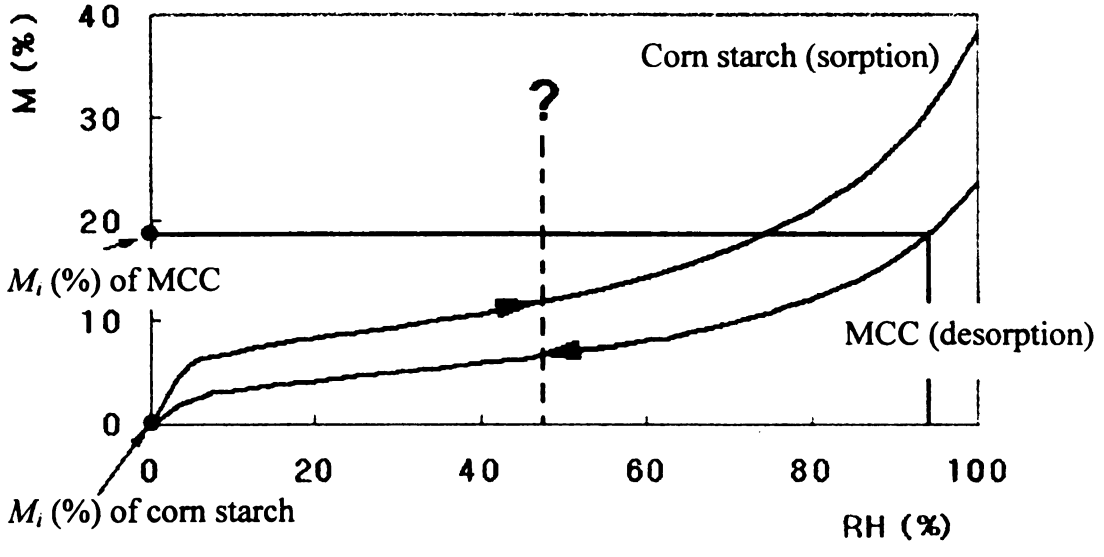
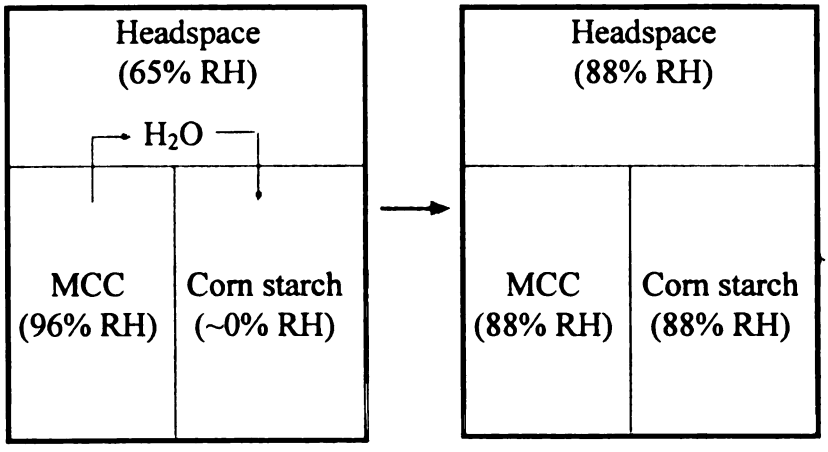


Figure 66 Graphical representation of changes in moisture during equilibration between MCC and corn starch

As shown in Figure 66, MCC will lose some moisture and corn starch will gain some moisture to reach equilibrium (somewhere between 0% and 96%). The equilibrium point between MCC and corn starch is dependent on the relative amounts of each component.

There are three different equilibrium vapor pressures in the bottle at the time t=0 when it is closed, as shown in Figure 67-(a). The system is not at equilibrium at this time (t=0).

- Package head space : 23°C/65% RH (13.71 mmHg)
- MCC : 23°C/96% RH (20.25 mmHg)
- Corn Starch : 23°C/0% RH (0 mmHg)



(a) at storage time t = 0 (b) at equilibrium

Figure 67 Graphical representation of moisture transfer and moisture equilibrium in the closed system

Moisture will be transferred from MCC to corn starch until equilibrium is reached as shown in Figure 67-(b). At equilibrium the head space, MCC, and corn starch have the same vapor pressure, but they each have a different moisture content. The water in the MCC and the water in the corn starch both have the same thermodynamic state as defined by the chemical potential (Bell, 1990).

Kontny et al. (1992) developed a mathematical model to predict the moisture content of components in a permeable package using a sorption-desorption moisture transfer (SDMT) model. They address the situation where an aspirin and desiccant, each

with an initial moisture content, are stored together in a permeable container at a given temperature, initial headspace humidity, and headspace volume. A method is shown in which the amount of moisture permeating into the container over the storage time can be determined. Then it is shown how the distribution of the moisture between the aspirin, desiccant, and headspace can be determined using sorption-desorption moisture transfer models. Kontny's description s reported in the following paragraphs.

The amount of moisture in the package at time t = 0 ($m_{T,\ at\ time=0}$) can be determined by Equation 90.

$$m_{T,\ at\ time=0} = W_{dA} M_A + W_{dB} M_B + m_h \tag{90}$$

Once the amount of moisture permeating into the package is calculated for a time interval *j*, this mass of water can be added to $m_{T,\ at\ time=0}$ to obtain $m_{T,\ at\ time=j}$, the amount of water inside the container at the end of this time increment. After time interval *j*, the total moisture in the system ($m_{T,\ at\ time=j}$) can be expressed by:

$$m_{T,\ at\ time=j} = m_{T,\ at\ time=0} + w \tag{91}$$

The sorption-desorption moisture transfer (SDMT) model also can be utilized to obtain the relative vapor pressure $(p/p_s)_{in}$ inside the package at a time equal to time interval *j*. This method can then be iterated to obtain $(p/p_s)_{in}$ at each time interval through the total storage time, where the time associated with a calculated $(p/p_s)_{in}$ is obtained by summing the time interval *j*.

In order to calculate the vapor pressure $(p/p_s)_{in}$ inside the package, the relationship of each component's moisture content with RH must be known and defined

mathematically. The GAB and Langmuir equations provide a good fit with moisture sorption isotherm data.

Referring to Equation 90, the mass of moisture (m_A) in component A can be calculated with the GAB or Langmuir equation:

$$m_A = W_{dA} \times M_{A(GAB)} (or\ M_{A(Langmuir)}) \tag{92}$$

where $M_{A(GAB)}$ (or $M_{A(Langmuir)}$) = the moisture content associated with component A as given by the GAB (or Langmuir) equation for component A at any relative humidity

The ideal gas law is used to calculate the mass of moisture in the headspace volume (m_h) for the total head space volume.

$$m_h = \frac{p_s \cdot V \cdot (p/p_s) \times 18}{R \cdot T} \tag{93}$$

where R = gas constant, 0.08205 L·atm/mol·K, T = absolute temperature (°K)

In order to get p_s, a psychrometric chart or look-up table can be used. Also, p_s can be calculated by using the saturation vapor pressure Equations 34, 37, and 38. Equation 38 was used to develop the computer program. When the temperature changes, the saturation vapor pressure at the new temperature is calculated easily by use of Equations 38.

Kontny used the GAB equation for aspirin and the Langmuir equation for desiccant, so Equation 90 written in its entirety takes the form:

$$m_{T,at\ time=0} = W_{dA}\left\{\frac{W_{mA}C_{gA}K_A(p/p_s)}{[1-K_A(p/p_s)]\times[1-K_A(p/p_s)+C_{gA}K_A(p/p_s)]}\right\} + W_{dB}\left\{\frac{W_{mB}C_{LB}(p/p_s)}{[1+C_{LB}(p/p_s)]}\right\} + \frac{p_s \cdot V \cdot (p/p_s)\times 18}{R \cdot T} \quad (94)$$

where, W_{mA}, C_{gA}, K_A = the GAB constants of component A
W_{mB}, C_{LB} = the Langmuir constants of component B

The permeated mass of moisture (w) into a package for a time interval j can be calculated by Equation 95.

$$w = P \times j \times [(p/p_s)_{out} - (p/p_s)_{in}] \quad (95)$$

where j = time interval

Therefore, Equation 91 written in its entirety takes the form:

$$m_{T,\ at\ time=j} = m_{T,\ at\ time=0} + \{P \times j \times [(p/p_s)_{out} - (p/p_s)_{in}]\} \quad (96)$$

where $(p/p_s)_{in}$ is the relative water vapor pressure in the equilibrated system at each time interval j. Rearrange Equation 94 and set (p/p_s) equal to x to obtain a fifth order polynomial equation, Equation 97.

$$x^5 + C_1x^4 + C_2x^3 + C_3x^2 + C_4x - C_5 = 0 \quad (97)$$

C_1, C_2, C_3, C_4, and C_5 are constants. See Appendix 1 in the paper "Prediction of moisture transfer in mixtures of solids: transfer via the vapor phase." (Zografi et al., 1988) for more information about the constant terms. To solve Equation 97, the real root between $(p/p_s) = 0$ and $(p/p_s) = 1$ must be found. Zografi et al. used Newton's method which is one of approximation techniques. If one more component is added in the moisture

transfer process, Equation 97 will be very complicated even though it is mathematically possible to calculate the constant values for a high-order system. See Appendix B. Moisture and Shelf Life Prediction Programming, and Verification for a simple method to determine (p/p_s).

Appendix B

Moisture and Shelf Life Prediction Programming, and Verification

represent the sorption function between the initial and final points of the isotherm, and the model using the nonlinear GAB equation has a limitation that it cannot be applied for more than one component in a package. Therefore, a model without any limitation, that represents the real relationship between the initial and final points of the isotherm and that can be applied for any number of components in a package needs to be developed. A model using piecewise linear equations can be integrated analytically and can be applied for any number of components in a package, and is close to the real relationship. The nonlinear section between the initial and final points is divided into sections, and then each section is represented by the linear equation.

Figure 68 shows a hypothetical graphical representation of piecewise linear relationships between M and a_w. There are two sorption isotherm curves. One is for hypothetical component A and the other is for hypothetical component B. M_{A1} denotes the initial equilibrium moisture content of component A, M_{B1} denotes the initial equilibrium moisture content of component B. $M_{A(i+1)}$ denotes the final moisture content of component A, and $M_{B(i+1)}$ denotes the final moisture content of component B. a_{w1} is the equilibrium water activity at the initial equilibrium moisture content (M_{A1} or M_{B1}), and $a_{w(i+1)}$ is the equilibrium water activity at the final moisture content ($M_{A(i+1)}$ or $M_{B(i+1)}$). The nonlinear sorption isotherm between the initial and final points is divided into as many as i or pieces, then linear equations are applied to each divided section. As can be seen in Figure 68, linear slopes (β_{A1}, β_{A2} ... β_{Ai}) for component A and linear slopes (β_{B1}, β_{B2} ... β_{Bi}) for component B can be achieved. Those linear slopes are used to make a close to real relationship between M and a_w (p/p_s or $RH(\%)/100$).

The moisture prediction computer program consists of two parts. One is the shelf life prediction program and the other is the moisture prediction program. The shelf life prediction program is useful for calculating the time required to reach some specific moisture content from the initial moisture content of components in a package at a given storage condition. It was developed using piecewise relationships between the initial and final moisture contents. And, the moisture prediction program is useful for calculating the moisture content of components in a package and relative humidity of the package headspace as a function of storage time.

The following are major assumptions for the models used in the moisture prediction program;

a. Initial concentrations of water in the solids (e.g. tablets, capsules and desiccant) and headspace reach equilibrium rapidly.
b. The equilibration of moisture with the solid components inside the container is rapid relative to the permeation of moisture into the container.
c. There is no gradient of water vapor in the headspace surrounding the solids.

1. Shelf life prediction program

A linear sorption isotherm equation can be used to develop the shelf life prediction models for one and two components in a package, and the nonlinear GAB sorption isotherm equation can be used to develop the shelf life prediction model for one component in a package with a limitation that it needs to be integrated (see Appendix A, Equation 82-84 on page 141). The linear equation may be too simple to adequately

represent the sorption function between the initial and final points of the isotherm, and the model using the nonlinear GAB equation has a limitation that it cannot be applied for more than one component in a package. Therefore, a model without any limitation, that represents the real relationship between the initial and final points of the isotherm and that can be applied for any number of components in a package needs to be developed. A model using piecewise linear equations can be integrated analytically and can be applied for any number of components in a package, and is close to the real relationship. The nonlinear section between the initial and final points is divided into sections, and then each section is represented by the linear equation.

Figure 68 shows a hypothetical graphical representation of piecewise linear relationships between M and a_w. There are two sorption isotherm curves. One is for hypothetical component A and the other is for hypothetical component B. M_{A1} denotes the initial equilibrium moisture content of component A, M_{B1} denotes the initial equilibrium moisture content of component B. $M_{A(i+1)}$ denotes the final moisture content of component A, and $M_{B(i+1)}$ denotes the final moisture content of component B. a_{w1} is the equilibrium water activity at the initial equilibrium moisture content (M_{A1} or M_{B1}), and $a_{w(i+1)}$ is the equilibrium water activity at the final moisture content ($M_{A(i+1)}$ or $M_{B(i+1)}$). The nonlinear sorption isotherm between the initial and final points is divided into as many as i or pieces, then linear equations are applied to each divided section. As can be seen in Figure 68, linear slopes (β_{A1}, β_{A2} ... β_{Ai}) for component A and linear slopes (β_{B1}, β_{B2} ... β_{Bi}) for component B can be achieved. Those linear slopes are used to make a close to real relationship between M and a_w (p/p_s or $RH(\%)/100$).

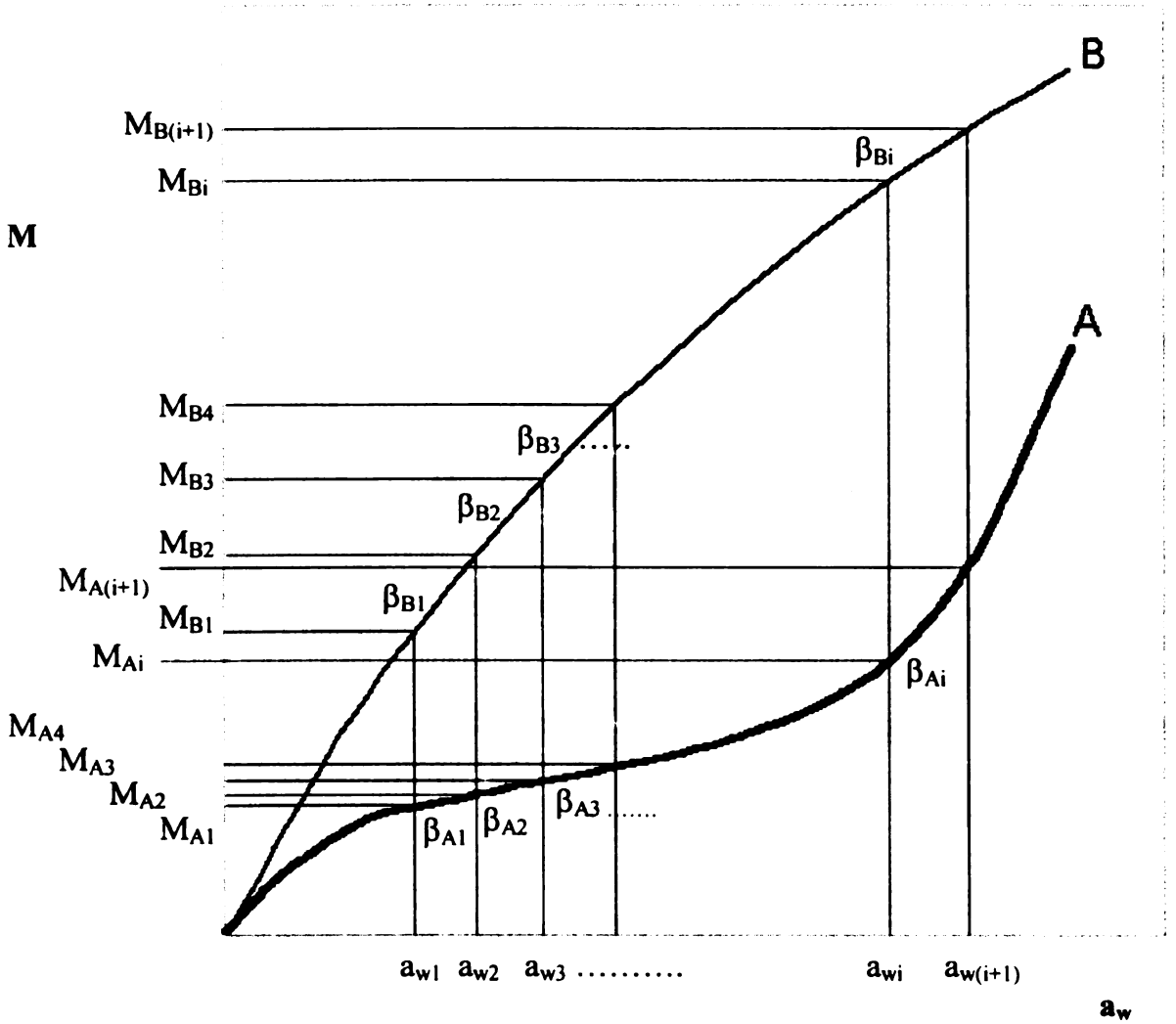


Figure 68 Hypothetical graphic representation of piecewise linear equations for two sorption isotherms for components A and B

Equation 98 shows the piecewise linear relationship between M and a_w.

$$M_{c(n+1)} = \beta_{cm} \cdot a_{w(n+1)} + C_{cm} \quad (0 \le n \le i, 1 \le m \le i) \tag{98}$$

where $\beta_{cm} = \dfrac{M_{c(n+1)} - M_{c(n)}}{a_{w(n+1)} - a_{w(n)}}$, c = the component (e.g., A, B, ... Z)

When components are packaged together, the amount of moisture change overall (dw) is equal to the moisture change in all components (A + B ....+ Z).

$$dw = W_{dA}dM_A + W_{dB}dM_B + ... + W_{dZ}dM_Z \quad (99)$$

Substitute Equation 99 into Equation 49 in Appendix A, then rearrange it. Equation 100 represents that the moisture change in all components can be calculated by using package permeability, package thickness and area, and the water vapor partial pressure difference between the inside and the outside of the package.

$$W_{dA}dM_A + W_{dB}dM_B + ... + W_{dZ}dM_Z = \frac{P \cdot A \cdot p_S}{\ell}\left[a_{w(out)} - a_{w(in)}\right]dt \quad (100)$$

The moisture sorption isotherms of the components are represented by piecewise linear equations:

$$M_{A(n+1)} = C_{Am} + \beta_{Am} \cdot a_{w(n+1)} \ (0 \le n \le i, 1 \le m \le i)\left(\frac{dM_A}{da_w} = \beta_A\right) \quad (101)$$

$$M_{B(n+1)} = C_{Bm} + \beta_{Bm} \cdot a_{w(n+1)} \ (0 \le n \le i, 1 \le m \le i)\left(\frac{dM_B}{da_w} = \beta_B\right) \quad (102)$$

.....

$$M_{Z(n+1)} = C_{Zm} + \beta_{Zm} \cdot a_{w(n+1)} \ (0 \le n \le i, 1 \le m \le i)\left(\frac{dM_Z}{da_w} = \beta_Z\right) \quad (103)$$

where $C_{Am}, \beta_{Am}, C_{Bm}, \beta_{Bm}, ..., C_{Zm}, \beta_{Zm}$ are the coefficients of each linear equation.

Then, dM_A, dM_B, ... dM_Z can be expressed as a function of dM_B:

$$dM_A = dM_B \frac{\beta_A}{\beta_B} \tag{104}$$

$$dM_B = dM_A \frac{\beta_B}{\beta_A} \tag{105}$$

.....

$$dM_Z = dM_A \frac{\beta_Z}{\beta_A} \tag{106}$$

Substitute Equation 105 and Equation 106 into Equation 100, then rearrange:

$$dM_A(W_{dA} + W_{dB}\frac{\beta_B}{\beta_A} + ... + W_{dZ}\frac{\beta_Z}{\beta_A}) = \frac{P \cdot A \cdot p_s}{\ell}\left[a_{w(out)} - a_{w(in)}\right]dt \tag{107}$$

Solve for *dt*.

$$dt = \frac{\ell}{P \cdot A \cdot p_s}(W_{dA} + W_{dB}\frac{\beta_B}{\beta_A} + ... + W_{dZ}\frac{\beta_Z}{\beta_A})\left[\frac{dM_A}{a_{w(out)} - a_{w(in)}}\right] \tag{108}$$

Integrate Equation 108.

$$t = \frac{\ell}{P \cdot A \cdot p_s}\left(W_{dA} + W_{dB}\frac{\beta_B}{\beta_A} + ... + W_{dZ}\frac{\beta_Z}{\beta_A}\right)\int_{M_{Ai}}^{M_{Af}} \frac{dM_A}{a_{w(out)} - a_{w(in)}} \tag{109}$$

Analytical integration and applying piecewise linear equations for Equation 109 gives Equation 110. See Equations 58-60 in Appendix A for more information about integrating.

$$t = \frac{\ell}{P \cdot A \cdot p_s}\sum_{m=1}^{i}(W_{dA}\beta_{Am} + W_{dB}\beta_{Bm} \cdots + W_{dZ}\beta_{Zm})\ln\left[\frac{(a_{w(out)} - a_{w(in)})_{t=i}}{(a_{w(out)} - a_{w(in)})_{t=i+1}}\right] \tag{110}$$

where $\beta_{Am} = \frac{M_{A(n+1)} - M_{A(n)}}{a_{w(n+1)} - a_{w(n)}}, \beta_{Bm} = \frac{M_{B(n+1)} - M_{B(n)}}{a_{w(n+1)} - a_{w(n)}}, \beta_{Zm} = \frac{M_{Z(n+1)} - M_{Z(n)}}{a_{w(n+1)} - a_{w(n)}}$

$(0 \leq n \leq i)$

Equation 110 can be used to calculate the shelf life of any number of components in a package by using the piecewise linear relationship between M and a_w.

2. Moisture prediction model

In Appendix 1 of the paper "Prediction of moisture transfer in mixtures of solids: transfer via the vapor phase", Zografi and coworkers (1988) showed that the polynomial constants C_1, C_2, C_3, C_4, and C_5 in Equation 97 are very complex even though only two components were considered. If one more component is added in the moisture transfer process, an increase of two additional roots results in Equation 97 in Appendix A. It makes finding the real root of the equation between $(p/p_s) = 0$ and $(p/p_s) = 1$ much more complex. The "Solver" function is a statistical program in Microsoft Excel that uses nonlinear regression. If it is used to determine the $(p/p_s)_{in}$ at each time interval j, the complex polynomial Equation 97 does not need to be developed. The Solver algorithm used in Excel is not available for inspection. The simple algorithm in Figure 69 describes how Solver works.

Equation 111 and Equation 112 can be extended to consider any number of components in a package, and $(p/p_s)_{in}$ can be determined easily by using the "Solver" function.

$$m_{T,\ at\ time=0} = W_{dA}M_A + W_{dB}M_B + ... + W_{dZ}M_Z + m_h \qquad (111)$$

$$m_{T,at\ time=0} = W_{dA}\left\{\frac{W_{mA}C_{gA}K_A(p/p_s)}{[1-K_A(p/p_s)]\times[1-K_A(p/p_s)+C_{gA}K_A(p/p_s)]}\right\}$$
$$+W_{dB}\left\{\frac{W_{mB}C_{LB}(p/p_s)}{[1+C_{LB}(p/p_s)]}\right\}+.....+W_{dZ}GAB_Z(or\ Langmuir_Z) \qquad (112)$$
$$+\frac{p_s\cdot V\cdot(p/p_s)\times 18}{R\cdot T}$$

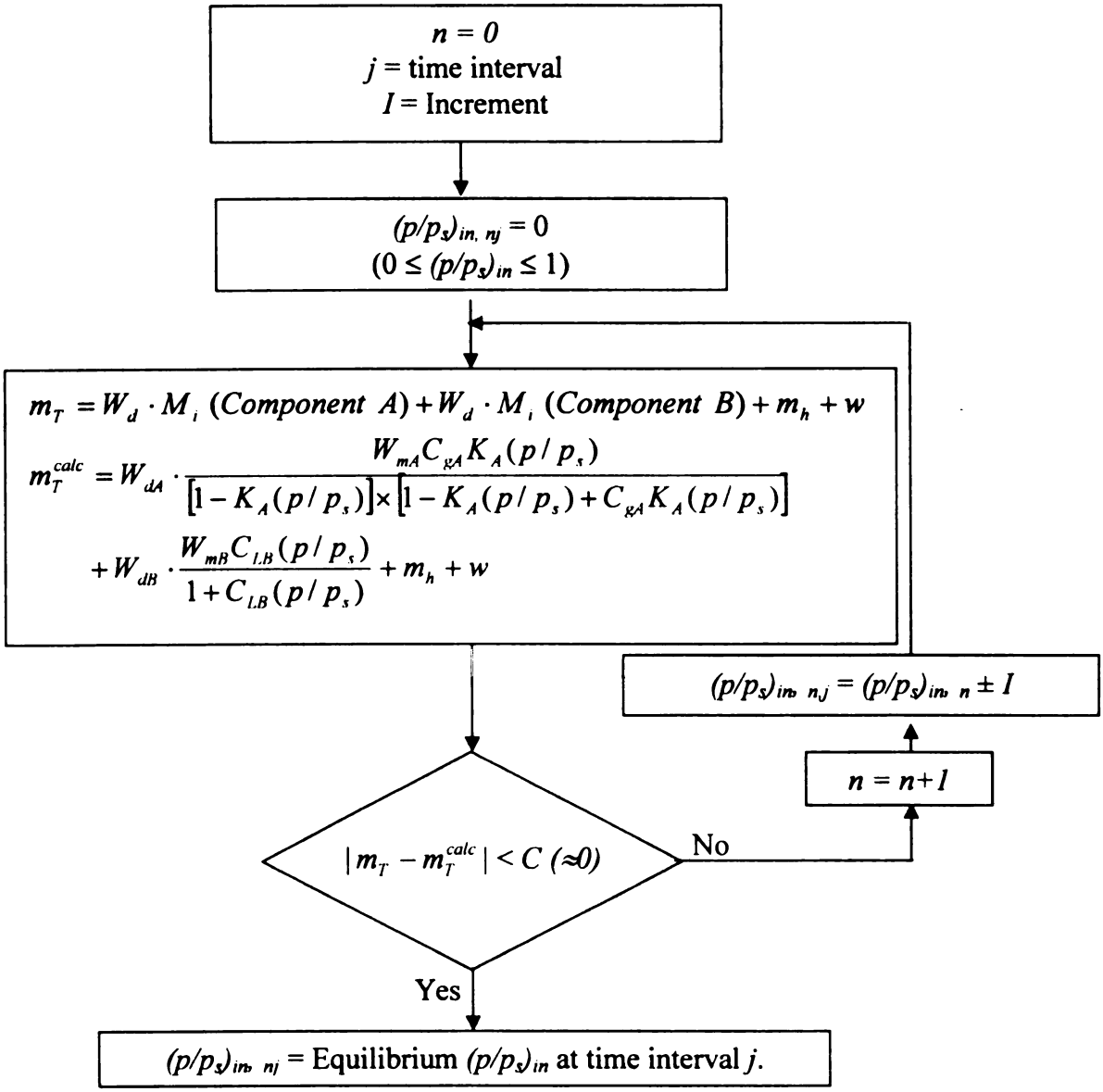


Figure 69 Algorithm used to calculate the equilibrium $(p/p_s)_{in}$

Since m_T remains constant for a time interval j, an estimate for the relative water vapor pressure $(p/p_s)_{in}$ can be used to determine m_T^{calc}, a calculated total moisture content in the system (components + package headspace). If m_T^{calc} is close to m_T in the range of C (Convergence), then the program stops. Otherwise, another estimated $(p/p_s)_{in}$ will be tried to make m_T^{calc} close to m_T in the range of C by changing $(p/p_s)_{in}$ in a series of very small increments (e.g., $I = 0.0000001$). Finally estimated $(p/p_s)_{in}$ is the predicted final relative water vapor pressure in the system following moisture transfer.

Figure 70 shows an example of an algorithm used to calculate the relative humidity of the headspace and moisture content of components in a package at each time interval over the total storage time t. The $(p/p_s)_{in}$ determined at each time interval j is used to calculate the moisture content of components by using the GAB or Langmuir equation.

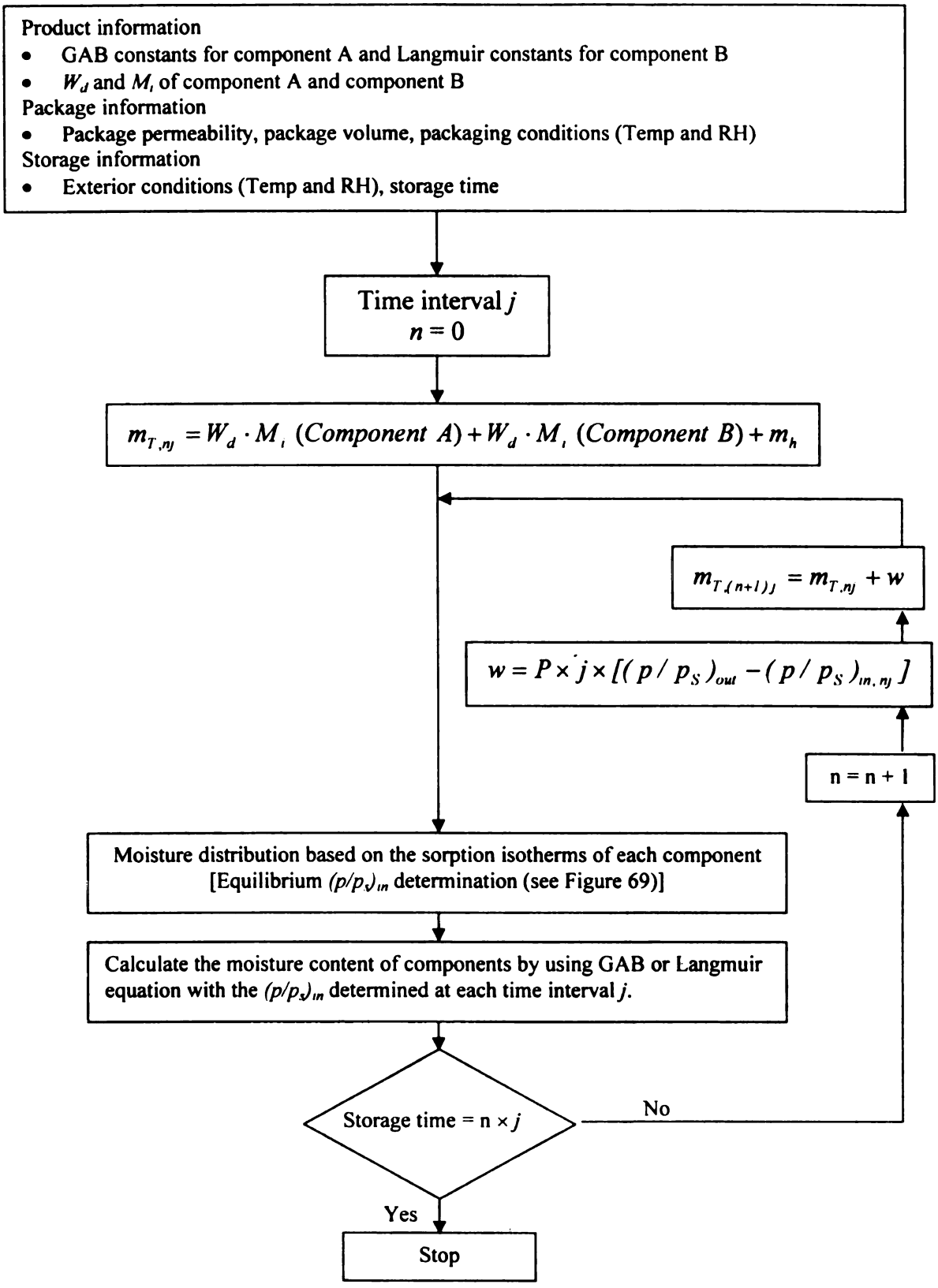


Figure 70 Example of an algorithm used to calculate the relative humidity of the headspace and moisture content of components in a package at each time interval j over the total storage time t

Figure 71 shows how the program determines the GAB and Langmuir constants with the experimental moisture sorption isotherm data. The program runs until the sum of square error between experimental and calculated data is minimized.

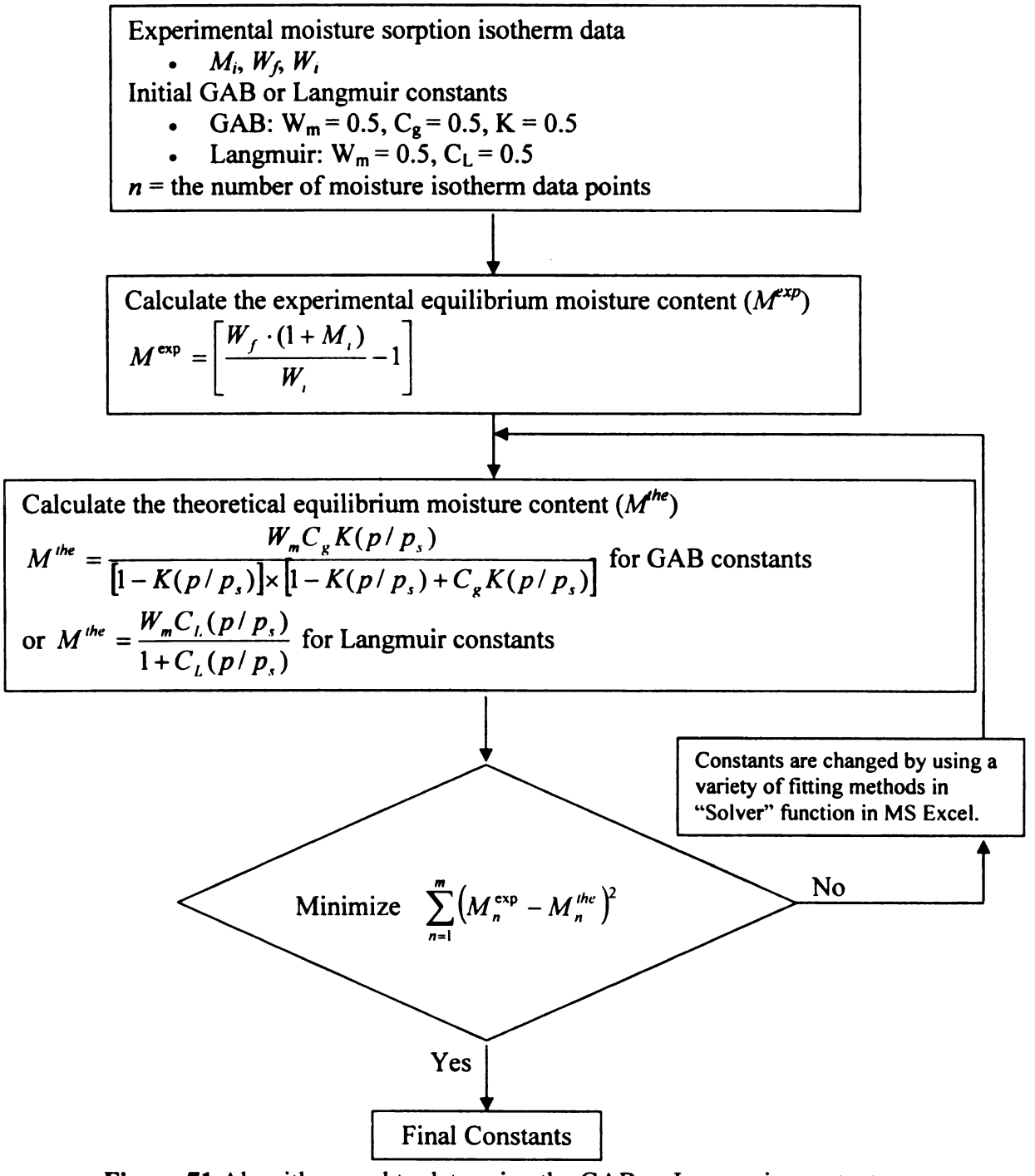


Figure 71 Algorithm used to determine the GAB or Langmuir constants

3. Verification of the moisture and shelf life prediction program

Figure 72 shows a result spreadsheet example from the moisture prediction program. It shows the relative humidities of the package headspace and moisture content of the solids at each time interval for a desired storage time. And, Figure 73 shows the shelf life prediction program. By changing the input data such as dry weight of solids, the final moisture content, and storage conditions, the shelf life can be calculated for a variety of situations. An example considering two solids in a package is shown below.

Parameters used in the moisture simulation program

- Solids
  - Dry weight: 3.6929g (tablets), 0.4863g (silica gel)
  - Initial moisture content: 1.9312% (tablets), 3.0310% (silica gel)
  - Sorption isotherm equations: GAB constants (W_m: 0.013392, C_g: 113.2096, K: 0.933012) for tablets, Langmuir constants (W_m: 0.819364, C_L: 0.924676) for silica gel
- Package (LDPE bag)
  - Volume: 0.02 L
  - Permeability: 0.0252 g/[day·package·p_s]
- Storage condition
  - Temperature at packaging line: 25°C
  - Relative humidity at packaging line: 40%
  - Temperature at storage: 40°C
  - Relative humidity at storage: 90%
  - Storage time (for moisture prediction part): 7 days
  - Final storage condition (for shelf life prediction part): 70% RH
  - Number of piecewise calculations (for shelf life prediction part): 100

Example spreadsheet showing results calculated by using above parameters

Figure 72 shows results obtained from the moisture prediction program. It shows the RH of the package headspace and moisture content of each solid at each time interval.

Input Data

Date of result calculation: 2003-03-25 pm 2:18:09

	Drug X Tablets		Desiccant		LDPE bag	
Wd (g):	3.6929	Wd (g):	0.4863	Temperature (°C) in packaging line:	25
IMC (%):	1.9312	IMC (%):	3.031	RH (%) in packaging line:	40
GAB, Wm:	0.013392	Wm:	0.819364	Volume (L) of package	0.02
Langmuir, Cg:	113.2096			Permeability (g/day·pkg·ps):	0.0252
or K:	0.933012			Exterior Temperature (°C):	40
Fractional		CL:	0.924676	Exterior RH (%):	90
Polynomial				Expected storage time (days):	7
Constants				Time interval (days):	1

	Name	Description
Component I	Drug X Tablets :	dry weight = 3.6929g
Component II	Desiccant :	dry weight = 0.4863g
Package	LDPE bag :	P = 0.0252 g/day.pkg.ps

Days	Package Headspace			Drug X Tablets			Desiccant			Moisture Permeated	Total Moisture (g)
	P/P0	RH (%)	AH(g)	MC (g)	MC (%)	RH (%)	MC (g)	MC (%)	RH (%)		
Initial value	0.4000	40.00%	0.0002	0.0713	1.93%	34.19%	0.0147	3.03%	4.15%		0.0862
Equilibrium (t = 0)	0.1053	10.53%	0.0000	0.0507	1.37%	10.53%	0.0354	7.27%	10.53%		0.0862
Final value	0.4421	44.21%	0.0005	0.0831	2.25%	44.21%	0.1156	23.78%	44.21%	0.1130	0.1992
0	0.1053	10.53%	0.0000	0.0507	1.37%	10.53%	0.0354	7.27%	10.53%	0	0.0862
1	0.1582	15.82%	0.0001	0.0552	1.49%	15.82%	0.0509	10.46%	15.82%	0.0200	0.1062
2	0.2116	21.16%	0.0001	0.0595	1.61%	21.16%	0.0652	13.41%	21.16%	0.0387	0.1249
3	0.2637	26.37%	0.0001	0.0639	1.73%	26.37%	0.0781	16.06%	26.37%	0.0561	0.1423
4	0.3134	31.34%	0.0001	0.0684	1.85%	31.34%	0.0895	18.41%	31.34%	0.0721	0.1583
5	0.3600	36.00%	0.0002	0.0732	1.98%	36.00%	0.0995	20.46%	36.00%	0.0869	0.1731
6	0.4030	40.30%	0.0002	0.0781	2.12%	40.30%	0.1082	22.24%	40.30%	0.1005	0.1867
7	0.4421	44.21%	0.0002	0.0831	2.25%	44.21%	0.1156	23.78%	44.21%	0.1130	0.1992

Figure 72 Example spreadsheet from the proprietary moisture prediction program

The package volume, temperature and relative humidity at the packaging line are used to calculate the amount of initial moisture in the package. If temperatures at the packaging line and storage are different, another sorption isotherm at the temperature of the packaging line is needed to calculate the amount of initial moisture in the package. However, as explained in Chapter 3.2.(2)(a) Moisture sorption isotherms of drug X tablets, the moisture sorption isotherms do not vary much over the range of 20-50°C. Therefore, for the purpose of simplifying computer programming, the moisture sorption isotherm obtained at the storage temperature (40°C) was used to calculate the amount of initial moisture in tablets packaged at 25°C. If two different sets of GAB constants are used, the program will be much larger.

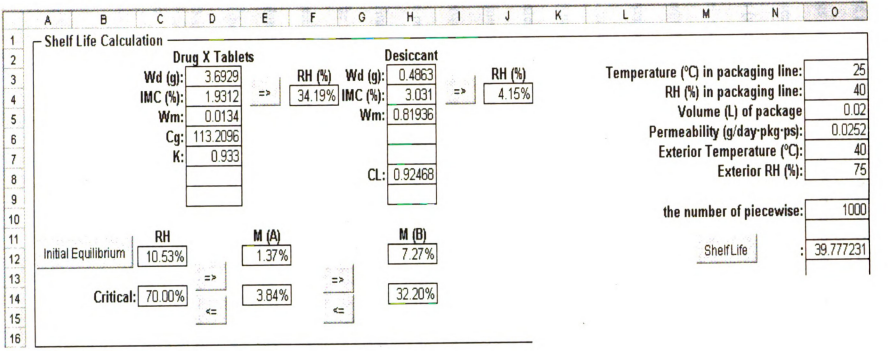


Figure 73 Example spreadsheet from the shelf life prediction program

To verify the moisture and shelf life prediction models, moisture content of tablets in LDPE bags and HDPE bottles was determined experimentally over time, and compared to moisture content calculated by the moisture prediction part in the moisture simulation program (see Figures 74-79). Each bag and bottle had different weights of tablets and silica gel, so the moisture prediction program was run 7 times using each weight of tablets and silica gel, and a different storage time. Moisture content was calculated for a given storage time using 1 day time intervals.

The results, initial equilibrium and final moisture content, obtained from the moisture prediction program were inserted into the shelf life prediction program, and then the shelf life was calculated at given storage conditions. The results were compared with the actual storage time to verify the shelf life program (see Tables 28-33). They show good agreement between the actual storage time and the shelf life calculated from the shelf life prediction program. The sorption isotherm curve between the initial and final points was divided into just 100 piecewise calculations to save program running time. It was very close to the shelf life result using 1000 piecewise calculations. Based on the example below, shelf life calculated using 100 piecewise calculations was 39.77 days, and shelf life calculated using 1000 piecewise calculations was 39.78 days. So, it is almost the same as the shelf life result would be using infinite piecewise calculations.

Appendix D shows all moisture raw data used to calculate moisture content of solids and shelf life.

(1) Tablets in LDPE bags without silica gel and with silica gel (0.5 g, 1 g, and 2 g) in LDPE bags

Each bag had a slightly different weight of tablets and silica gel, so the moisture prediction program was run 7 times using actual weights of tablets and silica gel at each storage time. Figure 74 and Table 28 show good agreement between the moisture content of tablets in LDPE bags without desiccant measured experimentally and calculated by the moisture prediction program in the moisture simulation program.

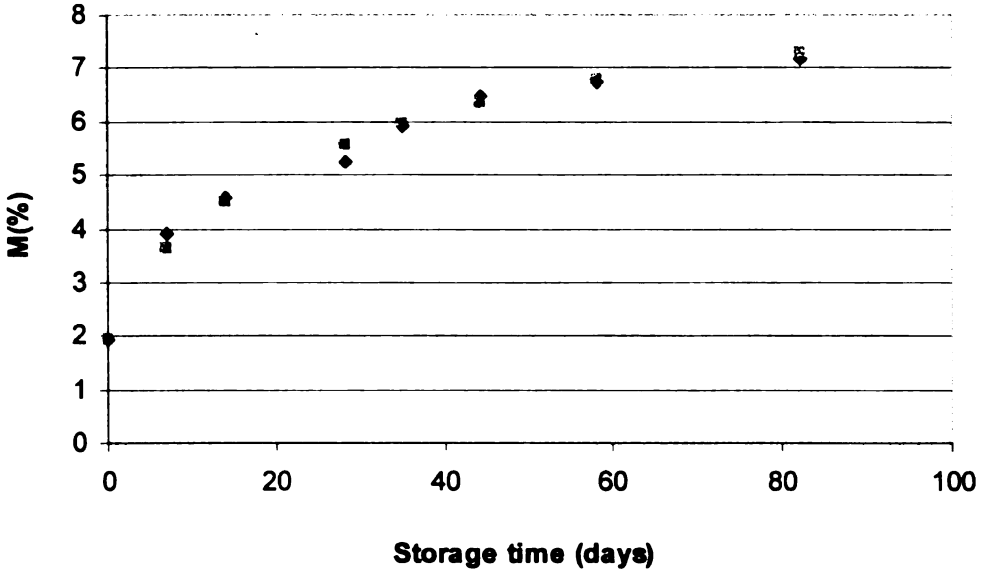
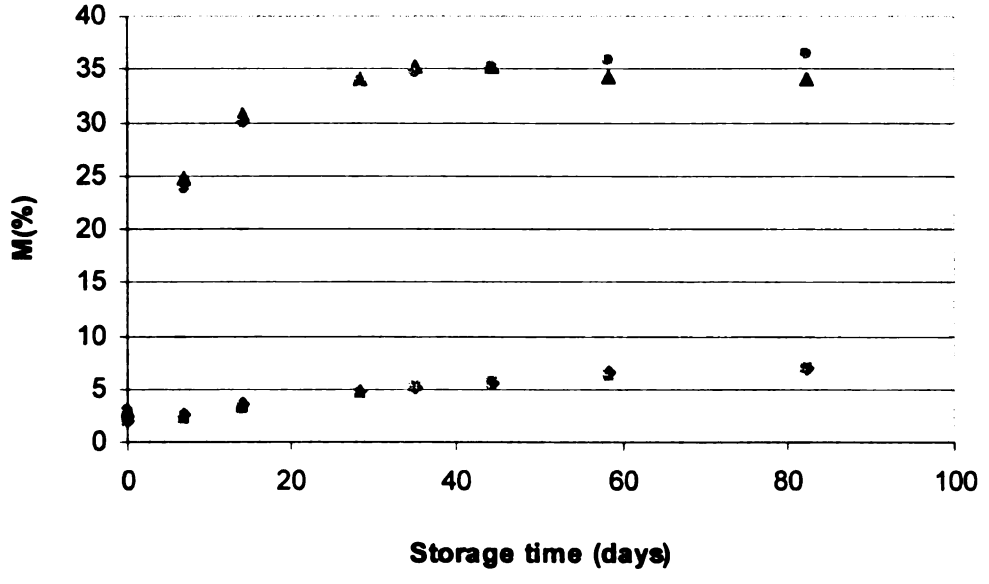


Figure 74 Comparison between experimental and calculated moisture content of tablets stored in LDPE bags without silica gel

Table 28 Comparison between experimental and calculated moisture content, and between actual storage time and calculated shelf life of tablets stored in LDPE bags without desiccant

Storage time (days)	*M(%)* of tablets measured experimentally	*M(%)* of tablets calculated by moisture prediction program	Shelf life (days) calculated by SL prediction program
7	3.91%	3.62%	7.5
14	4.58%	4.50%	14.7
28	5.23%	5.57%	28.9
35	5.90%	5.95%	36
44	6.46%	6.33%	45
58	6.74%	6.77%	59
82	7.17%	7.29%	83.5

Figure 75 and Table 29 show the moisture content of tablets stored in LDPE bags containing 0.5 g silica gel measured experimentally and calculated by the moisture prediction program. The *M (%)* of silica gel at 58 and 82 days storage time had differences of 1.63 and 2.35%, respectively, between the experimental and calculated values. The moisture gain of tablets was measured easily, but the "experimental" moisture gain of the silica gel was calculated by difference (see Chapter 2.2.(5)(c) Verification of moisture simulation program). In this case, only 0.5 g silica gel was used. The *M (%)* of silica gel is changed greatly by even a small amount of moisture change (e.g., 2% *M (%)* difference results from 0.01 g moisture change). Therefore, 1.63 and 2.35% *M (%)* differences at 58 and 82 days storage time are not bad.



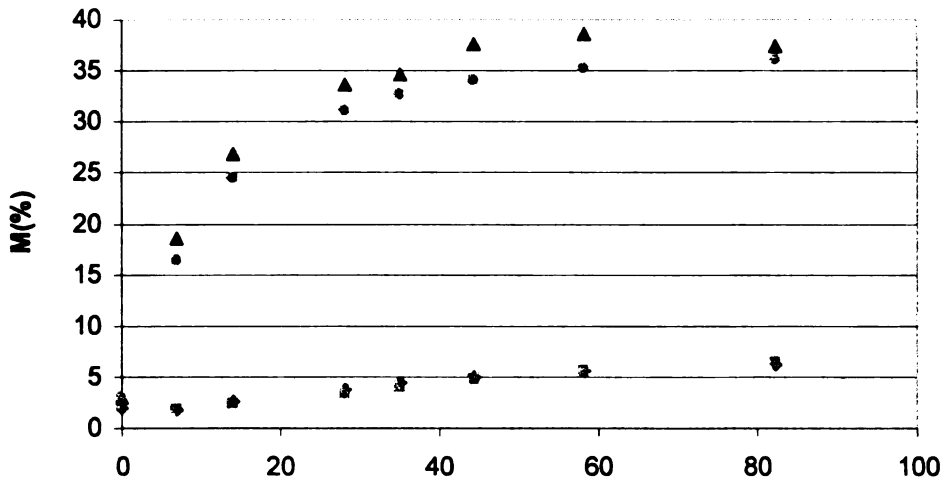
◆ M(%) of tablets measured experimentally ■ M(%) of tablets calculated by the moisture prediction program ▲ M(%) of silica gel by difference ● M(%) of silica gel calculated by the moisture prediction program

Figure 75 Comparison between experimental and calculated moisture content of tablets and silica gel (0.5 g) stored in LDPE bags

Table 29 Comparison between experimental and calculated moisture content of tablets and 0.5 g silica gel stored in LDPE bag, and between actual storage time and calculated shelf life.

Storage time (days)	*M(%)* measured experimentally		*M(%)* calculated by the moisture prediction program		Shelf life (days) calculated by SL prediction program
	Tablets	Silica gel	Tablets	Silica gel	
7	2.55%	24.69%	2.25%	23.78%	7
14	3.49%	30.76%	3.18%	29.95%	14.5
28	4.72%	34.08%	4.57%	33.80%	28.8
35	5.24%	35.31%	5.08%	34.60%	35
44	5.50%	35.34%	5.59%	35.23%	45
58	6.45%	34.21%	6.19%	35.84%	59
82	7.01%	34.03%	6.88%	36.38%	83.4

Figure 76 and Table 30 show the moisture content of tablets stored in LDPE bags containing 1 g silica gel measured experimentally and calculated by the moisture prediction program. The *M (%)* of silica gel measured experimentally are 1.49-3.45% higher than the *M(%)* calculated by the moisture prediction program.



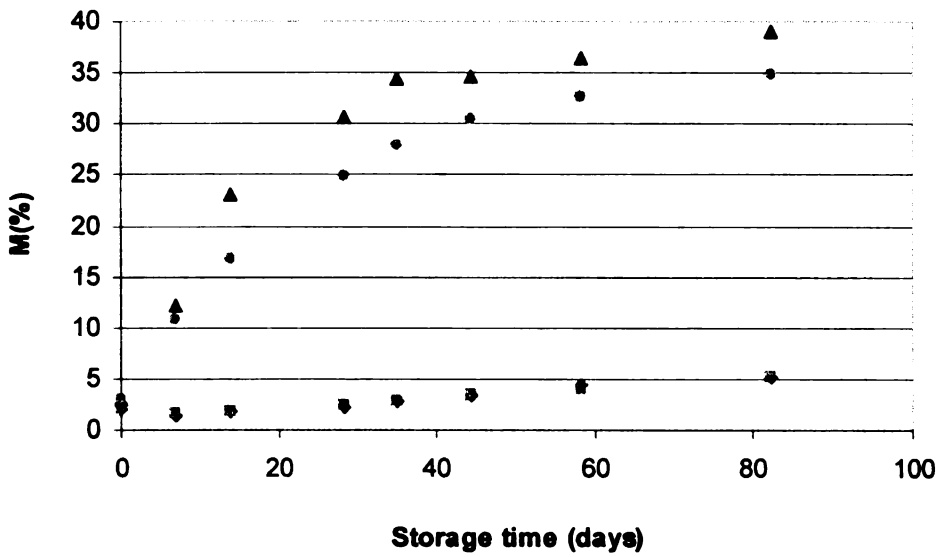
◆ M(%) of tablets measured experimentally ■ M(%) of tablets calculated by the moisture prediction program ▲ M(%) of silica gel by difference ● M(%) of silica gel calculated by the moisture prediction program

Figure 76 Comparison between experimental and calculated moisture content of tablets and silica gel (1 g) stored in LDPE bags

Table 30 Comparison between experimental and calculated moisture content of tablets and 1 g silica gel stored in LDPE bag, and between actual storage time and calculated shelf life.

Storage time (days)	*M(%)* measured experimentally		*M(%)* calculated by the moisture prediction program		Shelf life (days) calculated by SL prediction program
	Tablets	Silica gel	Tablets	Silica gel	
7	1.82%	18.51%	1.74%	16.30%	7
14	2.62%	26.94%	2.33%	24.51%	14
28	3.81%	33.68%	3.47%	31.06%	28.6
35	4.39%	34.69%	4.02%	32.66%	35.7
44	5.00%	37.54%	4.75%	34.10%	44.9
58	5.54%	38.60%	5.52%	35.15%	59
82	6.08%	37.37%	6.36%	35.98%	83

Figure 77 and Table 31 show the same situation as shown in Figure 76 and Table 30. The *M (%)* of silica gel measured experimentally is 1.37-6.50% higher than the *M (%)* calculated by moisture prediction program. The 6.50% difference is large, but the trend of silica gel moisture content is predicted well, as shown in Figure 77. The *M (%)* of tablets measured experimentally and calculated by the moisture prediction program are very close.



◆ M(%) of tablets measured experimentally ■ M(%) of tablets calculated by the moisture prediction program ▲ M(%) of silica gel by difference ● M(%) of silica gel calculated by the moisture prediction program

Figure 77 Comparison between experimental and calculated moisture content of tablets and silica gel (2 g) stored in LDPE bags

Table 31 Comparison between experimental and calculated moisture content of tablets and 2 g silica gel stored in LDPE bag, and between actual storage time and calculated shelf life.

Storage time (days)	M(%) measured experimentally		M(%) calculated by the moisture prediction program		Shelf life (days) calculated by SL prediction program
	Tablets	Silica gel	Tablets	Silica gel	
7	1.42%	12.21%	1.51%	10.84%	7
14	1.84%	23.02%	1.76%	16.65%	14
28	2.24%	30.59%	2.37%	24.91%	28
35	2.72%	34.37%	2.77%	27.87%	35
44	3.33%	34.72%	3.30%	30.43%	44.6
58	4.44%	36.51%	4.05%	32.71%	59
82	5.17%	39.09%	5.24%	34.81%	83

(2) Tablets in HDPE bottles without silica gel and with 0.5 g silica gel in HDPE bottles

Each bottle had a slightly different weight of tablets and silica gel, so the moisture prediction program was run 7 times using actual weights of tablets and silica gel at each storage time. As shown in Figure 78 and Table 32, there is good agreement between the moisture content measured experimentally and calculated by the moisture prediction program.

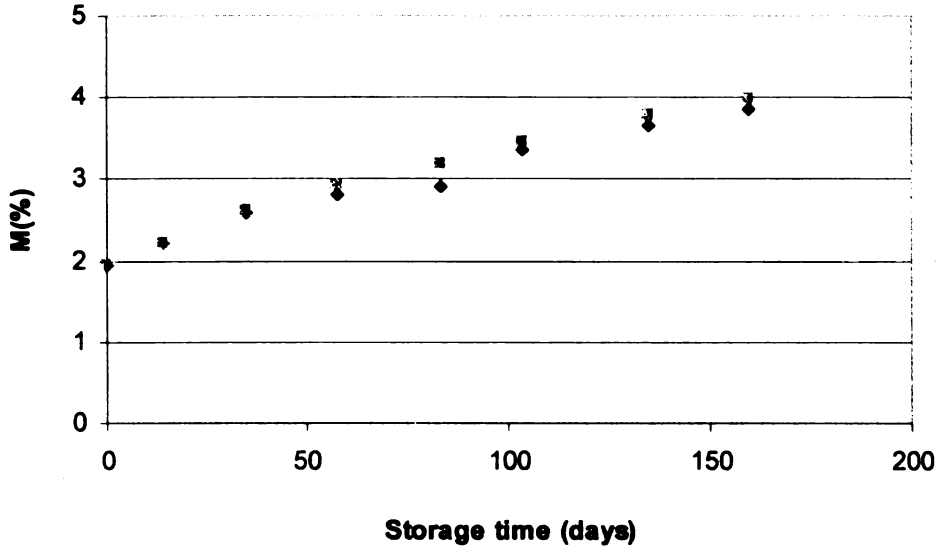
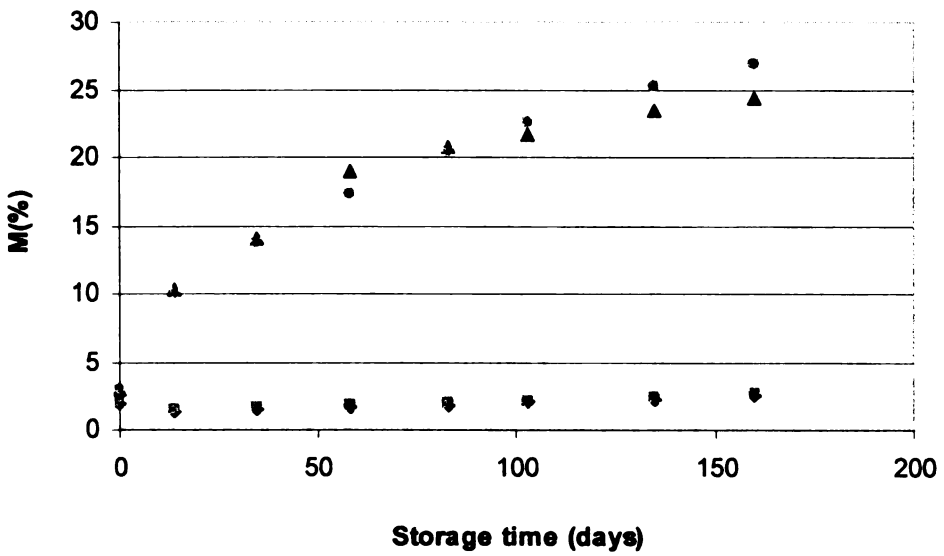


Figure 78 Comparison between experimental and calculated moisture content of tablets stored in HDPE bottles without silica gel

Table 32 Comparison between experimental and calculated moisture content of tablets stored in HDPE bottle without silica gel, and between actual storage time and calculated shelf life.

Storage time (days)	*M(%)* of tablets measured experimentally	*M(%)* of tablets calculated by the moisture prediction program	Shelf life (days) calculated by SL prediction program
14	2.21%	2.22%	13.8
35	2.60%	2.60%	34.5
58	2.81%	2.93%	57
83	2.91%	3.18%	82
103	3.35%	3.46%	102
135	3.65%	3.77%	133.8
160	3.86%	3.98%	158.8

Figure 79 and Table 33 show good agreement between the moisture content measured experimentally and calculated by the moisture prediction program. The *M (%)* of silica gel at 160 days storage time had difference of 2.59% between the experimental and calculated values. The moisture gain of tablets was measured easily, but the "experimental" moisture gain of the silica gel was calculated by difference. As explained before, 2.59% *M (%)* difference at 160 days storage time is not bad.



◆ M(%) of tablets measured experimentally ■ M(%) of tablets calculated by the moisture prediction program ▲ M(%) of silica gel by difference ● M(%) of silica gel calculated by the moisture prediction program

Figure 79 Comparison between experimental and calculated moisture content of tablets and silica gel (0.5 g) in HDPE bottles

Table 33 Comparison between experimental and calculated moisture content of tablets and 0.5 g silica gel in HDPE bottle, and between actual storage time and calculated shelf life.

Storage time (days)	*M(%)* measured experimentally		*M(%)* calculated by moisture prediction program		Shelf life (days) calculated by SL prediction program
	Tablets	Silica gel	Tablets	Silica gel	
14	1.36%	10.27%	1.48%	9.96%	13.9
35	1.43%	13.96%	1.63%	13.76%	34.9
58	1.69%	18.93%	1.79%	17.30%	57.8
83	1.77%	20.80%	1.98%	20.44%	82.6
103	2.07%	21.62%	2.14%	22.56%	102.4
135	2.23%	23.36%	2.40%	25.23%	134.3
160	2.47%	24.29%	2.62%	26.88%	159.2

Appendix C

Tablet Formulation, Manufacturing, and Interaction

1. Formulation

Table 34 shows the drug X tablet formulation.

Table 34 Drug X tablet formulation

	mg	%	Functions	Characteristics
Wet Granulation				
Drug X	20.40	8.16	Active pharmaceutical ingredient (API)	Sensitive to moisture and light, Poorly soluble in water
Mannitol (granular)	157.72	63.09	diluent	Non-hygroscopic (up to ~75%), soluble in water
Povidone	10.00	4.00	binder, dissolution aid, disintegrant	Enhance dissolution of poorly soluble drugs, very hygroscopic, soluble in acids and water
Croscarmellose Sodium	3.75	1.50	superdisintegrant	Insoluble, high absorption, high swelling (4~8 times)
Microcrystalline Cellulose (MCC)	25.00	10.00	binder, disintegrant	Hygroscopic, insoluble in water and dilute acids
Extragranulation				
Croscarmellose Sodium	1.25	0.50	superdisintegrant	
Microcrystalline Cellulose (MCC)	20.00	8.00	binder, disintegrant	
Magnesium Stearate	1.88	0.75	lubricant	Promote the flow of powder, insoluble in water, hydrophobic
Coating				
Color Mixture Yellow	10.00	4.00		Soluble in water
Carnauba	Trace			Natural wax
Total	250.00	100.00		

Drug X, mannitol, povidone, and portions of the croscarmellose sodium and microcrystalline cellulose were screened (10 mesh) into the high shear granulator. The powders were then dry mixed for 5 minutes to make a uniform blend prior to granulation (main blade: 200rpm, chopper blade: 1800rpm). Purified water was then used to granulate the powder mix in the high shear granulator for about 4 minutes (wet granulation). The granulation was dried using a fluid bed drying process. The milled granulation was then placed into an appropriately sized tumble bin.

The appropriate quantities of croscarmellose sodium (20 mesh), microcrystalline cellulose (20 mesh), and magnesium stearate (30 mesh) were sieved and added to the

tumble bin. The mixture was blended for 5 minutes, then compressed on a rotary tablet presser.

The color mixture yellow was mixed with purified water to form the coating suspension. The core tablets were placed into a side vented, perforated coating pan. The tablets were then spray coated with the suspension until an approximate 4.0% weight gain was achieved. Figure 80 shows the graphical representation of the manufacturing of drug X tablets.

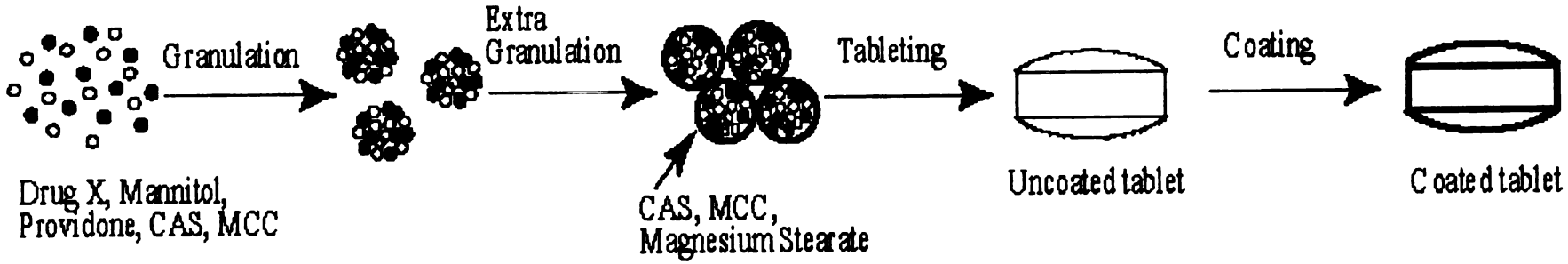


Figure 80 Graphical representation of the manufacturing of drug X tablets

From the extra granulation process, the granules were surrounded by croscarmellose sodium, microcrystalline cellulose, and magnesium stearate. The magnesium stearate is a lubricant and is hydrophobic, so the tablet dissolution rate decreases as the time of blending increases, but magnesium stearate increases tablet friability (Bolhuis, 1981 and Chowan, 1986). Blending times with magnesium stearate should thus be carefully controlled. Croscarmellose sodium and microcrystalline cellulose are hygroscopic, especially croscarmellose sodium absorbs moisture quickly, then it swells to 4-8 times its original volume (Kibbe, 2000). With the swelling of croscarmellose sodium, the boundary strength among granules becomes weak. It makes the tablet disintegrate quickly.

The general characteristics of excipients used for drug X tablets were reviewed based on the USP monograph, Handbook of Pharmaceutical Excipients (Kibbe, 2000), and Modern Pharmaceutics (Marshall et al., 1989).

(1) Drug X (API, Active Pharmaceutical Ingredient)

Drug X is sensitive to moisture and light, and it is poorly soluble in water.

(2) Mannitol

Mannitol can be used as a sweetening agent, diluent, or binder in tablets, and occurs as white, odorless, crystalline, or free-flowing granules. Figure 81 shows the structural formula of mannitol. Manniol is not hygroscopic, so it may be used with moisture sensitive active ingredients. Mannitol resists moisture sorption, even at high relative humidity as shown in Figure 82. Granulations containing mannitol have the

advantage of being dried easily. Granular mannitol flows well and imparts improved flow properties to other materials. Suitable binders for preparing granulations of powdered mannitol are gelatin, methylcellulose 400, starch paste, povidone, and sorbitol. Usually, 3-6 times as much magnesium stearate or 1.5-3 times as much calcium stearate is needed for lubrication of mannitol granulations than as needed for other excipients.

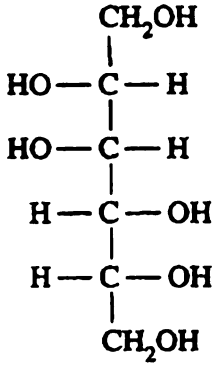


Figure 81 Structural formula of mannitol

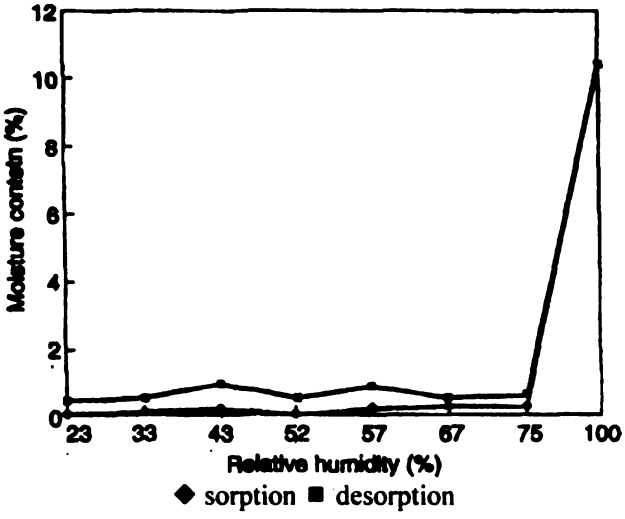


Figure 82 Moisture sorption-desorption isotherm of mannitol (Kibbe, 2000)

(3) Povidone

Povidone can be used as a disintegrant, dissolution aid, and tablet binder. It is a fine, white to creamy-white colored, odorless or almost odorless, hygroscopic powder. Figure 83 shows the structural formula of povidone and Figure 84 shows that significant amounts of moisture can be absorbed at low relative humidity. In tableting, povidone solutions are used as binders in wet-granulation processes. Povidone is also added to powder blends in dry form and granulated *in situ* by the addition of water, alcohol, or hydroalcoholic solutions. Povidone is used as a disintegrant and has been shown to enhance dissolution of poorly soluble drugs from solid-dosage forms. The solubility of a

number of poorly soluble active drugs may be increased by mixing with povidone. Povidone is freely soluble in acids, chloroform, ethanol, ketones, methanol, and water. It is practically insoluble in ether, hydrocarbons, and mineral oil.

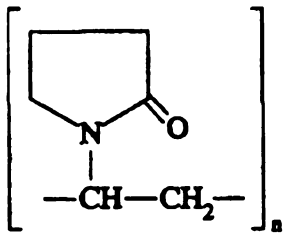


Figure 83 Structural formula of povidone

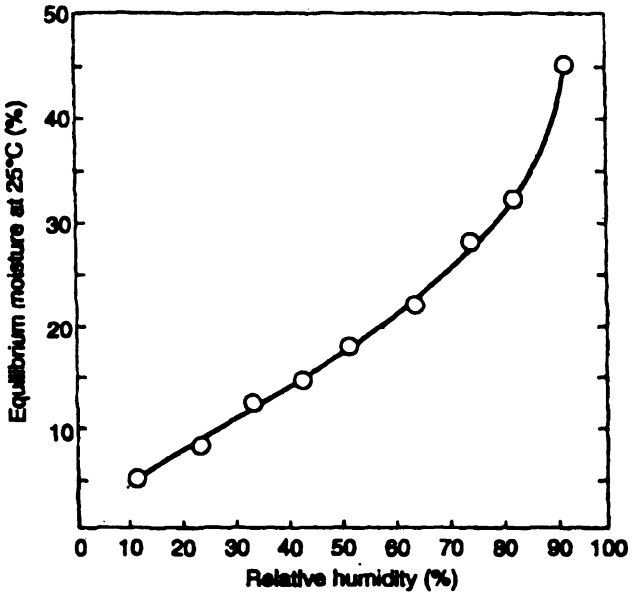


Figure 84 Moisture sorption isotherm of povidone (Kibbe, 2000)

(4) Croscarmellose sodium

Croscarmellose sodium can be used as a tablet super disintegrant due to its high swelling property. When croscarmellose sodium is used in wet granulations, it is best added in both the wet and dry stages of the process (intra and extragranularly) so that the wicking and swelling ability of the disintegrant is best utilized. It is insoluble, although croscarmellose sodium rapidly swells to 4-8 times its original volume on contact with water. Thibert and Hancock (1996) observed directly the hydration behavior of croscarmellose sodium particles by using ESEM (Environmental Scanning Electron Microscopy). At 40% RH, the croscarmellose sodium particles comprised twisted fibers. Upon exposure to 80% RH the particles experienced considerable additional twisting and

expansion. After the RH was reduced to 40% the particles did not regain their original shape. This may be linked to the hysteresis observed in the water vapor sorption isotherm for croscarmellose sodium.

(5) Microcrystalline cellulose

Microcrystalline cellulose (MCC) is a purified, partially depolymerized cellulose that occurs as a white, odorless, tasteless, crystalline powder composed of porous particles. MCC can be used as a diluent, binder, or disintegrant in tablets. It is hygroscopic and slightly soluble in 5% w/v sodium hydroxide solution, and practically insoluble in water, dilute acids, and most organic solvents. MCC has been shown to be highly porous, with strong "wicking" tendencies, so it is a good disintegrant. Also, MCC can enhance poor compression characteristics of starch (Banker and Rhodes, 1989). However, Thibert and Hancock observed that there were no changes in the particle morphology nor was there any swelling of the MCC particles after prolonged exposure to 80% RH. These results are consistent with the limited disintegrant properties of MCC and its low level of water vapor sorption. Figure 85 shows the structural formula of microcrystalline cellulose (MCC).

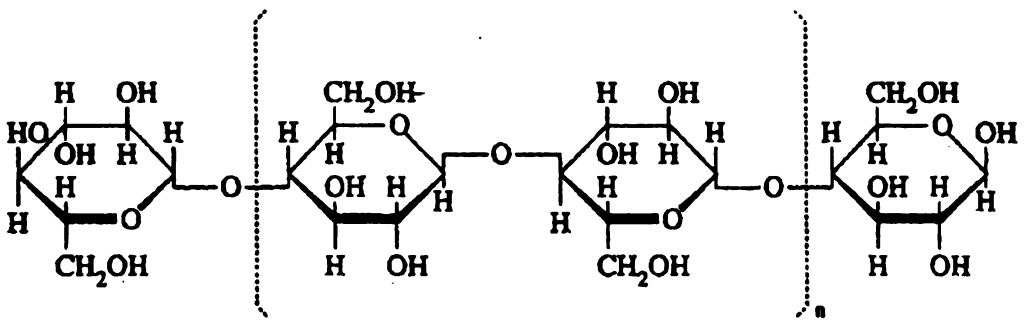


Figure 85 Structural formula of microcrystalline cellulose (MCC)

(6) Magnesium stearate

Magnesium stearate is a fine, white, precipitated or milled, impalpable powder of low bulk density, having a faint odor of stearic acid and a characteristic taste. It can be used as a lubricant in tablets. It is practically insoluble in ethanol, ethanol (95%), ether and water, and slightly soluble in warm benzene and warm ethanol (95%). Magnesium stearate is hydrophobic and may retard the dissolution of a drug from a solid dosage form, so the lowest possible concentration should be used. Tablet dissolution rate and crushing strength decrease as the time of blending increases (Chowan, 1986). It may also increase tablet friability. Blending time with magnesium stearate should thus be carefully controlled. The structural formula is $[CH_3(CH_2)_{16}COO]_2Mg$.

(7) Coating material

Many tablets are now coated because this can minimize the unpleasant taste of certain medicaments, protect the ingredients against decomposition, improve the manufacturing process (no dust), and enhance the appearance. The coating material must be soluble in water.

2. Manufacturing – wet granulation

The components of the formulation are mixed with a granulating liquid such as water to produce granules which will readily compress to give tablets. The wet granulated tablets are more robust than those produced by direct compression, so the content uniformity is better than with direct compression. The general purpose of wet granulation is (1) to enlarge the particle size, (2) to improve the particle shape and make

it fairly spherical, (3) to make the surface of the particles and the tablet hydrophilic (to promote wetting, and consequently disintegration and dissolution), and (4) to promote compressibility (Carstensen, 1993). The disintegration of the tablet must be followed by granular disintegration in order to promote rapid dissolution and hence absorption (Banker and Rhodes, 1989).

Appendix D

Summary Tables of Permeability, Moisture Sorption Isotherms, and Moisture Content Verification

1. Permeability

Table 35 Moisture gain (g) of LDPE bags using $CaCl_2$ at 40°C

Days	0	7	14	16	18	30	37	57	Leaking Test
1	11.3793	11.6928	11.8640	11.9128	11.9580	12.2448	12.3765	12.8089	Pass
2	10.9961	11.2880	11.4496	11.5225	11.5463	11.8114	11.9720	12.4051	Pass
3	11.7248	12.0478	12.1979	12.2482	12.3484	12.6051	12.7953	13.2500	Pass
4	11.8688	12.2805	12.5254	12.6198	12.7951	13.3334	13.6869	14.6863	Fail
5	11.6610	12.0170	12.1322	12.1802	12.2300	12.4880	12.6593	13.0937	Pass
Net Moisture Gain (g)									
1	0	0.3035	0.4747	0.5235	0.5687	0.8555	0.9872	1.4196	
2	0	0.2819	0.4435	0.5164	0.5402	0.8053	0.9659	1.3990	
3	0	0.3130	0.4631	0.5134	0.6136	0.8703	1.0605	1.5152	
4	0	0.4017	0.6466	0.7410	0.9163	1.4546	1.8081	2.8075	
5	0	0.3460	0.4612	0.5092	0.5590	0.8170	0.9883	1.4227	

Table 36 Moisture gain (g) of HDPE bottles using $CaCl_2$ at 40°C

Days	0	7	21	28	46	Leaking Test
1	45.9352	45.9550	45.9720	45.9805	46.0033	Pass
2	45.5874	45.6076	45.6245	45.6332	45.6559	Pass
3	45.6107	45.6307	45.6481	45.6567	45.6792	Pass
4	45.7392	45.7598	45.7760	45.7841	45.8062	Pass
5	45.9762	45.9962	46.0132	46.0214	46.0437	Pass
Net Moisture Gain (g)						
1	0	0.0072	0.02355	0.03175	0.05375	
2	0	0.0076	0.02385	0.03225	0.05415	
3	0	0.0074	0.02415	0.03245	0.05415	
4	0	0.0080	0.02355	0.03135	0.05265	
5	0	0.0074	0.02375	0.03165	0.05315	

Table 37 Moisture gain (g) of HDPE bottle blanks at 40°C

Days	0	7	21	28	46	160	Leaking Test
1	75.6306	75.6430	75.6437	75.6440	75.6445	75.6516	Pass
2	75.8447	75.8575	75.8581	75.8584	75.8595	75.8662	Pass
Net Moisture Gain (g)							
1	0	0.0124	0.0131	0.0134	0.0139	0.0210	
2	0	0.0128	0.0134	0.0137	0.0148	0.0215	
Average	0	0.0126	0.0132	0.0136	0.0143	0.0213	

2. Moisture Sorption Isotherms

Table 38 Moisture sorption isotherm data of uncoated tablets at 25°C

	IMC (%)	RH (%)	P_i (g)	P_f (g)	EMC (%)	EMC (%) using GAB equation
1	2.1199	0.00	251.060		0	0
2		4.95	251.060	248.694	1.1574	1.1587
3		9.87	251.060	249.071	1.3111	1.3713
4		14.89	251.060	249.494	1.4829	1.5100
5		19.93	251.060	249.880	1.6401	1.6326
6		25.02	251.060	250.254	1.7922	1.7561
7		29.86	251.060	250.573	1.9217	1.8805
8		35.07	251.060	250.903	2.0562	2.0275
9		40.01	251.060	251.247	2.1961	2.1837
10		44.92	251.060	251.660	2.3640	2.3608
11		50.13	251.060	252.317	2.6313	2.5788
12		55.14	251.060	252.996	2.9073	2.8269
13		60.06	251.060	253.788	3.2295	3.1193
14		64.87	251.060	254.612	3.5648	3.4671
15		69.85	251.060	255.595	3.9644	3.9170
16		74.86	251.060	256.787	4.4494	4.5023
17		80.31	251.060	258.537	5.1611	5.3715
18		85.07	251.060	261.103	6.2050	6.4552
19		89.99	251.060	266.394	8.3570	8.1570

Table 39 Moisture sorption isotherm data of coated tablets at 25°C

	IMC (%)	RH (%)	P_i (g)	P_f (g)	EMC (%)	EMC (%) using GAB equation
1	2.3410	0.00	261.593		0	0
2		5.01	261.593	259.118	1.3727	1.4217
3		10.19	261.593	259.399	1.4826	1.5500
4		14.92	261.593	259.873	1.6678	1.6458
5		19.91	261.593	260.201	1.7963	1.7482
6		24.97	261.593	260.562	1.9376	1.8600
7		30.05	261.593	260.919	2.0773	1.9842
8		34.97	261.593	261.251	2.2073	2.1192
9		40.02	261.593	261.584	2.3374	2.2767
10		45.04	261.593	262.010	2.5039	2.4573
11		49.91	261.593	262.614	2.7403	2.6611
12		55.04	261.593	263.263	2.9943	2.9147
13		59.89	261.593	264.002	3.2833	3.2026
14		64.94	261.593	264.819	3.6030	3.5695
15		70.01	261.593	265.895	4.0241	4.0321
16		74.88	261.593	267.064	4.4813	4.6050
17		80.03	261.593	268.874	5.1895	5.4166
18		85.01	261.593	271.618	6.2628	6.5301
19		89.95	261.593	277.211	8.4511	8.2021

Table 40 Moisture sorption isotherm data of uncoated tablets at 40°C

	IMC (%)	RH (%)	P_i (g)	P_f (g)	EMC (%)	EMC (%) using GAB equation
1	1.9312	0.00			0	0
2		4.80	248.612	246.730	1.1597	1.1797
3		9.72	248.612	247.048	1.2902	1.3528
4		14.94	248.612	247.444	1.4526	1.4756
5		19.85	248.612	247.775	1.5880	1.5821
6		24.88	248.612	248.113	1.7267	1.6944
7		29.99	248.612	248.457	1.8680	1.8181
8		34.88	248.612	248.800	2.0083	1.9497
9		39.97	248.612	249.198	2.1717	2.1042
10		44.93	248.612	249.667	2.3641	2.2780
11		49.91	248.612	250.184	2.5758	2.4812
12		54.85	248.612	250.805	2.8304	2.7198
13		59.87	248.612	251.506	3.1177	3.0126
14		64.92	248.612	252.290	3.4392	3.3773
15		69.89	248.612	253.205	3.8145	3.8311
16		74.91	248.612	254.436	4.3191	4.4310
17		79.87	248.612	256.087	4.9962	5.2404
18		84.86	248.612	259.070	6.2189	6.4155
19		90.00	248.612	264.708	8.5305	8.3418

Table 41 Moisture sorption isotherm data of coated tablets at 40°C

	IMC (%)	RH (%)	P_i (g)	P_f (g)	EMC (%)	EMC (%) using GAB equation
1	2.3086	0.00			0	0
2		4.94	260.046	257.524	1.3167	1.3873
3		9.82	260.046	257.896	1.4630	1.5033
4		14.78	260.046	258.276	1.6126	1.6005
5		19.95	260.046	258.630	1.7515	1.7037
6		24.98	260.046	258.972	1.8863	1.8119
7		29.86	260.046	259.306	2.0177	1.9283
8		34.99	260.046	259.684	2.1663	2.0660
9		39.91	260.046	260.085	2.3240	2.2164
10		45.13	260.046	260.566	2.5132	2.4005
11		49.86	260.046	261.085	2.7177	2.5957
12		54.85	260.046	261.711	2.9637	2.8380
13		60.04	260.046	262.394	3.2325	3.1420
14		64.94	260.046	263.080	3.5023	3.4954
15		70.00	260.046	263.990	3.8606	3.9538
16		74.96	260.046	265.204	4.3382	4.5366
17		79.71	260.046	267.064	5.0698	5.2816
18		85.08	260.046	269.998	6.2240	6.4843
19		90.03	260.046	275.693	8.4645	8.2053

Table 42 Moisture sorption isotherm data of silica gel at 25°C

	IMC (%)	RH (%)	P_i (g)	P_f (g)	EMC (%)	EMC (%) using Langmuir equ.	EMC (%) using GAB equ.
1	3.031	0.00	22.04		0	0.0000	0.0000
2		5.14	22.04	22.653	5.8966	3.6003	3.6006
3		10.12	22.04	23.183	8.3742	6.9210	6.9215
4		15.08	22.04	23.645	10.5339	10.0759	10.0764
5		20.13	22.04	24.139	12.8433	13.1423	13.1427
6		25.1	22.04	24.613	15.0591	16.0262	16.0265
7		29.97	22.04	25.132	17.4853	18.7314	18.7315
8		35.16	22.04	25.693	20.1078	21.4913	21.4912
9		39.92	22.04	26.271	22.8098	23.9178	23.9176
10		45.15	22.04	26.909	25.7922	26.4756	26.4752
11		49.88	22.04	27.531	28.6999	28.6968	28.6962
12		54.95	22.04	28.148	31.5842	30.9863	30.9857
13		60.02	22.04	28.719	34.2535	33.1867	33.1861
14		65.1	22.04	29.205	36.5254	35.3073	35.3067
15		69.94	22.04	29.639	38.5543	37.2536	37.2531
16		75.11	22.04	29.987	40.1811	39.2571	39.2567
17		79.94	22.04	30.302	41.6536	41.0621	41.0620
18		85.16	22.04	30.598	43.0373	42.9442	42.9445
19		90.18	22.04	30.807	44.0143	44.6904	44.6911
20		95.25	22.04	30.921	44.5473	46.3939	46.3952

Table 43 Moisture sorption isotherm data of silica gel at 40°C

	IMC (%)	RH (%)	P_i (g)	P_f (g)	EMC (%)	EMC (%) using Langmuir equ.	EMC (%) using GAB equ.
1	0	0.00	110.059		0	0.0000	0.0000
2		5.28	110.059	114.359	3.9071	3.8156	3.8158
3		10.02	110.059	117.074	6.3734	6.9486	6.9488
4		14.85	110.059	119.634	8.6995	9.8907	9.8909
5		20.10	110.059	122.383	11.1975	12.8427	12.8427
6		25.10	110.059	125.211	13.7671	15.4362	15.4361
7		29.91	110.059	128.130	16.4188	17.7518	17.7515
8		35.08	110.059	131.116	19.1318	20.0687	20.0683
9		40.06	110.059	134.246	21.9761	22.1492	22.1486
10		45.04	110.059	137.269	24.7226	24.0899	24.0893
11		50.04	110.059	140.100	27.2948	25.9182	25.9176
12		55.05	110.059	142.611	29.5768	27.6402	27.6396
13		60.08	110.059	144.615	31.3973	29.2634	29.2629
14		65.16	110.059	146.053	32.7042	30.8067	30.8062
15		69.92	110.059	146.986	33.5516	32.1737	32.1734
16		75.02	110.059	147.694	34.1949	33.5600	33.5599
17		79.63	110.059	148.203	34.6571	34.7473	34.7475
18		84.90	110.059	148.751	35.1553	36.0360	36.0365
19		89.99	110.059	149.282	35.6378	37.2131	37.2139
20		95.38	110.059	149.774	36.0845	38.3987	38.4000

3. Verification

Table 44 Moisture content of tablets in LDPE bags without silica gel as a function of storage time

	Initial				After Storage			
	Package (g)	Product (g)	Product dry weight (g)	Total (g)	Storage time (Days)	Total (g)	Product (g)	Leaking Test
1	1.1010	3.7609	3.6896	4.8619	7		3.8340	Pass
2	1.1728	3.7666	3.6952	4.9394	14		3.8646	Pass
3	1.0943	3.7749	3.7034	4.8692	28		3.8970	Pass
4	1.1199	3.7658	3.6945	4.8857	35		3.9124	Pass
5	1.1239	3.7668	3.6954	4.8907	44		3.9342	Pass
6	1.1532	3.7673	3.6959	4.9205	58		3.9450	Pass
7	1.2387	3.7752	3.7037	5.0139	82		3.9692	Pass

Table 45 Moisture content of tablets and 0.5 g silica gel in LDPE bags as a function of storage time

	Initial					
	Package (g)	Product (g)	Product dry weight (g)	Silica gel (g)	Silica gel dry weight (g)	Total (g)
1	1.1690	3.7642	3.6929	0.5010	0.4863	5.4342
2	1.1062	3.7665	3.6951	0.5043	0.4895	5.3770
3	1.1428	3.7751	3.7036	0.5051	0.4902	5.4230
4	1.0884	3.7569	3.6857	0.5031	0.4883	5.3484
5	1.1603	3.7672	3.6958	0.5038	0.4890	5.4313
6	1.2139	3.7800	3.7084	0.5009	0.4862	5.4948
7	1.1861	3.7698	3.6984	0.5095	0.4945	5.4654

After Storage					
Storage time (Days)	Total (g)	Package (g)	Product (g)	Silica gel (g)	Leaking Test
7	5.5825	1.1890	3.7872	0.6063	Pass
14	5.5904	1.1262	3.8242	0.6400	Pass
28	5.6985	1.1628	3.8784	0.6573	Pass
35	5.6481	1.1084	3.8790	0.6607	Pass
44	5.7413	1.1803	3.8992	0.6618	Pass
58	5.8338	1.2339	3.9474	0.6525	Pass
82	5.8265	1.2061	3.9576	0.6628	Pass

Table 46 Moisture content of tablets and 1 g silica gel in LDPE bags as a function of storage time

	Initial					
	Package (g)	Product (g)	Product dry weight (g)	Silica gel (g)	Silica gel dry weight (g)	Total (g)
1	1.1528	3.7754	3.7039	1.0709	1.0394	5.9991
2	1.1497	3.7707	3.6993	1.0060	0.9764	5.9264
3	1.2255	3.7788	3.7072	1.0714	1.0399	6.0757
4	1.1396	3.7715	3.7000	1.0763	1.0446	5.9874
5	1.1655	3.7666	3.6952	1.0148	0.9849	5.9469
6	1.1501	3.7645	3.6932	1.0063	0.9767	5.9209
7	1.1657	3.7585	3.6873	1.0533	1.0223	5.9775
After Storage						
Storage time (days)	Total (g)	Package (g)	Product (g)	Silica gel (g)	Leaking Test	
7	6.1758	1.1728	3.7712	1.2318	Pass	
14	6.2051	1.1697	3.7960	1.2394	Pass	
28	6.4842	1.2455	3.8486	1.3901	Pass	
35	6.4292	1.1596	3.8626	1.4070	Pass	
44	6.4203	1.1855	3.8801	1.3547	Pass	
58	6.4217	1.1701	3.8979	1.3537	Pass	
82	6.5015	1.1857	3.9114	1.4044	Pass	

Table 47 Moisture content of tablets and 2 g silica gel in LDPE bags as a function of storage time

	Initial					
	Package (g)	Product (g)	Product dry weight (g)	Silica gel (g)	Silica gel dry weight (g)	Total (g)
1	1.1897	3.7747	3.7032	2.0570	1.9965	7.0214
2	1.1550	3.7793	3.7077	2.0225	1.9630	6.9568
3	1.2203	3.7801	3.7085	2.0346	1.9747	7.0350
4	1.1423	3.7632	3.6919	2.0053	1.9463	6.9108
5	1.1456	3.7806	3.7090	2.0020	1.9431	6.9282
6	1.1847	3.7551	3.6840	2.0490	1.9887	6.9888
7	1.1772	3.7747	3.7032	2.0174	1.9581	6.9693
After Storage						
Storage time (days)	Total (g)	Package (g)	Product (g)	Silica gel (g)	Leaking Test	
7	7.2059	1.2097	3.7559	2.2403	Pass	
14	7.3658	1.1750	3.7760	2.4148	Pass	
28	7.6107	1.2403	3.7915	2.5789	Pass	
35	7.5700	1.1623	3.7925	2.6152	Pass	
44	7.6159	1.1656	3.8325	2.6178	Pass	
58	7.7670	1.2047	3.8475	2.7148	Pass	
82	7.8152	1.1972	3.8945	2.7235	Pass	

Table 48 Moisture content of tablets only in HDPE bottles as a function of storage time

	Initial				After Storage			
	Package (g)	Product (g)	Product dry weight (g)	Total (g)	Storage time (days)	Total (g)	Product (g)	Leaking Test
1	13.8743	3.7781	3.7065	17.6524	14		3.7885	Pass
2	13.9523	3.7743	3.7028	17.7266	35		3.7989	Pass
3	13.9853	3.7759	3.7044	17.7612	58		3.8085	Pass
4	13.9199	4.0327	3.9563	17.9526	83		4.0716	Pass
5	13.8608	3.7972	3.7253	17.6580	103		3.8501	Pass
6	13.9392	3.7796	3.7080	17.7188	135		3.8432	Pass
7	13.9496	3.7759	3.7044	17.7255	160		3.8472	Pass

Table 49 Moisture content of tablets and 0.5 g silica gel in HDPE bottles as a function of storage time

	Initial					
	Package (g)	Product (g)	Product dry weight (g)	Silica gel (g)	Silica gel dry weight (g)	Total (g)
1	13.9370	3.7643	3.6930	0.5032	0.4884	18.2045
2	13.9006	3.7762	3.7047	0.5004	0.4857	18.1772
3	13.8637	3.7689	3.6975	0.5010	0.4863	18.1336
4	13.9122	3.7789	3.7073	0.5040	0.4892	18.1951
5	13.9266	3.7700	3.6986	0.5038	0.4890	18.2004
6	13.8595	3.7863	3.7146	0.5038	0.4890	18.1496
7	13.8869	3.7761	3.7046	0.5022	0.4874	18.1652
	After Storage					
Storage time (days)	Total (g)	Package (g)	Product (g)	Silica gel (g)	Leaking Test	
14	18.2315	13.9498	3.7431	0.5386	Pass	
35	18.2260	13.9147	3.7578	0.5535	Pass	
58	18.2176	13.8792	3.7601	0.5783	Pass	
83	18.2931	13.9292	3.7730	0.5909	Pass	
103	18.3146	13.9448	3.7751	0.5947	Pass	
135	18.2801	13.8796	3.7973	0.6032	Pass	
160	18.3105	13.9085	3.7962	0.6058	Pass	

Appendix E

Dissolution Raw Data and Dissolution Profiles at 25°C

1. Dissolution raw data

Table 50 Initial dissolution raw data of uncoated tablets

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4065	0.4846	0.5200	0.5287	0.5019	0.4597		
20	0.5595	0.5688	0.5657	0.5707	0.5587	0.5676		
30	0.5724	0.5753	0.5715	0.5783	0.5684	0.5772		
	% Dissolved							
10	68.23	81.38	87.34	88.79	84.28	77.18	81.20	7.603
20	93.71	95.39	94.94	95.79	93.75	95.16	94.79	0.868
30	95.85	96.46	95.90	97.05	95.34	96.74	96.23	0.635

Table 51 Initial dissolution raw data of coated tablets

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3677	0.3754	0.1924	0.3538	0.4342	0.0965		
20	0.5705	0.5785	0.5791	0.5700	0.5762	0.5577		
30	0.5768	0.5807	0.5361	0.5782	0.5830	0.5864		
	% Dissolved							
10	61.71	63.00	32.22	59.37	72.90	16.09	50.88	21.82
20	95.48	96.83	96.63	95.38	96.55	92.90	95.63	1.470
30	96.52	97.19	89.53	96.74	97.67	97.63	95.88	3.144

Table 52 Dissolution raw data of uncoated tablets stored for 1 month at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4697	0.5088	0.5177	0.5096	0.5096	0.5165		
20	0.5478	0.5707	0.5686	0.5578	0.5672	0.5729		
30	0.5737	0.5837	0.5760	0.5739	0.5734	0.5848		
	% Dissolved							
10	78.87	85.45	86.94	85.59	85.58	86.74	84.86	3.004
20	91.88	95.75	95.42	93.62	95.18	96.13	94.66	1.614
30	96.15	97.90	96.64	96.27	96.20	98.10	96.88	0.888

Table 53 Dissolution raw data of coated tablets stored for 1 month at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3739	0.4833	0.414	0.5039	0.4767	0.4907		
20	0.5545	0.5441	0.5595	0.5660	0.5551	0.5545		
30	0.5858	0.5602	0.5822	0.5781	0.5722	0.5709		
	% Dissolved							
10	62.75	81.15	69.50	84.62	80.04	82.40	76.74	8.633
20	92.83	91.29	93.72	94.97	93.10	93.03	93.16	1.204
30	98.00	93.94	97.47	96.97	95.92	95.73	96.34	1.463

Table 54 Dissolution raw data of uncoated tablets stored for 1 month at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1146	0.1131	0.2890	0.2109	0.2359	0.1463		
20	0.4007	0.4257	0.5018	0.4862	0.5013	0.4423		
30	0.5020	0.5047	0.5343	0.5189	0.5500	0.5106		
	% Dissolved							
10	19.13	18.88	48.47	35.33	39.54	24.46	30.97	12.062
20	66.78	70.93	83.90	81.18	83.74	73.76	76.72	7.236
30	83.48	83.96	89.27	86.57	91.77	85.02	86.68	3.255

Table 55 Dissolution raw data of coated tablets stored for 1 month at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0609	0.0241	0.0435	0.0285	0.0194	0.0255		
20	0.3616	0.0652	0.3154	0.3655	0.2450	0.1655		
30	0.4913	0.3483	0.4857	0.5075	0.4425	0.4588		
	% Dissolved							
10	10.10	3.90	7.17	4.64	3.11	4.15	5.51	2.638
20	60.17	10.74	52.45	60.77	40.69	27.46	42.05	19.910
30	81.57	57.42	80.53	84.18	73.25	75.81	75.46	9.689

Table 56 Dissolution raw data of uncoated tablets stored for 1 month at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2179	0.1698	0.2293	0.2457	0.1708	0.2030		
20	0.4913	0.4690	0.5011	0.4999	0.4934	0.4873		
30	0.5326	0.5242	0.5456	0.5438	0.5269	0.5237		
	% Dissolved							
10	36.50	28.41	38.42	41.18	28.59	34.00	34.52	5.220
20	82.04	78.25	83.70	83.52	82.32	81.35	81.86	1.984
30	88.85	87.35	91.02	90.75	87.84	87.35	88.86	1.666

Table 57 Dissolution raw data of coated tablets stored for 1 month at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0157	0.0200	0.0317	0.0384	0.0176	0.0182		
20	0.1068	0.2162	0.1604	0.2604	0.0483	0.0395		
30	0.3701	0.3948	0.4399	0.4699	0.3193	0.0745		
	% Dissolved							
10	2.49	3.21	5.18	6.30	2.81	2.91	3.82	1.549
20	17.66	35.90	26.62	43.29	7.92	6.45	22.97	14.973
30	61.07	65.33	72.70	77.82	52.60	12.22	56.96	23.622

Table 58 Dissolution raw data of uncoated tablets stored for 1 month at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3926	0.3456	0.4145	0.4895	0.3730	0.3206		
20	0.5509	0.5342	0.5532	0.5550	0.5578	0.5378		
30	0.5685	0.5498	0.5665	0.5687	0.5732	0.5589		
	% Dissolved							
10	65.90	57.98	69.57	82.20	62.60	53.79	65.34	9.976
20	92.27	89.41	92.68	93.11	93.39	89.96	91.80	1.694
30	95.16	91.97	94.88	95.37	95.92	93.43	94.46	1.476

Table 59 Dissolution raw data of coated tablets stored for 1 month at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0236	0.0354	0.0227	0.0238	0.0209	0.0352		
20	0.1808	0.1956	0.0670	0.1729	0.1151	0.2843		
30	0.4506	0.4846	0.3995	0.4704	0.4417	0.4590		
	% Dissolved							
10	3.82	5.81	3.66	3.85	3.37	5.77	4.38	1.105
20	29.99	32.48	11.05	28.69	19.06	47.26	28.09	12.351
30	74.48	80.14	65.87	77.73	72.90	76.07	74.53	4.934

Table 60 Dissolution raw data of uncoated tablets stored for 1 month at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3537	0.3793	0.3809	0.4063	0.4440	0.3652		
20	0.5557	0.5670	0.5693	0.5708	0.5734	0.5786		
30	0.5729	0.5757	0.5745	0.5809	0.5807	0.5869		
	% Dissolved							
10	59.35	63.65	63.93	68.20	74.58	61.29	65.17	5.487
20	92.99	94.92	95.30	95.61	96.10	96.83	95.29	1.307
30	95.83	96.36	96.16	97.27	97.31	98.20	96.86	0.890

Table 61 Dissolution raw data of coated tablets stored for 1 month at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3537	0.2786	0.3278	0.3102	0.1825	0.2527		
20	0.5561	0.5674	0.5624	0.5716	0.5652	0.5750		
30	0.5754	0.5808	0.5712	0.5779	0.5763	0.5831		
	% Dissolved							
10	59.36	46.72	54.99	52.04	30.55	42.36	47.67	10.311
20	93.07	94.82	94.08	95.57	94.29	96.04	94.64	1.073
30	96.25	97.03	95.51	96.61	96.13	97.38	96.48	0.670

Table 62 Dissolution raw data of uncoated tablets stored for 1 month at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5340	0.5316	0.5475	0.5392	0.5469	0.5258		
20	0.5635	0.5588	0.5736	0.5661	0.5708	0.5550		
30	0.5728	0.5673	0.5833	0.5767	0.5757	0.5612		
	% Dissolved							
10	89.69	89.28	91.96	90.55	91.86	88.30	90.3	1.462
20	94.6	93.8	96.3	95.0	95.8	93.2	94.8	1.191
30	96.1	95.2	97.9	96.8	96.6	94.2	96.1	1.294

Table 63 Dissolution raw data of coated tablets stored for 1 month at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5528	0.5540	0.5498	0.5608	0.5625	0.5556		
20	0.5686	0.5728	0.5704	0.5762	0.5744	0.5782		
30	0.5733	0.5789	0.5726	0.5824	0.5787	0.5822		
	% Dissolved							
10	92.86	93.06	92.35	94.20	94.49	93.33	93.4	0.817
20	95.5	96.2	95.8	96.8	96.5	97.1	96.3	0.601
30	96.3	97.2	96.1	97.8	97.2	97.7	97.0	0.707

Table 64 Dissolution raw data of uncoated tablets stored for 1 month at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5598	0.5500	0.5634	0.5594	0.5572	0.5470		
20	0.5806	0.5721	0.5737	0.5723	0.5678	0.5620		
30	0.5872	0.5780	0.5770	0.5770	0.5728	0.5650		
	% Dissolved							
10	94.03	92.38	94.64	93.95	93.58	91.88	93.4	1.062
20	97.5	96.1	96.4	96.1	95.4	94.4	96.0	1.042
30	98.6	97.0	96.9	96.9	96.2	94.9	96.8	1.191

Table 65 Dissolution raw data of coated tablets stored for 1 month at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5018	0.4577	0.4737	0.2351	0.5411	0.5636		
20	0.5661	0.5875	0.5819	0.5794	0.5709	0.5718		
30	0.5710	0.5931	0.5879	0.5860	0.5734	0.5762		
	% Dissolved							
10	84.27	76.84	79.55	39.40	90.88	94.67	77.6	19.880
20	95.0	98.5	97.6	96.7	95.8	96.0	96.6	1.261
30	95.8	99.4	98.5	97.8	96.3	96.8	97.4	1.399

Table 66 Dissolution raw data of uncoated tablets stored for 1 month at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5458	0.5527	0.5463	0.5460	0.5509	0.5422		
20	0.5767	0.5709	0.5778	0.5679	0.5708	0.5818		
30	0.5811	0.5760	0.5849	0.5767	0.5780	0.5853		
	% Dissolved							
10	91.67	92.84	91.76	91.70	92.54	91.06	91.9	0.647
20	96.8	95.9	97.0	95.4	95.8	97.7	96.4	0.875
30	97.5	96.7	98.2	96.8	97.0	98.2	97.4	0.687

Table 67 Dissolution raw data of coated tablets stored for 1 month at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5259	0.3704	0.4167	0.4045	0.2629	0.0729		
20	0.5453	0.5665	0.5703	0.5776	0.5805	0.5558		
30	0.5681	0.5847	0.5739	0.5855	0.5863	0.5775		
	% Dissolved							
10	88.32	62.17	69.95	67.91	44.07	12.12	57.4	26.363
20	91.6	94.8	95.5	96.7	97.0	92.5	94.7	2.214
30	95.3	97.8	96.1	98.0	97.9	96.1	96.9	1.176

Table 68 Dissolution raw data of uncoated tablets stored for 1 month at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5214	0.5364	0.5581	0.5328	0.5333	0.5445		
20	0.5690	0.5653	0.5759	0.5750	0.5749	0.5697		
30	0.5775	0.5730	0.5809	0.5789	0.5770	0.5749		
	% Dissolved							
10	87.57	90.10	93.73	89.48	89.58	91.46	90.3	2.088
20	95.5	94.9	96.7	96.5	96.5	95.6	96.0	0.723
30	96.9	96.2	97.5	97.2	96.8	96.5	96.9	0.477

Table 69 Dissolution raw data of coated tablets stored for 1 month at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3319	0.0929	0.2139	0.2264	0.4708	0.1924		
20	0.5702	0.5410	0.5890	0.5836	0.5638	0.5593		
30	0.5873	0.5679	0.5949	0.5983	0.5715	0.5735		
	% Dissolved							
10	55.69	15.47	35.83	37.94	79.06	32.22	42.7	21.964
20	95.4	90.1	98.3	97.4	94.5	93.3	94.8	2.958
30	98.2	94.5	99.3	99.8	95.8	95.7	97.2	2.177

Table 70 Dissolution raw data of uncoated tablets stored for 1 month at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3577	0.4806	0.4195	0.3970	0.3735	0.3481		
20	0.5619	0.5717	0.5819	0.5774	0.5757	0.5774		
30	0.5825	0.5779	0.5892	0.5828	0.5796	0.5824		
	% Dissolved							
10	60.02	80.70	70.42	66.64	62.69	58.41	66.5	8.233
20	94.0	95.9	97.5	96.7	96.4	96.6	96.2	1.169
30	97.4	96.9	98.7	97.6	97.0	97.4	97.5	0.635

Table 71 Dissolution raw data of coated tablets stored for 1 month at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2047	0.3557	0.2964	0.1247	0.1951	0.3762		
20	0.5836	0.5686	0.5721	0.5640	0.5832	0.5636		
30	0.5968	0.5711	0.5789	0.5729	0.5923	0.5678		
	% Dissolved							
10	34.28	59.69	49.71	20.83	32.68	63.13	43.4	16.745
20	97.4	95.2	95.6	94.0	97.3	94.3	95.6	1.449
30	99.6	95.6	96.8	95.5	98.8	95.0	96.9	1.900

Table 72 Dissolution raw data of uncoated tablets stored for 2 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3798	0.3650	0.4209	0.4650	0.4404	0.4672		
20	0.5169	0.5022	0.5194	0.5330	0.5244	0.5421		
30	0.5517	0.5330	0.5439	0.5463	0.5470	0.5495		
	% Dissolved							
10	63.74	61.25	70.67	78.08	73.94	78.44	71.02	7.239
20	86.59	84.11	87.06	89.40	87.93	90.92	87.67	2.361
30	92.32	89.19	91.11	91.59	91.65	92.15	91.33	1.135

Table 73 Dissolution raw data of coated tablets stored for 2 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4153	0.2295	0.3584	0.3664	0.4144	0.3978		
20	0.5165	0.4744	0.5142	0.5011	0.5213	0.5183		
30	0.5438	0.5277	0.5460	0.5301	0.5476	0.5464		
	% Dissolved							
10	69.71	38.46	60.14	61.49	69.56	66.78	61.02	11.761
20	86.58	79.24	86.10	83.93	87.38	86.85	85.01	3.067
30	91.07	88.03	91.33	88.71	91.70	91.47	90.39	1.588

Table 74 Dissolution raw data of uncoated tablets stored for 2 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1058	0.0765	0.0851	0.1028	0.0937	0.1401		
20	0.3867	0.3843	0.4105	0.3607	0.3696	0.4363		
30	0.4895	0.4700	0.4894	0.4673	0.4650	0.5016		
	% Dissolved							
10	17.64	12.73	14.17	17.14	15.61	23.43	16.78	3.732
20	64.44	63.99	68.36	60.10	61.56	72.76	65.20	4.655
30	81.39	78.12	81.38	77.68	77.29	83.52	79.89	2.546

Table 75 Dissolution raw data of coated tablets stored for 2 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0171	0.0028	0.0048	0.0225	0.0157	0.0036		
20	0.1354	0.0164	0.0657	0.2832	0.0220	0.2446		
30	0.4002	0.2451	0.4185	0.4273	0.2977	0.4034		
	% Dissolved							
10	2.73	0.32	0.65	3.64	2.49	0.46	1.71	1.413
20	22.42	2.59	10.79	47.06	3.54	40.59	21.16	19.040
30	66.08	40.28	68.96	70.82	48.99	66.77	60.32	12.566

Table 76 Dissolution raw data of uncoated tablets stored for 2 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0947	0.1070	0.1044	0.1334	0.0885	0.0937		
20	0.3008	0.3278	0.3879	0.4350	0.2179	0.2755		
30	0.4469	0.4251	0.4663	0.4936	0.3731	0.3414		
	% Dissolved							
10	15.77	17.84	17.40	22.29	14.73	15.62	17.28	2.720
20	50.10	54.63	64.63	72.53	36.28	45.90	54.01	13.050
30	74.20	70.67	77.56	82.19	61.88	56.75	70.54	9.629

Table 77 Dissolution raw data of coated tablets stored for 2 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0296	0.0256	0.0215	0.0201	0.0229	0.0192		
20	0.0396	0.0430	0.0805	0.0389	0.1309	0.2603		
30	0.2632	0.2145	0.3239	0.2169	0.3539	0.4435		
	% Dissolved							
10	4.83	4.15	3.47	3.23	3.70	3.08	3.74	0.654
20	6.49	7.05	13.30	6.36	21.69	43.24	16.35	14.451
30	43.37	35.33	53.42	35.71	58.46	73.44	49.96	14.808

Table 78 Dissolution raw data of uncoated tablets stored for 2 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1244	0.1731	0.2085	0.2121	0.1852	0.1728		
20	0.4073	0.4503	0.4529	0.4534	0.4389	0.4467		
30	0.4509	0.4836	0.4994	0.4847	0.4850	0.4862		
	% Dissolved							
10	20.77	28.97	34.93	35.53	31.01	28.93	30.02	5.354
20	67.89	75.13	75.62	75.71	73.26	74.53	73.69	2.981
30	75.08	80.62	83.30	80.89	80.86	81.05	80.30	2.741

Table 79 Dissolution raw data of coated tablets stored for 2 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0085	0.0124	0.0052	0.0091	0.0113	0.0118		
20	0.1757	0.1560	0.4489	0.0543	0.1866	0.2139		
30	0.4034	0.3699	0.5322	0.4364	0.3799	0.3737		
	% Dissolved							
10	1.28	1.94	0.72	1.38	1.75	1.83	1.48	0.455
20	29.12	25.85	74.63	8.90	30.95	35.49	34.16	21.827
30	66.66	61.12	88.35	71.91	62.81	61.84	68.78	10.391

Table 80 Dissolution raw data of uncoated tablets stored for 2 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3132	0.3224	0.3405	0.3263	0.3568	0.3523		
20	0.5359	0.5325	0.5407	0.5316	0.5414	0.5289		
30	0.5455	0.5428	0.5434	0.5384	0.5422	0.5304		
	% Dissolved							
10	52.54	54.08	57.13	54.74	59.87	59.11	56.25	2.927
20	89.63	89.08	90.48	88.94	90.63	88.53	89.55	0.856
30	91.22	90.79	90.93	90.06	90.76	88.78	90.42	0.888

Table 81 Dissolution raw data of coated tablets stored for 2 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2389	0.2300	0.1606	0.1198	0.0988	0.2447		
20	0.5421	0.5412	0.5311	0.5523	0.5336	0.5442		
30	0.5493	0.5546	0.5384	0.5676	0.5532	0.5554		
	% Dissolved							
10	40.04	38.55	26.87	20.00	16.46	41.01	30.49	10.832
20	90.55	90.37	88.57	92.03	88.89	90.90	90.22	1.292
30	91.72	92.59	89.78	94.56	92.11	92.75	92.25	1.555

Table 82 Dissolution raw data of uncoated tablets stored for 2 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5353	0.5472	0.5389	0.5515	0.5467	0.5488		
20	0.5666	0.5661	0.5655	0.5683	0.5636	0.5669		
30	0.5782	0.5709	0.5750	0.5728	0.5679	0.5718		
	% Dissolved							
10	89.91	91.90	90.51	92.62	91.83	92.17	91.49	1.048
20	95.11	95.05	94.93	95.44	94.63	95.20	95.06	0.271
30	97.03	95.85	96.50	96.17	95.35	96.00	96.15	0.575

Table 83 Dissolution raw data of coated tablets stored for 2 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5427	0.5438	0.5531	0.5494	0.5701	0.5558		
20	0.5669	0.5596	0.5759	0.5731	0.5754	0.5767		
30	0.5700	0.5683	0.5816	0.5723	0.5788	0.5822		
	% Dissolved							
10	91.15	91.33	92.90	92.27	95.76	93.35	92.79	1.687
20	95.18	93.97	96.70	96.22	96.65	96.84	95.93	1.136
30	95.68	95.40	97.64	96.09	97.21	97.74	96.63	1.027

Table 84 Dissolution raw data of uncoated tablets stored for 2 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5446	0.5480	0.5544	0.5565	0.5502	0.5556		
20	0.5750	0.5685	0.5701	0.5698	0.5710	0.5700		
30	0.5781	0.5714	0.5740	0.5729	0.5754	0.5760		
	% Dissolved							
10	91.47	92.05	93.12	93.47	92.41	93.33	92.64	0.796
20	96.54	95.46	95.74	95.69	95.88	95.71	95.84	0.368
30	97.05	95.94	96.38	96.19	96.60	96.71	96.48	0.394

Table 85 Dissolution raw data of coated tablets stored for 2 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3726	0.4290	0.4652	0.5070	0.4862	0.5384		
20	0.5747	0.5477	0.5661	0.5616	0.5673	0.5662		
30	0.5803	0.5799	0.5744	0.5679	0.5801	0.5741		
	% Dissolved							
10	62.53	72.03	78.10	85.15	81.64	90.43	78.31	9.934
20	96.20	91.79	94.91	94.24	95.15	95.05	94.56	1.496
30	97.12	97.10	96.29	95.28	97.26	96.36	96.57	0.754

Table 86 Dissolution raw data of uncoated tablets stored for 2 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4999	0.5131	0.5053	0.5137	0.5174	0.4799		
20	0.5346	0.5398	0.5446	0.5334	0.5279	0.5331		
30	0.5330	0.5386	0.5477	0.5351	0.5341	0.5434		
	% Dissolved							
10	83.95	86.18	84.86	86.28	86.89	80.58	84.79	2.322
20	89.72	90.61	91.41	89.55	88.64	89.45	89.90	0.974
30	89.46	90.42	91.92	89.84	89.67	91.14	90.41	0.958

Table 87 Dissolution raw data of coated tablets stored for 2 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1695	0.0159	0.3646	0.2401	0.4130	0.0441		
20	0.5382	0.5417	0.5384	0.5497	0.5340	0.5446		
30	0.5508	0.5480	0.5441	0.5555	0.5413	0.5584		
	% Dissolved							
10	28.37	2.53	61.18	40.24	69.33	7.27	34.82	27.419
20	89.77	90.09	90.13	91.80	89.48	90.62	90.31	0.823
30	91.85	91.13	91.07	92.77	90.69	92.90	91.74	0.931

Table 88 Dissolution raw data of uncoated tablets stored for 2 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5306	0.5694	0.5699	0.5500	0.5599	0.5207		
20	0.5700	0.5808	0.5735	0.5751	0.5711	0.5590		
30	0.5760	0.5853	0.5800	0.5821	0.5777	0.5708		
	% Dissolved							
10	89.11	95.65	95.73	92.38	94.04	87.45	92.39	3.453
20	95.68	97.54	96.32	96.56	95.91	93.83	95.97	1.234
30	96.66	98.28	97.39	97.71	96.99	95.77	97.14	0.873

Table 89 Dissolution raw data of coated tablets stored for 2 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3814	0.2371	0.3502	0.1131	0.3438	0.4319		
20	0.5668	0.5778	0.5702	0.5086	0.5752	0.5739		
30	0.5724	0.5796	0.5751	0.5408	0.5874	0.5841		
	% Dissolved							
10	64.01	39.74	58.77	18.87	57.69	72.50	51.93	19.446
20	94.88	96.49	95.40	84.74	96.23	96.15	93.98	4.566
30	95.82	96.78	96.21	90.06	98.24	97.84	95.82	2.972

Table 90 Dissolution raw data of uncoated tablets stored for 2 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3957	0.3955	0.4178	0.4242	0.3904	0.3841		
20	0.5706	0.5718	0.5746	0.5685	0.5786	0.5710		
30	0.5807	0.5793	0.5784	0.5757	0.5877	0.5828		
	% Dissolved							
10	66.41	66.39	70.14	71.21	65.52	64.47	67.36	2.689
20	95.54	95.74	96.25	95.24	96.87	95.60	95.88	0.587
30	97.21	96.98	96.87	96.44	98.38	97.53	97.24	0.667

Table 91 Dissolution raw data of coated tablets stored for 2 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2369	0.3447	0.2596	0.3483	0.1093	0.1025		
20	0.5694	0.5748	0.5954	0.5746	0.5691	0.5441		
30	0.5726	0.5820	0.5893	0.5798	0.5805	0.5865		
	% Dissolved							
10	39.70	57.83	43.51	58.45	18.24	17.08	39.14	18.249
20	95.08	96.16	99.45	96.14	94.82	90.65	95.38	2.847
30	95.61	97.35	98.45	96.99	96.70	97.64	97.12	0.954

Table 92 Dissolution raw data of uncoated tablets stored for 3 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4412	0.4009	0.4099	0.3733	0.3793	0.4480		
20	0.5310	0.5083	0.5210	0.4998	0.4887	0.5281		
30	0.5598	0.5453	0.5536	0.5382	0.5334	0.5481		
	% Dissolved							
10	74.07	67.30	68.81	62.65	63.67	75.22	68.62	5.201
20	89.02	85.17	87.31	83.73	81.88	88.56	85.95	2.836
30	93.77	91.28	92.68	90.04	89.26	91.85	91.48	1.666

Table 93 Dissolution raw data of coated tablets stored for 3 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3580	0.2260	0.3109	0.0543	0.3575	0.2876		
20	0.5105	0.4494	0.5194	0.3896	0.4899	0.4889		
30	0.5532	0.5241	0.5682	0.5054	0.5357	0.5400		
	% Dissolved							
10	60.08	37.87	52.15	8.99	59.99	48.24	44.55	19.288
20	85.47	75.09	86.87	64.83	82.04	81.76	79.34	8.197
30	92.51	87.39	94.92	83.91	89.59	90.19	89.75	3.853

Table 94 Dissolution raw data of uncoated tablets stored for 3 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0692	0.1048	0.1007	0.1608	0.1286	0.1242		
20	0.2379	0.3960	0.3972	0.4445	0.3923	0.3778		
30	0.4401	0.4935	0.4964	0.5249	0.4860	0.4776		
	% Dissolved							
10	11.49	17.48	16.78	26.90	21.48	20.74	19.15	5.199
20	39.58	65.93	66.17	74.15	65.40	62.97	62.37	11.786
30	72.93	82.06	82.53	87.41	80.85	79.44	80.87	4.733

Table 95 Dissolution raw data of coated tablets stored for 3 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0438	0.0178	0.0487	0.0276	0.0167	0.0169		
20	0.0982	0.0374	0.4051	0.2999	0.0373	0.0309		
30	0.4201	0.2803	0.4965	0.4488	0.2755	0.2891		
	% Dissolved							
10	7.22	2.84	8.04	4.49	2.66	2.68	4.65	2.416
20	16.27	6.10	67.40	49.85	6.10	5.02	25.12	26.850
30	69.34	46.16	82.47	74.40	45.36	47.59	60.89	16.460

Table 96 Dissolution raw data of uncoated tablets stored for 3 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0707	0.0634	0.0784	0.0725	0.0739	0.0692		
20	0.3165	0.1977	0.2880	0.3364	0.3456	0.1376		
30	0.4215	0.3283	0.3756	0.4540	0.4275	0.1922		
	% Dissolved							
10	11.75	10.51	13.04	12.04	12.28	11.49	11.85	0.847
20	52.68	32.89	47.95	56.00	57.53	22.87	44.99	14.014
30	69.99	54.41	62.39	75.38	71.03	31.89	60.85	16.005

Table 97 Dissolution raw data of coated tablets stored for 3 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0139	0.0163	0.0211	0.0164	0.0178	0.0231		
20	0.0326	0.0359	0.0441	0.0364	0.0434	0.1951		
30	0.2732	0.2262	0.3344	0.2721	0.0735	0.4013		
	% Dissolved							
10	2.18	2.59	3.40	2.60	2.84	3.74	2.89	0.575
20	5.31	5.86	7.23	5.94	7.11	32.38	10.64	10.678
30	44.97	37.24	55.10	44.80	12.07	66.39	43.43	18.379

Table 98 Dissolution raw data of uncoated tablets stored for 3 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1669	0.1313	0.0921	0.1088	0.0947	0.2359		
20	0.4216	0.3408	0.2946	0.4058	0.1774	0.4595		
30	0.4888	0.4440	0.3655	0.4826	0.2148	0.5043		
	% Dissolved							
10	27.92	21.93	15.35	18.16	15.78	39.54	23.11	9.305
20	70.35	56.82	49.06	67.61	29.56	76.78	58.37	17.245
30	81.42	73.85	60.76	80.28	35.72	84.16	69.36	18.488

Table 99 Dissolution raw data of coated tablets stored for 3 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0250	0.0213	0.0319	0.0177	0.0522	0.0263		
20	0.2823	0.1861	0.1384	0.0425	0.2148	0.2607		
30	0.4489	0.3064	0.3792	0.2883	0.3929	0.4406		
	% Dissolved							
10	4.06	3.43	5.21	2.83	8.62	4.27	4.74	2.066
20	46.91	30.88	22.95	6.96	35.71	43.31	31.12	14.625
30	74.38	50.71	62.65	47.49	65.08	72.98	62.21	11.149

Table 100 Dissolution raw data of uncoated tablets stored for 3 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3255	0.4356	0.4508	0.3949	0.4168	0.4218		
20	0.5625	0.5698	0.5733	0.5725	0.5727	0.5654		
30	0.5800	0.5755	0.5790	0.5808	0.5807	0.5772		
	% Dissolved							
10	54.60	73.13	75.68	66.29	69.97	70.82	68.42	7.464
20	94.09	95.49	96.10	95.87	95.93	94.73	95.37	0.794
30	96.97	96.42	97.04	97.24	97.25	96.68	96.93	0.328

Table 101 Dissolution raw data of coated tablets stored for 3 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1588	0.1404	0.1819	0.1098	0.0811	0.1220		
20	0.5394	0.5572	0.5506	0.5513	0.4910	0.5411		
30	0.5554	0.5585	0.5647	0.5590	0.5366	0.5691		
	% Dissolved							
10	26.57	23.47	30.45	18.31	13.50	20.38	22.11	6.048
20	89.96	92.90	91.85	91.85	81.76	90.18	89.75	4.069
30	92.60	93.10	94.18	93.12	89.28	94.79	92.84	1.920

Table 102 Dissolution raw data of uncoated tablets stored for 3 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5300	0.5364	0.5118	0.5354	0.5277	0.5415		
20	0.5718	0.5683	0.5608	0.5616	0.5586	0.5757		
30	0.5809	0.5776	0.5693	0.5686	0.5710	0.5823		
	% Dissolved							
10	89.02	90.09	85.95	89.92	88.62	90.95	89.09	1.743
20	95.97	95.41	94.11	94.28	93.78	96.64	95.03	1.150
30	97.48	96.94	95.51	95.44	95.81	97.73	96.49	1.024

Table 103 Dissolution raw data of coated tablets stored for 3 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5295	0.5665	0.5494	0.5497	0.5426	0.5437		
20	0.5698	0.5749	0.5784	0.5777	0.5696	0.5724		
30	0.5763	0.5842	0.5853	0.5845	0.5747	0.5799		
	% Dissolved							
10	88.93	95.16	92.28	92.33	91.13	91.32	91.86	2.034
20	95.64	96.55	97.10	96.99	95.62	96.09	96.33	0.650
30	96.71	98.08	98.24	98.12	96.48	97.34	97.49	0.769

Table 104 Dissolution raw data of uncoated tablets stored for 3 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5591	0.5586	0.5550	0.5483	0.5559	0.5454		
20	0.5779	0.5747	0.5686	0.5637	0.5696	0.5668		
30	0.5848	0.5801	0.5789	0.5708	0.5755	0.5732		
	% Dissolved							
10	93.92	93.83	93.22	92.08	93.37	91.61	93.01	0.948
20	97.04	96.51	95.48	94.66	95.64	95.17	95.75	0.879
30	98.17	97.40	97.18	95.82	96.63	96.22	96.90	0.853

Table 105 Dissolution raw data of coated tablets stored for 3 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4896	0.3429	0.5264	0.4363	0.4643	0.4495		
20	0.5662	0.5574	0.5650	0.5793	0.5736	0.5725		
30	0.5806	0.5787	0.5692	0.5847	0.5825	0.5801		
	% Dissolved							
10	82.22	57.54	88.40	73.24	77.97	75.46	75.81	10.438
20	94.98	93.26	94.83	97.06	96.16	95.96	95.38	1.321
30	97.35	96.77	95.53	97.96	97.63	97.21	97.08	0.856

Table 106 Dissolution raw data of uncoated tablets stored for 3 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5396	0.5449	0.5227	0.5558	0.5315	0.5419		
20	0.5653	0.5726	0.5706	0.5732	0.5696	0.5700		
30	0.5695	0.5749	0.5776	0.5732	0.5775	0.5752		
	% Dissolved							
10	90.62	91.52	87.79	93.36	89.26	91.01	90.59	1.915
20	94.90	96.14	95.76	96.25	95.61	95.69	95.73	0.478
30	95.60	96.52	96.92	96.25	96.91	96.56	96.46	0.495

Table 107 Dissolution raw data of coated tablets stored for 3 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1445	0.0923	0.3389	0.1542	0.1771	0.1875		
20	0.5371	0.5633	0.5793	0.5574	0.5654	0.5722		
30	0.5766	0.5804	0.5871	0.5712	0.5793	0.5820		
	% Dissolved							
10	24.16	15.38	56.87	25.79	29.63	31.38	30.54	14.055
20	89.55	93.82	96.91	92.95	94.32	95.46	93.84	2.510
30	96.06	96.65	98.20	95.21	96.60	97.07	96.63	0.999

Table 108 Dissolution raw data of uncoated tablets stored for 3 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5486	0.5325	0.5362	0.5408	0.4899	0.5682		
20	0.5641	0.5745	0.5726	0.5735	0.5777	0.5782		
30	0.5713	0.5790	0.5723	0.5788	0.5846	0.5847		
	% Dissolved							
10	92.14	89.43	90.05	90.83	82.26	95.43	90.02	4.357
20	94.72	96.42	96.12	96.27	96.88	97.11	96.25	0.841
30	95.91	97.18	96.07	97.15	98.02	98.18	97.08	0.950

Table 109 Dissolution raw data of coated tablets stored for 3 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1335	0.5076	0.4506	0.5087	0.2102	0.1359		
20	0.5482	0.5743	0.5750	0.5760	0.5758	0.5608		
30	0.5823	0.5825	0.5810	0.5835	0.5846	0.5832		
	% Dissolved							
10	22.30	85.24	75.66	85.43	35.22	22.71	54.43	30.883
20	91.37	96.36	96.38	96.63	96.11	93.47	95.05	2.150
30	97.00	97.71	97.36	97.88	97.56	97.17	97.45	0.333

Table 110 Dissolution raw data of uncoated tablets stored for 3 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4340	0.3970	0.3927	0.3733	0.4039	0.4364		
20	0.5749	0.5802	0.5752	0.5754	0.5664	0.5757		
30	0.5850	0.5888	0.5859	0.5929	0.5776	0.5805		
	% Dissolved							
10	72.86	66.63	65.92	62.65	67.79	73.27	68.19	4.147
20	96.33	97.14	96.31	96.31	94.86	96.46	96.24	0.748
30	97.99	98.56	98.07	99.20	96.71	97.26	97.97	0.892

Table 111 Dissolution raw data of coated tablets stored for 3 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2546	0.2923	0.3037	0.2249	0.2307	0.3025		
20	0.5666	0.5787	0.5782	0.5772	0.5766	0.5646		
30	0.5762	0.5850	0.5854	0.5924	0.5878	0.5649		
	% Dissolved							
10	42.68	49.03	50.94	37.68	38.66	50.74	44.95	6.061
20	94.64	96.73	96.67	96.37	96.27	94.39	95.84	1.046
30	96.24	97.76	97.84	98.87	98.11	94.44	97.21	1.607

Table 112 Dissolution raw data of uncoated tablets stored for 4 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3775	0.3485	0.3986	0.3914	0.4305	0.4366		
20	0.4950	0.4906	0.5085	0.4818	0.5216	0.5271		
30	0.5356	0.5378	0.5432	0.5192	0.5490	0.5534		
	% Dissolved							
10	63.36	58.48	66.90	65.70	72.28	73.30	66.67	5.558
20	82.93	82.15	85.22	80.76	87.44	88.37	84.48	3.036
30	89.63	89.92	90.94	86.92	91.96	92.71	90.35	2.046

Table 113 Dissolution raw data of coated tablets stored for 4 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2658	0.2279	0.3542	0.2056	0.2249	0.2131		
20	0.4569	0.4355	0.5024	0.4292	0.4105	0.4383		
30	0.5234	0.5025	0.5416	0.5111	0.4948	0.5147		
	% Dissolved							
10	44.57	38.19	59.44	34.44	37.68	35.70	41.67	9.380
20	76.40	72.76	84.11	71.67	68.60	73.20	74.46	5.357
30	87.36	83.81	90.58	85.19	82.49	85.81	85.87	2.847

Table 114 Dissolution raw data of uncoated tablets stored for 4 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1247	0.0694	0.0693	0.0701	0.1099	0.0895		
20	0.4232	0.2989	0.1965	0.1772	0.4012	0.4055		
30	0.5248	0.4625	0.4465	0.4269	0.5114	0.4969		
	% Dissolved							
10	20.82	11.53	11.50	11.65	18.33	14.91	14.79	4.007
20	70.54	49.76	32.70	29.48	66.86	67.54	52.81	18.366
30	87.29	76.72	73.90	70.64	85.02	82.60	79.36	6.606

Table 115 Dissolution raw data of coated tablets stored for 4 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0104	0.0380	0.0235	0.0240	0.0572	0.0752		
20	0.1876	0.2375	0.2912	0.1197	0.3812	0.3739		
30	0.3855	0.4263	0.4850	0.3708	0.5001	0.4961		
	% Dissolved							
10	1.59	6.25	3.80	3.89	9.47	12.50	6.25	4.066
20	31.11	39.48	48.39	19.83	63.44	62.26	44.08	17.327
30	63.74	70.59	80.34	61.23	83.05	82.40	73.56	9.710

Table 116 Dissolution raw data of uncoated tablets stored for 4 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0531	0.0594	0.0675	0.0561	0.0633	0.0752		
20	0.1111	0.1296	0.2545	0.1162	0.2821	0.1357		
30	0.1990	0.2107	0.3651	0.1720	0.3718	0.1857		
	% Dissolved							
10	8.78	9.83	11.21	9.29	10.50	12.51	10.35	1.360
20	18.44	21.54	42.36	19.30	46.94	22.57	28.52	12.662
30	32.93	34.91	60.59	28.49	61.73	30.82	41.58	15.322

Table 117 Dissolution raw data of coated tablets stored for 4 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0244	0.0166	0.0203	0.0226	0.0227	0.0306		
20	0.0972	0.0355	0.0384	0.0442	0.0466	0.1764		
30	0.3606	0.1741	0.2843	0.2938	0.3925	0.3579		
	% Dissolved							
10	3.95	2.65	3.25	3.65	3.67	5.00	3.70	0.783
20	16.08	5.79	6.28	7.24	7.65	29.29	12.05	9.254
30	59.51	28.64	46.82	48.40	64.67	59.21	51.21	13.043

Table 118 Dissolution raw data of uncoated tablets stored for 4 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1374	0.1380	0.0988	0.1134	0.1065	0.1435		
20	0.3190	0.3706	0.4066	0.4219	0.3409	0.3284		
30	0.3705	0.4270	0.4674	0.4770	0.4501	0.3976		
	% Dissolved							
10	22.97	23.07	16.48	18.92	17.76	23.99	20.53	3.195
20	53.21	61.81	67.73	70.30	56.81	54.78	60.77	7.057
30	61.70	71.11	77.77	79.39	74.80	66.19	71.83	6.872

Table 119 Dissolution raw data of coated tablets stored for 4 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0227	0.0474	0.0231	0.0245	0.1167	0.0237		
20	0.0391	0.3745	0.2525	0.1210	0.4187	0.0561		
30	0.2851	0.5097	0.4277	0.3555	0.5123	0.3241		
	% Dissolved							
10	3.67	7.83	3.74	3.97	19.48	3.84	7.09	6.282
20	6.41	62.30	41.94	20.05	69.78	9.23	34.95	27.235
30	46.96	84.59	70.83	58.71	85.21	53.42	66.62	16.186

Table 120 Dissolution raw data of uncoated tablets stored for 4 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3988	0.3950	0.4526	0.3313	0.3723	0.3421		
20	0.5571	0.5743	0.5743	0.5743	0.5738	0.5701		
30	0.5764	0.5820	0.5820	0.5889	0.5859	0.5816		
	% Dissolved							
10	66.94	66.30	76.00	55.59	62.48	57.41	64.12	7.406
20	93.30	96.16	96.27	96.06	96.04	95.37	95.53	1.138
30	96.49	97.43	97.54	98.46	98.04	97.26	97.54	0.676

Table 121 Dissolution raw data of coated tablets stored for 4 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1449	0.0443	0.0279	0.2971	0.1719	0.1092		
20	0.5576	0.5158	0.4608	0.5654	0.5676	0.5656		
30	0.5764	0.5877	0.5708	0.5813	0.5818	0.5738		
	% Dissolved							
10	24.22	7.30	4.54	49.83	28.77	18.22	22.15	16.495
20	92.97	85.83	76.64	94.52	94.67	94.24	89.81	7.276
30	96.05	97.68	94.78	97.13	97.02	95.59	96.38	1.093

Table 122 Dissolution raw data of uncoated tablets stored for 4 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5149	0.5177	0.5218	0.5142	0.5151	0.5234		
20	0.5522	0.5593	0.5589	0.5489	0.5410	0.5663		
30	0.5620	0.5732	0.5760	0.5659	0.5565	0.5753		
	% Dissolved							
10	86.47	86.94	87.63	86.35	86.51	87.91	86.97	0.657
20	92.68	93.87	93.82	92.13	90.82	95.05	93.06	1.497
30	94.30	96.16	96.64	94.94	93.37	96.53	95.32	1.335

Table 123 Dissolution raw data of coated tablets stored for 4 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5436	0.5362	0.5487	0.5375	0.5333	0.5317		
20	0.5669	0.5708	0.5798	0.5686	0.5661	0.5704		
30	0.5789	0.5775	0.5906	0.5762	0.5742	0.5758		
	% Dissolved							
10	91.29	90.06	92.15	90.27	89.56	89.31	90.44	1.085
20	95.18	95.82	97.34	95.46	95.04	95.75	95.77	0.832
30	97.16	96.93	99.12	96.71	96.36	96.63	97.15	1.000

Table 124 Dissolution raw data of uncoated tablets stored for 4 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5550	0.5700	0.5444	0.5488	0.5419	0.5532		
20	0.5820	0.5812	0.5722	0.5856	0.5667	0.5803		
30	0.5891	0.5901	0.5787	0.5909	0.5738	0.5855		
	% Dissolved							
10	93.23	95.75	91.43	92.18	91.02	92.92	92.75	1.690
20	97.72	97.61	96.06	98.31	95.14	97.44	97.05	1.194
30	98.88	99.07	97.15	99.18	96.32	98.29	98.15	1.169

Table 125 Dissolution raw data of coated tablets stored for 4 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5483	0.1944	0.4424	0.4404	0.4579	0.1451		
20	0.5741	0.5717	0.5644	0.5758	0.5776	0.5496		
30	0.5861	0.5845	0.5751	0.5790	0.5834	0.5721		
	% Dissolved							
10	92.09	32.56	74.28	73.93	76.88	24.26	62.33	27.240
20	96.39	95.40	94.60	96.49	96.82	91.63	95.22	1.942
30	98.37	97.51	96.35	97.02	97.78	95.35	97.06	1.084

Table 126 Dissolution raw data of uncoated tablets stored for 4 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4958	0.5500	0.5069	0.5148	0.5260	0.5409		
20	0.5726	0.5759	0.5697	0.5783	0.5741	0.5686		
30	0.5791	0.5809	0.5729	0.5854	0.5796	0.5759		
	% Dissolved							
10	83.25	92.38	85.13	86.46	88.33	90.84	87.73	3.466
20	96.04	96.68	95.59	97.03	96.35	95.46	96.19	0.615
30	97.12	97.51	96.11	98.20	97.26	96.66	97.14	0.716

Table 127 Dissolution raw data of coated tablets stored for 4 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2172	0.0854	0.1228	0.3418	0.0636	0.0363		
20	0.5628	0.5462	0.5731	0.5825	0.5258	0.5284		
30	0.5875	0.5928	0.5828	0.5879	0.5842	0.5774		
	% Dissolved							
10	36.38	14.21	20.51	57.36	10.54	5.96	24.16	19.392
20	93.95	90.96	95.51	97.44	87.53	87.92	92.22	4.077
30	98.02	98.64	97.11	98.33	97.16	96.00	97.54	0.975

Table 128 Dissolution raw data of uncoated tablets stored for 4 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5392	0.5510	0.5574	0.5676	0.4996	0.5521		
20	0.5680	0.5706	0.5722	0.5772	0.5782	0.5722		
30	0.5744	0.5763	0.5798	0.5773	0.5871	0.5797		
	% Dissolved							
10	90.56	92.55	93.62	95.33	83.90	92.73	91.45	4.010
20	95.36	95.82	96.09	96.94	96.99	96.08	96.21	0.641
30	96.42	96.75	97.34	96.95	98.46	97.32	97.21	0.705

Table 129 Dissolution raw data of coated tablets stored for 4 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3728	0.2678	0.2065	0.1076	0.3896	0.2662		
20	0.5624	0.5489	0.5470	0.5784	0.5569	0.5605		
30	0.5746	0.5754	0.5681	0.5945	0.5709	0.5823		
	% Dissolved							
10	62.57	44.89	34.60	17.94	65.40	44.63	45.01	17.694
20	94.15	91.72	91.31	96.37	93.26	93.65	93.41	1.825
30	96.15	96.09	94.78	99.03	95.57	97.24	96.48	1.484

Table 130 Dissolution raw data of uncoated tablets stored for 4 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3704	0.3879	0.4135	0.4275	0.4181	0.4519		
20	0.5825	0.5736	0.5601	0.5765	0.5670	0.5743		
30	0.5968	0.5816	0.5687	0.5827	0.5726	0.5813		
	% Dissolved							
10	62.16	65.11	69.42	71.78	70.19	75.88	69.09	4.867
20	97.49	96.04	93.83	96.58	94.98	96.27	95.87	1.286
30	99.84	97.35	95.25	97.62	95.92	97.42	97.23	1.591

Table 131 Dissolution raw data of coated tablets stored for 4 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1605	0.3679	0.3295	0.3720	0.3859	0.1001		
20	0.5688	0.5797	0.5714	0.5740	0.5650	0.5644		
30	0.5894	0.5893	0.5816	0.5802	0.5746	0.5890		
	% Dissolved							
10	26.85	61.75	55.28	62.43	64.76	16.69	47.96	20.779
20	94.86	97.02	95.58	96.07	94.60	94.02	95.36	1.087
30	98.26	98.60	97.25	97.10	96.19	98.08	97.58	0.897

Table 132 Dissolution raw data of uncoated tablets stored for 5 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3259	0.3722	0.3023	0.3313	0.3587	0.3939		
20	0.4624	0.4777	0.4499	0.4553	0.4713	0.5016		
30	0.5129	0.5217	0.4987	0.5057	0.5176	0.5362		
	% Dissolved							
10	54.68	62.47	50.71	55.59	60.19	66.12	58.29	5.661
20	77.41	80.04	75.29	76.23	78.95	84.05	78.66	3.158
30	85.74	87.29	83.33	84.54	86.58	89.76	86.21	2.244
60 (200 rpm)	95.64	94.77	94.95	95.49	96.32	96.32	95.58	0.658

Table 133 Dissolution raw data of coated tablets stored for 5 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0278	0.0555	0.1077	0.0712	0.0671	0.0360		
20	0.1550	0.1838	0.3106	0.2361	0.2700	0.1451		
30	0.3110	0.2871	0.4133	0.3456	0.3843	0.2615		
	% Dissolved							
10	4.53	9.18	17.97	11.82	11.13	5.90	10.09	4.806
20	25.71	30.56	51.76	39.29	44.93	24.08	36.06	11.105
30	51.43	47.58	68.69	57.34	63.78	43.26	55.35	9.747
60 (200 rpm)	91.54	89.90	94.22	89.64	91.63	91.32	91.38	1.638

Table 134 Dissolution raw data of uncoated tablets stored for 5 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0673	0.0697	0.0760	0.0576	0.0825	0.0895		
20	0.3141	0.2534	0.3355	0.1645	0.3472	0.2987		
30	0.4669	0.4248	0.4780	0.3188	0.4749	0.3906		
	% Dissolved							
10	11.16	11.58	12.63	9.54	13.73	14.91	12.26	1.917
20	52.27	42.17	55.85	27.34	57.82	49.74	47.53	11.302
30	77.47	70.42	79.35	52.78	78.87	64.89	70.63	10.414
60 (200 rpm)	95.58	96.27	97.35	96.26	96.73	96.03	96.37	0.608

Table 135 Dissolution raw data of coated tablets stored for 5 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0198	0.0333	0.0314	0.0460	0.0206	0.0282		
20	0.0352	0.0622	0.3075	0.2490	0.0898	0.2093		
30	0.3396	0.3062	0.4875	0.4359	0.3585	0.4510		
	% Dissolved							
10	3.18	5.45	5.13	7.59	3.32	4.59	4.88	1.622
20	5.75	10.26	51.11	41.39	14.85	34.76	26.35	18.579
30	55.93	50.49	80.79	72.21	59.14	74.61	65.53	11.993
60 (200 rpm)	96.53	95.86	96.98	96.85	94.83	98.21	96.54	1.137

Table 136 Dissolution raw data of uncoated tablets stored for 5 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0544	0.0361	0.0448	0.0343	0.0487	0.0535		
20	0.1267	0.0829	0.0911	0.0798	0.1593	0.1078		
30	0.1815	0.2162	0.1349	0.1465	0.2442	0.1572		
	% Dissolved							
10	9.00	5.93	7.38	5.62	8.03	8.85	7.47	1.442
20	21.05	13.72	15.09	13.19	26.46	17.90	17.90	5.115
30	30.07	35.69	22.32	24.20	40.46	26.03	29.79	7.069
60 (200 rpm)	92.78	93.78	82.61	90.88	93.82	83.77	89.61	5.096

Table 137 Dissolution raw data of coated tablets stored for 5 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0211	0.0282	0.0324	0.0269	0.0237	0.0112		
20	0.0499	0.1233	0.1764	0.1031	0.0515	0.0346		
30	0.3496	0.3614	0.4286	0.3249	0.2828	0.1780		
	% Dissolved							
10	3.40	4.59	5.30	4.38	3.83	1.73	3.87	1.236
20	8.19	20.44	29.29	17.06	8.46	5.63	14.84	9.108
30	57.61	59.69	70.86	53.63	46.60	29.27	52.94	14.068
60 (200 rpm)	96.18	95.69	96.56	96.94	98.06	97.41	96.81	0.856

Table 138 Dissolution raw data of uncoated tablets stored for 5 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1214	0.0843	0.0635	0.0993	0.0944	0.1030		
20	0.2520	0.2510	0.1112	0.1494	0.3383	0.1496		
30	0.3812	0.3192	0.1383	0.1799	0.4028	0.1741		
	% Dissolved							
10	20.27	14.03	10.52	16.56	15.72	17.18	15.71	3.266
20	42.02	41.79	18.47	24.90	56.35	24.94	34.75	14.333
30	63.33	53.04	22.94	29.92	66.99	28.98	44.20	19.240
60 (200 rpm)	86.04	90.28	86.71	86.54	92.49	86.62	88.11	2.641

Table 139 Dissolution raw data of coated tablets stored for 5 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0393	0.0452	0.0361	0.0295	0.0322	0.0245		
20	0.0529	0.0840	0.0744	0.0703	0.0894	0.0580		
30	0.2300	0.2899	0.3953	0.2483	0.2583	0.1112		
	% Dissolved							
10	6.46	7.45	5.92	4.81	5.27	3.97	5.65	1.237
20	8.72	13.92	12.31	11.61	14.79	9.55	11.82	2.375
30	37.92	47.87	65.21	40.95	42.64	18.32	42.15	15.178
60 (200 rpm)	97.02	99.64	99.32	98.54	97.89	99.79	98.70	1.094

Table 140 Dissolution raw data of uncoated tablets stored for 5 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3704	0.4120	0.3998	0.3524	0.3567	0.3207		
20	0.5617	0.5622	0.5717	0.5765	0.5700	0.5653		
30	0.5757	0.5750	0.5817	0.5875	0.5760	0.5788		
	% Dissolved							
10	62.16	69.16	67.11	59.14	59.86	53.81	61.87	5.608
20	94.03	94.18	95.74	96.46	95.39	94.55	95.06	0.962
30	96.34	96.29	97.39	98.27	96.38	96.76	96.90	0.786
60 (200 rpm)	96.92	96.18	97.04	99.32	96.75	97.65	97.31	1.090

Table 141 Dissolution raw data of coated tablets stored for 5 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0576	0.0829	0.1888	0.0593	0.2550	0.0938		
20	0.5348	0.5340	0.5647	0.5251	0.5591	0.5552		
30	0.5796	0.5751	0.5780	0.5691	0.5755	0.5816		
	% Dissolved							
10	9.54	13.80	31.61	9.82	42.75	15.62	20.52	13.575
20	89.02	88.93	94.22	87.41	93.40	92.48	90.91	2.802
30	96.41	95.71	96.41	94.66	96.10	96.83	96.02	0.762
60 (200 rpm)	97.19	96.66	96.74	97.63	96.18	97.58	97.00	0.571

Table 142 Dissolution raw data of uncoated tablets stored for 5 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5101	0.5197	0.5165	0.4886	0.5009	0.5059		
20	0.5618	0.5640	0.5615	0.5582	0.5510	0.5534		
30	0.5740	0.5758	0.5751	0.5744	0.5656	0.5666		
	% Dissolved							
10	85.67	87.28	86.74	82.05	84.12	84.96	85.14	1.902
20	94.28	94.65	94.24	93.65	92.46	92.87	93.69	0.868
30	96.29	96.61	96.48	96.31	94.87	95.05	95.94	0.766
60 (200 rpm)	96.13	97.48	97.38	97.52	96.84	95.85	96.87	0.726

Table 143 Dissolution raw data of coated tablets stored for 5 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5307	0.5225	0.5117	0.5214	0.5168	0.5138		
20	0.5643	0.5724	0.5655	0.5580	0.5692	0.5533		
30	0.5729	0.5847	0.5765	0.5668	0.5808	0.5603		
	% Dissolved							
10	89.13	87.75	85.93	87.56	86.80	86.29	87.24	1.161
20	94.73	96.06	94.89	93.66	95.52	92.86	94.62	1.181
30	96.15	98.08	96.71	95.12	97.43	94.02	96.25	1.501
60 (200 rpm)	96.46	98.30	96.76	96.53	97.56	94.99	96.77	1.122

Table 144 Dissolution raw data of uncoated tablets stored for 5 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5409	0.5637	0.5453	0.5514	0.5397	0.5491		
20	0.5749	0.5716	0.5700	0.5687	0.5794	0.5750		
30	0.5829	0.5684	0.5690	0.5659	0.5743	0.5684		
	% Dissolved							
10	90.84	94.68	91.58	92.61	90.65	92.23	92.10	1.475
20	96.50	96.00	95.71	95.49	97.25	96.54	96.25	0.646
30	97.83	95.47	95.53	95.03	96.42	95.45	95.96	1.027
60 (200 rpm)	96.24	95.39	95.38	95.05	96.67	95.61	95.72	0.611

Table 145 Dissolution raw data of coated tablets stored for 5 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4591	0.3310	0.4533	0.3914	0.1946	0.0563		
20	0.5739	0.5699	0.5715	0.5673	0.5719	0.5378		
30	0.5887	0.5809	0.5831	0.5814	0.5864	0.5846		
	% Dissolved							
10	77.08	55.54	76.10	65.69	32.58	9.32	52.72	26.852
20	96.21	95.32	95.80	94.99	95.43	89.52	94.55	2.499
30	98.65	97.13	97.71	97.31	97.82	97.23	97.64	0.564
60 (200 rpm)	98.35	97.53	98.13	97.44	98.25	98.99	98.12	0.573

Table 146 Dis

Stirring time (minutes)
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10
20
30
60 (200 rpm

Table 147 Dis

Stirring time (minutes)
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20
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60 (200 rpm

Table 148 Di

Stirring tim (minutes)
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60 (200 rpn

Table 149 Di

Stirring tim (minutes)
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20
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10
20
30
60 (200 rpn

Table 146 Dissolution raw data of uncoated tablets stored for 5 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4490	0.4452	0.5333	0.4894	0.5205	0.5255		
20	0.5691	0.5635	0.5635	0.5594	0.5652	0.5658		
30	0.5754	0.5727	0.5703	0.5709	0.5685	0.5793		
	% Dissolved							
10	75.39	74.75	89.57	82.18	87.42	88.26	82.93	6.589
20	95.38	94.46	94.60	93.85	94.86	94.96	94.68	0.520
30	96.42	95.97	95.72	95.74	95.40	97.20	96.07	0.646
60 (200 rpm)	96.94	96.50	95.61	96.08	95.74	97.43	96.38	0.711

Table 147 Dissolution raw data of coated tablets stored for 5 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2864	0.1793	0.0278	0.0340	0.0300	0.0921		
20	0.5634	0.5573	0.5209	0.5370	0.4480	0.5393		
30	0.5753	0.5730	0.5773	0.5693	0.5241	0.5676		
	% Dissolved							
10	48.04	30.01	4.52	5.56	4.89	15.34	18.06	17.673
20	94.16	92.96	86.65	89.28	74.52	89.82	87.90	7.087
30	96.13	95.56	95.95	94.67	87.06	94.48	93.98	3.454
60 (200 rpm)	97.26	96.26	97.18	95.88	96.79	95.99	96.56	0.602

Table 148 Dissolution raw data of uncoated tablets stored for 5 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5194	0.5244	0.5374	0.5074	0.4729	0.5422		
20	0.5613	0.5613	0.5732	0.5697	0.5702	0.5718		
30	0.5716	0.5651	0.5767	0.5699	0.5801	0.5752		
	% Dissolved							
10	87.23	88.07	90.27	85.21	79.41	91.06	86.87	4.221
20	94.22	94.21	96.22	95.59	95.62	95.99	95.31	0.879
30	95.90	94.84	96.80	95.62	97.25	96.55	96.16	0.878
60 (200 rpm)	96.53	94.78	96.00	95.46	96.85	96.61	96.04	0.791

Table 149 Dissolution raw data of coated tablets stored for 5 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2944	0.2183	0.2581	0.1673	0.4324	0.0596		
20	0.5717	0.5559	0.5637	0.5172	0.5619	0.5527		
30	0.5839	0.5697	0.5922	0.5470	0.5737	0.5778		
	% Dissolved							
10	49.37	36.58	43.27	27.99	72.59	9.87	39.95	21.092
20	95.56	92.80	94.18	86.28	94.16	92.01	92.50	3.286
30	97.57	95.08	98.86	91.19	96.11	96.14	95.82	2.626
60 (200 rpm)	96.98	95.45	98.38	97.38	95.70	97.34	96.87	1.109

Table 150 Dissolution raw data of uncoated tablets stored for 5 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3814	0.3752	0.3464	0.4219	0.3543	0.4328		
20	0.5633	0.5631	0.5744	0.5714	0.5775	0.5684		
30	0.5789	0.5724	0.5880	0.5761	0.5882	0.5761		
	% Dissolved							
10	64.02	62.97	58.13	70.83	59.45	72.66	64.68	5.917
20	94.31	94.26	96.10	95.73	96.63	95.25	95.38	0.960
30	96.88	95.80	98.35	96.49	98.39	96.51	97.07	1.065
60 (200 rpm)								

Table 151 Dissolution raw data of coated tablets stored for 5 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1994	0.1639	0.0224	0.3564	0.0772	0.0851		
20	0.5558	0.5690	0.4960	0.5666	0.5593	0.5536		
30	0.5722	0.5907	0.5634	0.5776	0.5710	0.5718		
	% Dissolved							
10	33.39	27.42	3.61	59.81	12.84	14.16	25.21	20.053
20	92.76	94.89	82.49	94.81	93.13	92.19	91.71	4.649
30	95.46	98.47	93.62	96.63	95.06	95.20	95.74	1.647
60 (200 rpm)	96.29	99.04	97.42	96.99	95.54	96.79	97.01	1.184

Table 152 Dissolution raw data of uncoated tablets stored for 6 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3347	0.2884	0.3440	0.3078	0.3352	0.3098		
20	0.4734	0.4366	0.4663	0.4481	0.4543	0.4419		
30	0.5221	0.4963	0.5170	0.5053	0.4939	0.4984		
	% Dissolved							
10	56.15	48.37	57.67	51.63	56.23	51.96	53.67	3.576
20	79.26	73.05	78.09	74.99	76.08	73.97	75.91	2.401
30	87.29	82.90	86.45	84.44	82.60	83.29	84.49	1.959

Table 153 Dissolution raw data of coated tablets stored for 6 months at 40°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1348	0.1542	0.0612	0.1260	0.0711	0.1083		
20	0.3374	0.3713	0.2563	0.3384	0.2907	0.3647		
30	0.4468	0.4617	0.3676	0.4414	0.4100	0.4606		
	% Dissolved							
10	22.53	25.79	10.14	21.05	11.81	18.06	18.23	6.169
20	56.27	61.95	42.63	56.42	48.38	60.77	54.40	7.481
30	74.30	76.85	60.98	73.40	68.06	76.58	71.70	6.132

Table 154 Dissolution raw data of uncoated tablets stored for 6 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.1017	0.0601	0.0776	0.0484	0.0594	0.0615		
20	0.3135	0.1347	0.2319	0.2898	0.2224	0.1717		
30	0.4731	0.4144	0.4340	0.4404	0.4380	0.3719		
	% Dissolved							
10	16.96	9.97	12.91	7.99	9.85	10.20	11.31	3.185
20	52.23	22.38	38.60	48.19	36.99	28.55	37.82	11.323
30	78.54	68.50	71.93	73.03	72.53	61.56	71.02	5.651

Table 155 Dissolution raw data of coated tablets stored for 6 months at 40°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0758	0.0422	0.0359	0.0580	0.0646	0.1022		
20	0.2726	0.1147	0.1476	0.2928	0.4144	0.4064		
30	0.4926	0.4421	0.4625	0.4955	0.5439	0.5229		
	% Dissolved							
10	12.59	6.95	5.89	9.60	10.72	17.05	10.47	4.048
20	45.37	19.03	24.49	48.72	68.97	67.70	45.71	20.959
30	81.64	73.00	76.41	82.14	90.33	86.92	81.74	6.410

Table 156 Dissolution raw data of uncoated tablets stored for 6 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0530	0.0447	0.0495	0.0415	0.0458	0.0431		
20	0.0768	0.1287	0.1030	0.0809	0.2143	0.1109		
30	0.1175	0.1994	0.1641	0.1169	0.3015	0.1719		
	% Dissolved							
10	8.77	7.37	8.18	6.82	7.55	7.11	7.63	0.720
20	12.72	21.35	17.08	13.38	35.62	18.39	19.76	8.407
30	19.44	33.01	27.16	19.33	49.99	28.46	29.57	11.341

Table 157 Dissolution raw data of coated tablets stored for 6 months at 40°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0399	0.0389	0.0329	0.0344	0.0332	0.0655		
20	0.1236	0.1937	0.1261	0.0744	0.1581	0.2740		
30	0.3697	0.3167	0.3887	0.3445	0.3984	0.4492		
	% Dissolved							
10	6.55	6.39	5.38	5.64	5.44	10.88	6.71	2.098
20	20.50	32.17	20.90	12.29	26.23	45.60	26.28	11.541
30	61.08	52.45	64.20	56.84	65.85	74.48	62.48	7.651

Table 158 Dissolution raw data of uncoated tablets stored for 6 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0843	0.0880	0.0816	0.0944	0.0593	0.0831		
20	0.2465	0.1250	0.1184	0.1290	0.0854	0.1099		
30	0.3242	0.1664	0.1493	0.1633	0.1201	0.1382		
	% Dissolved							
10	14.04	14.66	13.58	15.73	9.83	13.83	13.61	2.005
20	41.04	20.81	19.71	21.49	14.18	18.29	22.59	9.406
30	53.85	27.64	24.81	27.15	19.89	22.97	29.39	12.321

Table 159 Dissolution raw data of coated tablets stored for 6 months at 40°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.0503	0.0339	0.0276	0.0523	0.0372	0.0390		
20	0.0771	0.0563	0.0550	0.2834	0.1312	0.0790		
30	0.3111	0.1203	0.2171	0.4306	0.3946	0.1132		
	% Dissolved							
10	8.31	5.54	4.50	8.65	6.11	6.40	6.59	1.610
20	12.77	9.28	9.04	47.14	21.76	13.07	18.84	14.610
30	51.36	19.83	35.78	71.40	65.19	18.70	43.71	22.561

Table 160 Dissolution raw data of uncoated tablets stored for 6 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3873	0.3776	0.4023	0.3780	0.3672	0.4273		
20	0.5724	0.5753	0.5689	0.5738	0.5646	0.5769		
30	0.5869	0.5817	0.5776	0.5676	0.5617	0.5683		
	% Dissolved							
10	65.01	63.37	67.53	63.44	61.63	71.74	65.45	3.663
20	95.83	96.31	95.27	96.05	94.51	96.65	95.77	0.772
30	98.23	97.35	96.70	95.03	94.03	95.23	96.10	1.591

Table 161 Dissolution raw data of coated tablets stored for 6 months at 40°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2171	0.0618	0.0305	0.1440	0.0547	0.2623		
20	0.5796	0.5100	0.4086	0.5668	0.5646	0.5718		
30	0.5990	0.5790	0.5349	0.5858	0.5837	0.5883		
	% Dissolved							
10	36.37	10.24	4.98	24.08	9.06	43.98	21.45	16.046
20	96.75	84.89	67.96	94.49	93.98	95.52	88.93	11.108
30	99.95	96.27	88.78	97.63	97.13	98.24	96.34	3.900

Table 162 Dissolution raw data of uncoated tablets stored for 6 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5153	0.4968	0.4961	0.4942	0.5027	0.5231		
20	0.5607	0.5401	0.5374	0.5385	0.5401	0.5517		
30	0.5643	0.5470	0.5494	0.5514	0.5548	0.5596		
	% Dissolved							
10	86.54	83.44	83.32	82.99	84.42	87.86	84.76	1.992
20	94.10	90.65	90.19	90.38	90.65	92.62	91.43	1.575
30	94.70	91.78	92.16	92.49	93.07	93.92	93.02	1.110

Table 163 Dissolution raw data of coated tablets stored for 6 months at 25°C/90%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5097	0.4844	0.5077	0.4951	0.5094	0.5017		
20	0.5465	0.5360	0.5422	0.5449	0.5501	0.5519		
30	0.5560	0.5485	0.5497	0.5542	0.5609	0.5601		
	% Dissolved							
10	85.59	81.35	85.27	83.14	85.55	84.25	84.19	1.681
20	91.72	89.93	91.01	91.44	92.33	92.61	91.51	0.966
30	93.29	92.00	92.24	92.97	94.11	93.97	93.10	0.869

Table 164 Dissolution raw data of uncoated tablets stored for 6 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5424	0.5442	0.5606	0.5331	0.5330	0.5464		
20	0.5671	0.5660	0.5710	0.5587	0.5609	0.5661		
30	0.5719	0.5747	0.5754	0.5653	0.5714	0.5678		
	% Dissolved							
10	91.10	91.41	94.16	89.54	89.52	91.77	91.25	1.714
20	95.22	95.03	95.90	93.81	94.16	95.06	94.86	0.757
30	96.00	96.46	96.61	94.88	95.89	95.33	95.86	0.661

Table 165 Dissolution raw data of coated tablets stored for 6 months at 25°C/75%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3641	0.1156	0.0580	0.4667	0.3046	0.2065		
20	0.5553	0.5398	0.5261	0.5611	0.5548	0.5154		
30	0.5703	0.5659	0.5555	0.5729	0.5688	0.5412		
	% Dissolved							
10	61.10	19.30	9.60	78.37	51.09	34.60	42.34	26.037
20	92.95	89.96	87.56	94.08	92.76	86.03	90.56	3.248
30	95.42	94.25	92.41	96.03	95.07	90.30	93.91	2.170

Table 166 Dissolution raw data of uncoated tablets stored for 6 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4587	0.5400	0.5424	0.5302	0.5485	0.5271		
20	0.5789	0.5680	0.5714	0.5734	0.5763	0.5799		
30	0.5915	0.5785	0.5772	0.5784	0.5724	0.5872		
	% Dissolved							
10	77.02	90.69	91.09	89.05	92.12	88.52	88.08	5.580
20	97.03	95.37	95.94	96.25	96.76	97.33	96.44	0.732
30	99.12	97.09	96.88	97.07	96.11	98.52	97.46	1.125

Table 167 Dissolution raw data of coated tablets stored for 6 months at 25°C/65%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2015	0.1265	0.1422	0.1805	0.0741	0.3291		
20	0.5582	0.5608	0.5592	0.5781	0.5590	0.572		
30	0.5781	0.5831	0.5750	0.5893	0.5921	0.5797		
	% Dissolved							
10	33.75	21.13	23.77	30.22	12.32	55.21	29.40	14.681
20	93.16	93.47	93.23	96.43	93.08	95.69	94.18	1.483
30	96.43	97.13	95.83	98.28	98.53	96.94	97.19	1.046

Table 168 Dissolution raw data of uncoated tablets stored for 6 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.5312	0.5538	0.4973	0.5526	0.5457	0.5601		
20	0.5860	0.5768	0.5689	0.5807	0.5853	0.5704		
30	0.5919	0.5835	0.5777	0.5907	0.5845	0.5827		
	% Dissolved							
10	89.21	93.01	83.51	92.81	91.65	94.07	90.71	3.900
20	98.34	96.85	95.43	97.50	98.25	95.80	97.03	1.227
30	99.31	97.95	96.88	99.15	98.12	97.83	98.21	0.903

Table 169 Dissolution raw data of coated tablets stored for 6 months at 25°C/50%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.3376	0.1986	0.0906	0.4570	0.1840	0.0793		
20	0.5675	0.5685	0.5628	0.5709	0.5685	0.5458		
30	0.5820	0.5813	0.5775	0.5848	0.5868	0.5762		
	% Dissolved							
10	56.65	33.26	15.09	76.73	30.80	13.19	37.62	24.744
20	94.94	94.87	93.73	95.70	94.85	90.89	94.16	1.722
30	97.32	96.97	96.16	98.00	97.87	95.90	97.04	0.868

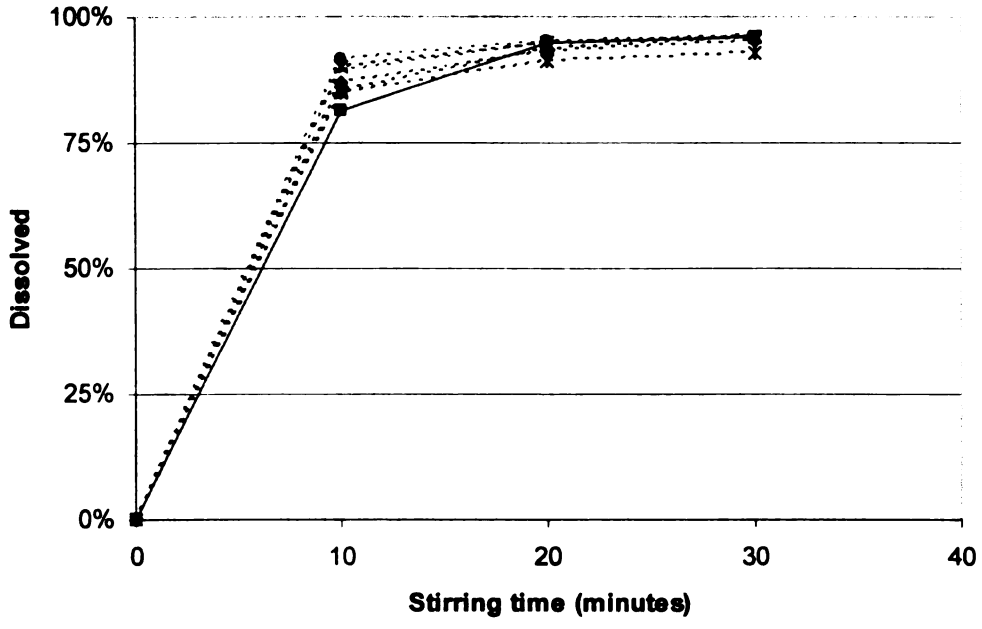
Table 170 Dissolution raw data of uncoated tablets stored for 6 months at 25°C/0%

Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.4190	0.3749	0.4070	0.3796	0.4671	0.4535		
20	0.5809	0.5950	0.5858	0.5822	0.5940	0.5863		
30	0.5914	0.5940	0.5910	0.5889	0.5940	0.5940		
	% Dissolved							
10	70.33	62.93	68.33	63.71	78.43	76.15	69.98	6.345
20	97.30	99.58	98.10	97.46	99.57	98.25	98.38	0.996
30	99.04	99.41	98.96	98.57	99.57	99.53	99.18	0.393

Table 171 Dissolution raw data of coated tablets stored for 6 months at 25°C/0%

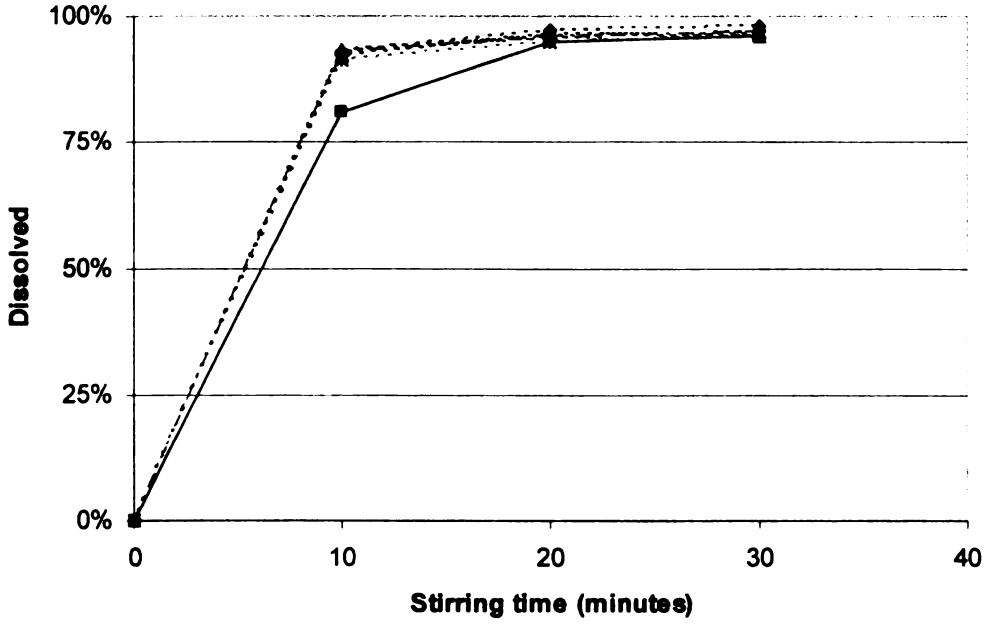
Stirring time (minutes)	Number of trial							
	1	2	3	4	5	6	Average	SD
	Absorbance							
10	0.2877	0.3722	0.3024	0.2628	0.2186	0.3262		
20	0.5811	0.5758	0.5873	0.5789	0.5805	0.5839		
30	0.5909	0.5845	0.5933	0.5893	0.5908	0.5925		
	% Dissolved							
10	48.25	62.47	50.73	44.06	36.63	54.72	49.48	8.874
20	97.12	96.37	98.17	96.71	96.90	97.64	97.15	0.658
30	98.73	97.80	99.16	98.43	98.59	99.07	98.63	0.492

2. Dissolution profiles of drug X uncoated tablets stored at 25°C



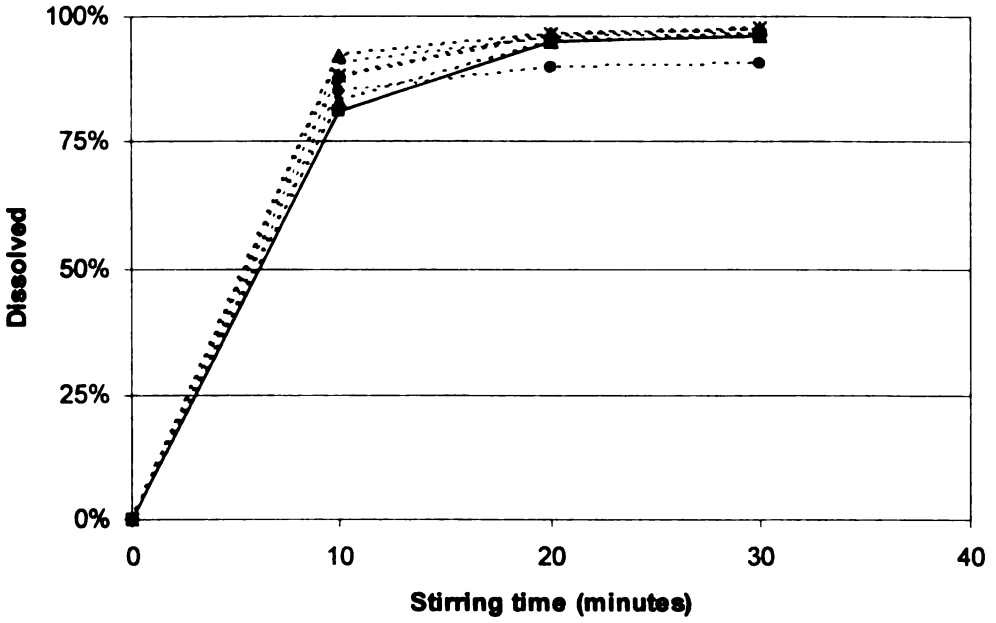
■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 86 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 25°C/90% RH (each point is average value for 6 tablets)



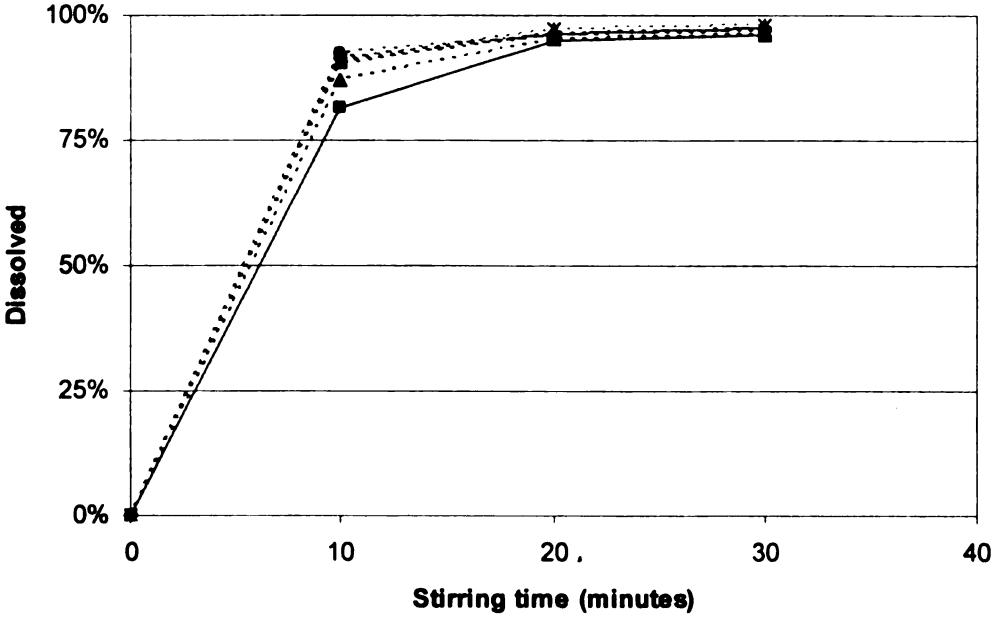
■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 87 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 25°C/75% RH (each point is average value for 6 tablets)



■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 88 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 25°C/65% RH (each point is average value for 6 tablets)



■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 89 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 25°C/50% RH (each point is average value for 6 tablets)

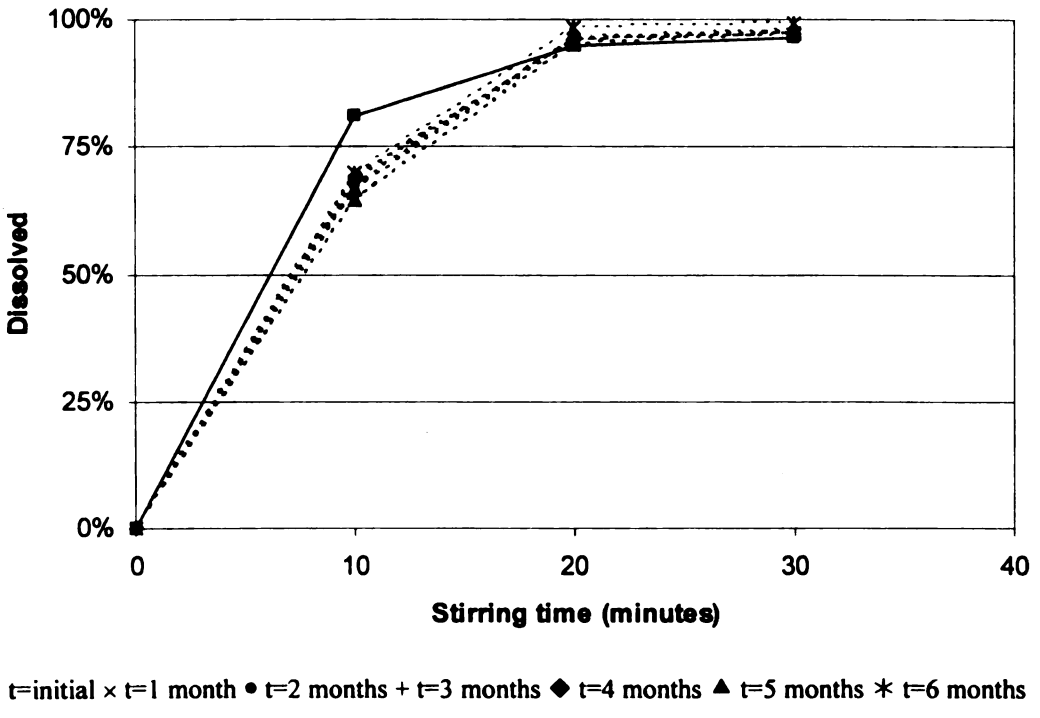
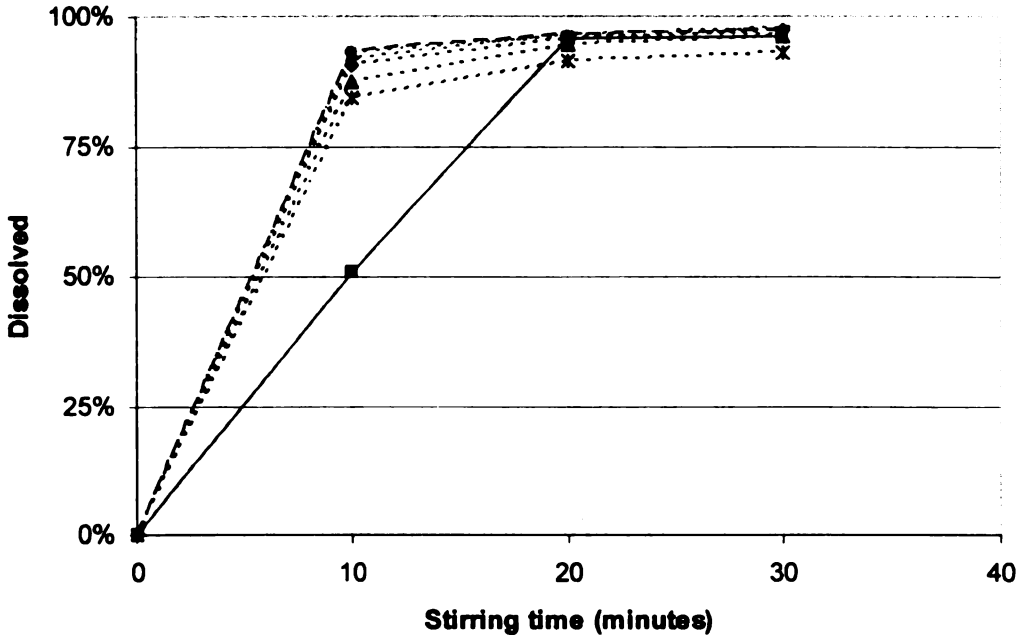


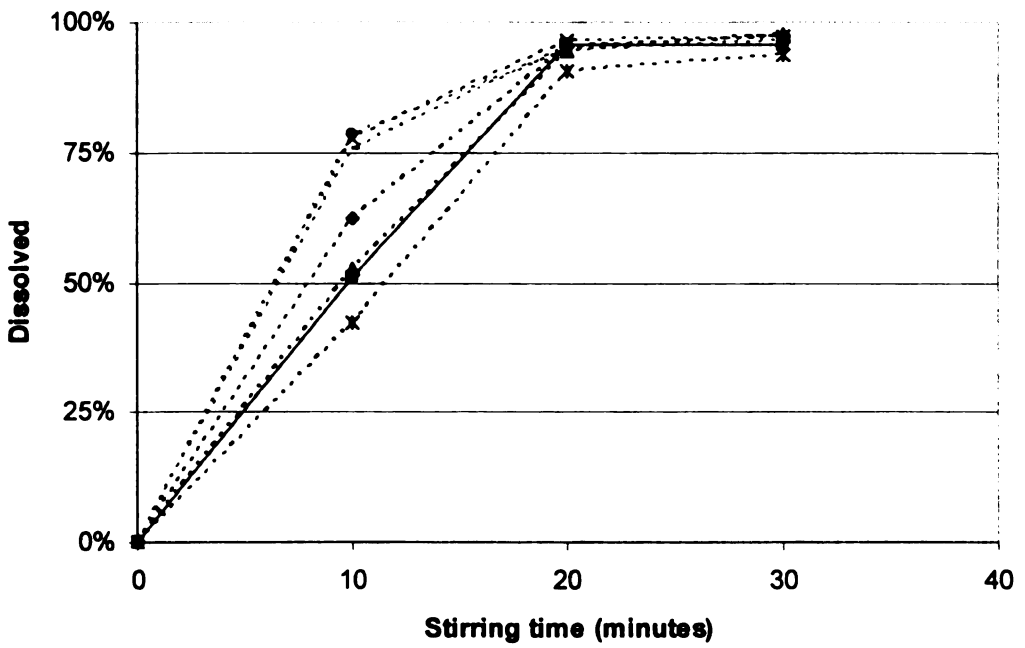
Figure 90 Dissolution profiles of drug X uncoated tablets stored in open dishes for 6 months at 25°C/0% RH (each point is average value for 6 tablets)

3. Dissolution profiles of drug X coated tablets stored at 25°C



■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 91 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 25°C/90% RH (each point is average value for 6 tablets)



■ t=initial × t=1 month • t=2 months + t=3 months ◆ t=4 months ▲ t=5 months ✳ t=6 months

Figure 92 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 25°C/75% RH (each point is average value for 6 tablets)

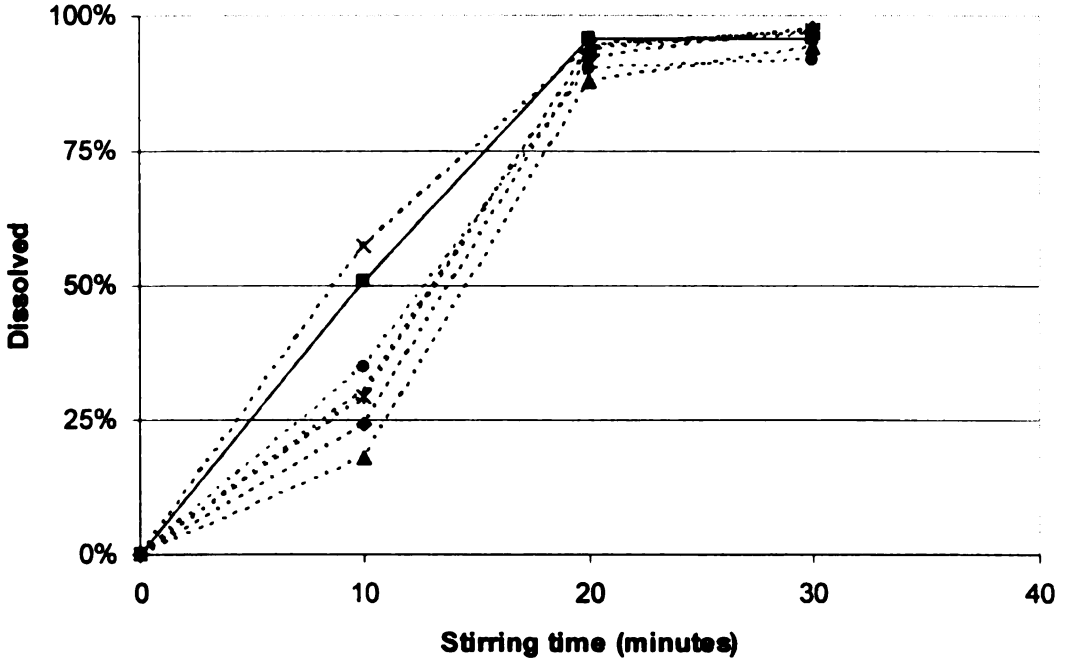


Figure 93 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 25°C/65% RH (each point is average value for 6 tablets)

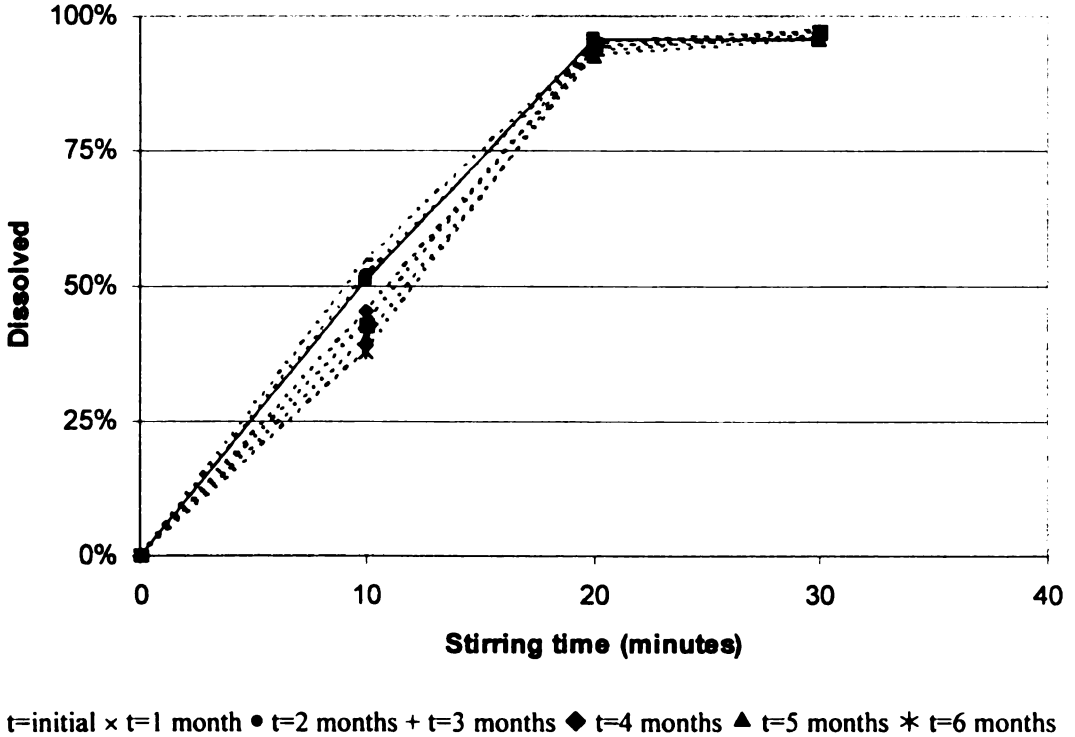


Figure 94 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 25°C/50% RH (each point is average value for 6 tablets)

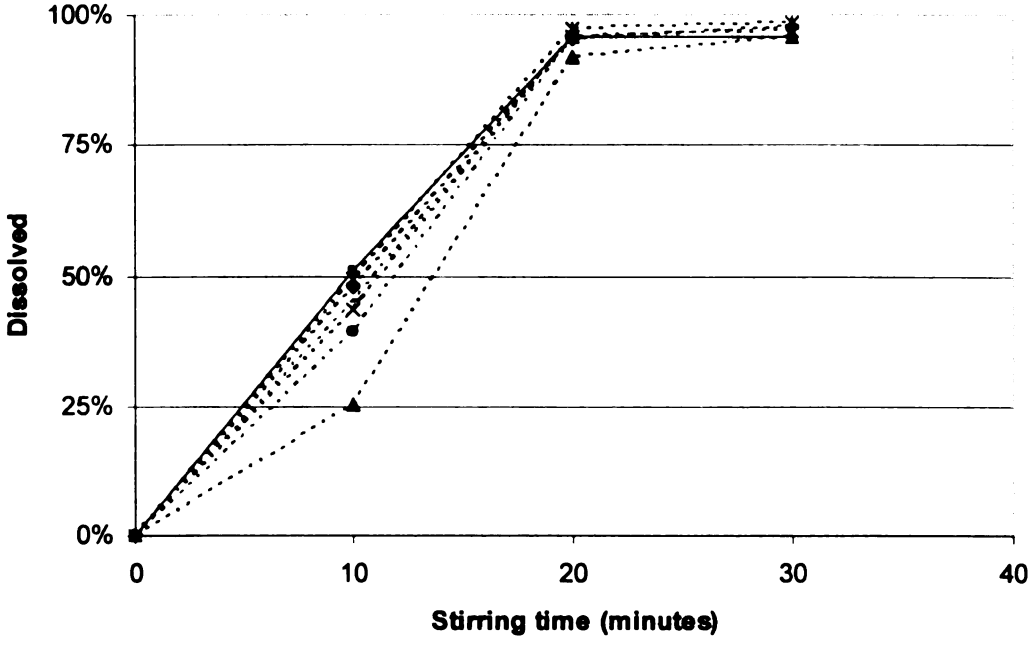


Figure 95 Dissolution profiles of drug X coated tablets stored in open dishes for 6 months at 25°C/0% RH (each point is average value for 6 tablets)

Appendix F

Dimensions (Swelling) and Raw Data

In order to explain the tablet swelling, the dimensions of tablets were measured at each condition. Figures 96 and 97 show how the dimensions of drug X tablets increase as a function of moisture content because excipients such as croscarmellose sodium in tablets swell when they absorb moisture.

The thickness dimensions at 90% RH were increased at most about 0.17mm and the diameter dimensions at 90% RH were increased at most about 0.15mm. Figure 96 shows the percent thickness increase and Figure 97 shows the percent diameter increase as a function of relative humidity at 25°C and 40°C. When tablets were stored at higher RH, they swelled quickly as they absorbed moisture. After the initial swelling, the dimensions did not increase further as a function of storage time.

Drug X tablets are formulated with croscarmellose sodium that is a high swelling material. The croscarmellose sodium swells to 4-8 times its original volume on contact with water. The swollen croscarmellose reduce boundary strength among excipient granules. Therefore, the tablets disintegrate quickly in a short time when they are dropped into the dissolution medium.

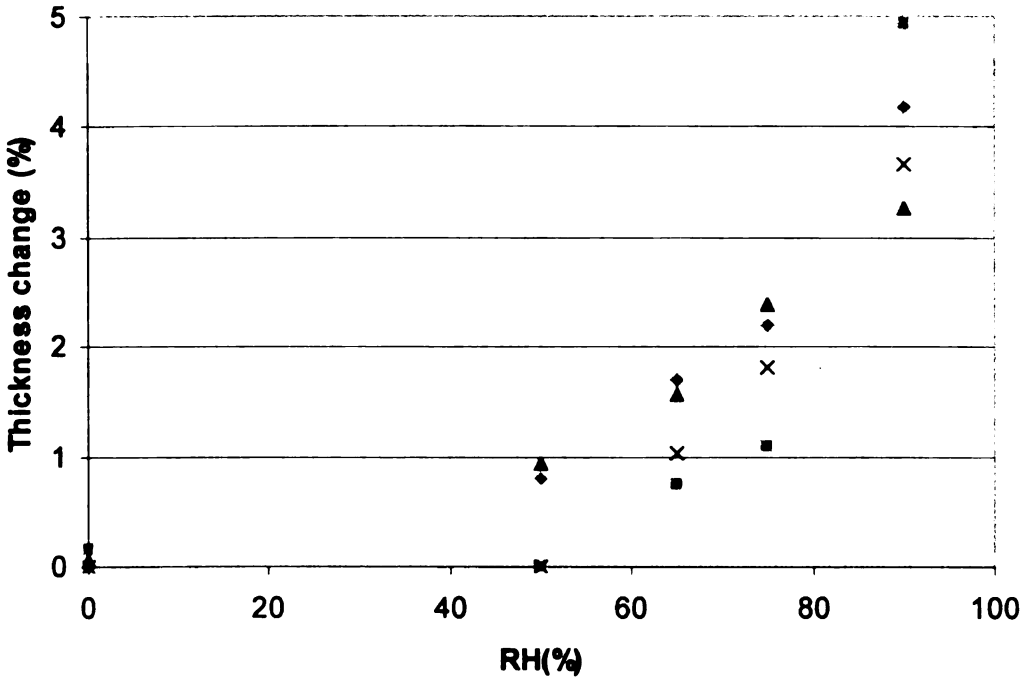


Figure 96 Percent thickness dimension change of drug X tablets as a function of RH (each point is average value for 5 tablets)

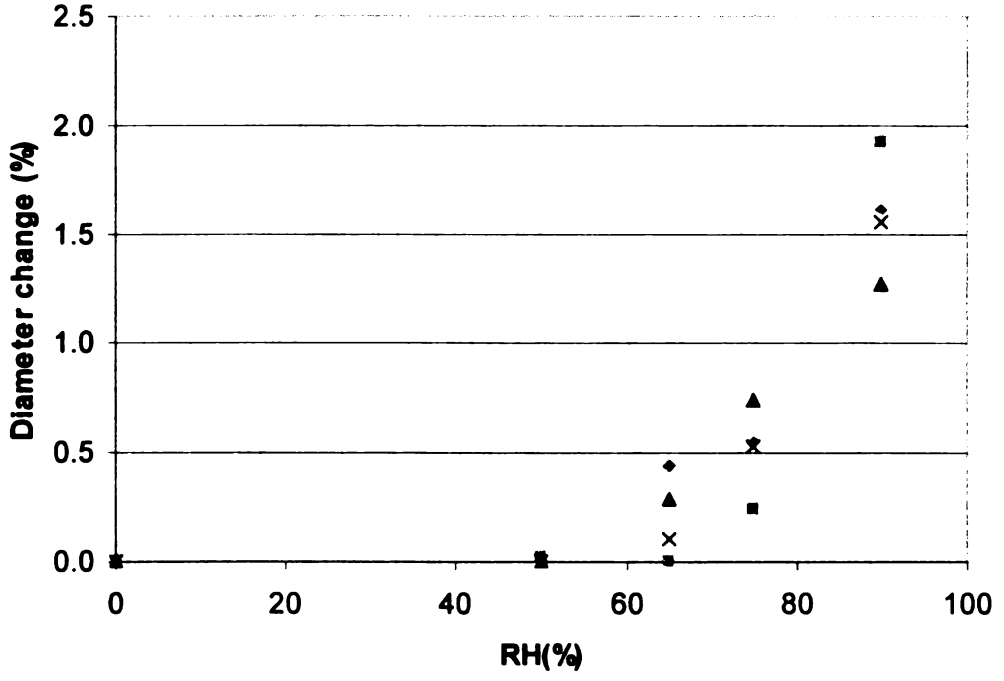


Figure 97 Percent diameter dimension change of drug X tablets as a function of RH (each point is average value for 5 tablets)

Table 172 shows the dimensions of initial drug X tablets and Tables 173-202 show the dimensions of drug X tablets stored at 25/40°C, 0%, 50%, 65%, 75%, and 90% RH for 6 months.

Table 172 Dimensions (mm) of initial tablets

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.01	9.07	4.09	9.22
2	4.04	9.04	4.11	9.11
3	4.01	9.06	4.10	9.12
4	4.01	9.04	4.10	9.18
5	4.01	9.03	4.09	9.10
Avg.	4.02	9.048	4.098	9.146
SD	0.013	0.016	0.008	0.052

Table 173 Dimensions (mm) of tablets stored for 20 days at 40°C/90%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.22	9.18	4.26	9.23
2	4.20	9.18	4.24	9.26
3	4.18	9.19	4.26	9.28
4	4.18	9.19	4.24	9.27
5	4.18	9.18	4.24	9.25
Avg.	4.192	9.184	4.248	9.258
SD	0.018	0.005	0.011	0.019

Table 174 Dimensions (mm) of tablets stored for 20 days at 40°C/75%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.12	9.12	4.14	9.19
2	4.12	9.14	4.15	9.19
3	4.13	9.11	4.14	9.19
4	4.12	9.12	4.14	9.20
5	4.12	9.11	4.14	9.20
Avg.	4.122	9.12	4.14	9.19
SD	0.004	0.012	0.004	0.005

Table 175 Dimensions (mm) of tablets stored for 20 days at 40°C/65%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.12	9.1	4.15	9.16
2	4.08	9.08	4.15	9.20
3	4.11	9.09	4.15	9.19
4	4.09	9.08	4.14	9.17
5	4.09	9.1	4.13	9.17
Avg.	4.098	9.09	4.14	9.18
SD	0.016	0.010	0.009	0.016

Table 176 Dimensions (mm) of tablets stored for 20 days at 40°C/50%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.04	9.09	4.12	9.15
2	4.03	9.04	4.11	9.13
3	4.06	9.09	4.10	9.13
4	4.04	9.08	4.12	9.12
5	4.04	9.06	4.10	9.13
Avg.	4.042	9.072	4.11	9.13
SD	0.011	0.022	0.010	0.011

Table 177 Dimensions (mm) of tablets stored for 20 days at 40°C/0%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.03	9.05	4.09	9.15
2	4.02	9.06	4.05	9.08
3	4.00	9.04	4.10	9.14
4	4.00	9.02	4.10	9.12
5	4.00	9.04	4.10	9.12
Avg.	4.01	9.042	4.09	9.12
SD	0.014	0.015	0.022	0.027

Table 178 Dimensions (mm) of tablets stored for 20 days at 25°C/90%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.17	9.21	4.22	9.24
2	4.17	9.22	4.21	9.29
3	4.17	9.20	4.25	9.27
4	4.18	9.20	4.25	9.29
5	4.16	9.20	4.20	9.25
Avg.	4.17	9.206	4.226	9.268
SD	0.007	0.009	0.023	0.023

Table 179 Dimensions (mm) of tablets stored for 20 days at 25°C/75%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.12	9.11	4.20	9.2
2	4.12	9.12	4.16	9.2
3	4.10	9.11	4.16	9.16
4	4.07	9.11	4.16	9.19
5	4.14	9.13	4.16	9.19
Avg.	4.11	9.116	4.17	9.19
SD	0.026	0.009	0.018	0.016

Table 180 Dimensions (mm) of tablets stored for 20 days at 25°C/65%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.07	9.09	4.16	9.16
2	4.11	9.11	4.14	9.18
3	4.11	9.08	4.18	9.18
4	4.09	9.08	4.16	9.18
5	4.09	9.09	4.12	9.15
Avg.	4.094	9.09	4.15	9.17
SD	0.017	0.012	0.023	0.014

Table 181 Dimensions (mm) of tablets stored for 20 days at 25°C/50%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.05	9.06	4.08	9.15
2	4.04	9.06	4.09	9.12
3	4.05	9.07	4.11	9.15
4	4.05	9.05	4.10	9.15
5	4.05	9.05	4.16	9.16
Avg.	4.048	9.058	4.11	9.15
SD	0.004	0.008	0.031	0.015

Table 182 Dimensions (mm) of tablets stored for 20 days at 25°C/0%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.01	9.05	4.06	9.11
2	4.02	9.02	4.11	9.11
3	4.01	9.03	4.10	9.11
4	4.02	9.03	4.10	9.11
5	4.02	9.02	4.10	9.11
Avg.	4.016	9.03	4.09	9.11
SD	0.005	0.012	0.019	0.000

Table 183 Dimensions (mm) of tablets stored for 70 days at 40°C/90%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.16	9.18	4.26	9.24
2	4.22	9.18	4.22	9.26
3	4.17	9.19	4.24	9.25
4	4.17	9.18	4.22	9.25
5	4.21	9.18	4.23	9.27
Avg.	4.186	9.182	4.234	9.254
SD	0.027	0.004	0.017	0.011

Table 184 Dimensions (mm) of tablets stored for 70 days at 40°C/75%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.10	9.10	4.14	9.16
2	4.09	9.13	4.17	9.17
3	4.10	9.10	4.21	9.19
4	4.10	9.10	4.19	9.21
5	4.11	9.12	4.18	9.19
Avg.	4.10	9.11	4.18	9.18
SD	0.007	0.014	0.026	0.019

Table 185 Dimensions (mm) of tablets stored for 70 days at 40°C/65%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.10	9.09	4.17	9.17
2	4.09	9.09	4.13	9.16
3	4.09	9.10	4.16	9.16
4	4.10	9.07	4.14	9.16
5	4.09	9.12	4.13	9.17
Avg.	4.094	9.094	4.15	9.16
SD	0.005	0.018	0.018	0.005

Table 186 Dimensions (mm) of tablets stored for 70 days at 40°C/50%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.04	9.04	4.12	9.13
2	4.04	9.05	4.12	9.10
3	4.03	9.05	4.09	9.10
4	4.02	9.03	4.09	9.12
5	4.05	9.04	4.07	9.11
Avg.	4.036	9.042	4.10	9.11
SD	0.011	0.008	0.022	0.013

Table 187 Dimensions (mm) of tablets stored for 70 days at 40°C/0%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.00	9.02	4.08	9.12
2	4.01	9.01	4.08	9.12
3	4.01	9.02	4.04	9.07
4	4.02	9.01	4.06	9.09
5	3.98	9.01	4.07	9.12
Avg.	4.004	9.014	4.07	9.10
SD	0.015	0.005	0.017	0.023

Table 188 Dimensions (mm) of tablets stored for 70 days at 25°C/90%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.22	9.23	4.24	9.33
2	4.19	9.22	4.24	9.29
3	4.23	9.22	4.28	9.34
4	4.17	9.23	4.23	9.26
5	4.20	9.22	4.26	9.28
Avg.	4.202	9.224	4.25	9.30
SD	0.024	0.005	0.020	0.034

Table 189 Dimensions (mm) of tablets stored for 70 days at 25°C/75%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.10	9.10	4.17	9.24
2	4.07	9.13	4.17	9.17
3	4.08	9.12	4.16	9.20
4	4.06	9.09	4.17	9.17
5	4.09	9.13	4.16	9.19
Avg.	4.08	9.114	4.17	9.19
SD	0.016	0.018	0.005	0.029

Table 190 Dimensions (mm) of tablets stored for 70 days at 25°C/65%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.04	9.07	4.13	9.16
2	4.08	9.07	4.17	9.17
3	4.06	9.07	4.13	9.15
4	4.09	9.09	4.13	9.17
5	4.08	9.07	4.17	9.18
Avg.	4.07	9.074	4.15	9.17
SD	0.020	0.009	0.022	0.011

Table 191 Dimensions (mm) of tablets stored for 70 days at 25°C/50%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.03	9.08	4.10	9.13
2	4.04	9.05	4.09	9.14
3	4.05	9.05	4.08	9.10
4	4.04	9.04	4.08	9.13
5	4.09	9.09	4.08	9.13
Avg.	4.05	9.062	4.09	9.13
SD	0.023	0.022	0.009	0.015

Table 192 Dimensions (mm) of tablets stored for 70 days at 25°C/0%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.00	9.00	4.09	9.12
2	4.00	9.01	4.08	9.10
3	4.00	9.01	4.04	9.09
4	4.00	9.01	4.07	9.09
5	4.03	9.02	4.10	9.11
Avg.	4.006	9.01	4.08	9.10
SD	0.013	0.007	0.023	0.013

Table 193 Dimensions (mm) of tablets stored for 180 days at 40°C/90%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.20	9.21	4.20	9.24
2	4.19	9.20	4.24	9.26
3	4.16	9.19	4.26	9.25
4	4.21	9.20	4.23	9.27
5	4.16	9.18	4.23	9.26
Avg.	4.184	9.196	4.232	9.256
SD	0.023	0.011	0.022	0.011

Table 194 Dimensions (mm) of tablets stored for 180 days at 40°C/75%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.11	9.10	4.19	9.22
2	4.12	9.10	4.17	9.22
3	4.09	9.10	4.22	9.20
4	4.10	9.10	4.20	9.20
5	4.10	9.10	4.20	9.20
Avg.	4.104	9.10	4.20	9.21
SD	0.011	0.000	0.018	0.011

Table 195 Dimensions (mm) of tablets stored for 180 days at 40°C/65%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.10	9.09	4.15	9.15
2	4.08	9.09	4.16	9.17
3	4.08	9.09	4.18	9.17
4	4.08	9.09	4.16	9.17
5	4.08	9.09	4.16	9.17
Avg.	4.084	9.09	4.16	9.17
SD	0.009	0.000	0.011	0.009

Table 196 Dimensions (mm) of tablets stored for 180 days at 40°C/50%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.07	9.04	4.12	9.10
2	4.04	9.04	4.14	9.15
3	4.05	9.04	4.14	9.14
4	4.04	9.04	4.14	9.14
5	4.04	9.04	4.14	9.14
Avg.	4.048	9.04	4.14	9.13
SD	0.013	0.000	0.009	0.019

Table 197 Dimensions (mm) of tablets stored for 180 days at 40°C/0%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.00	9.00	4.13	9.12
2	4.00	9.00	4.09	9.12
3	4.00	9.00	4.10	9.12
4	4.00	9.00	4.09	9.12
5	4.00	9.00	4.09	9.12
Avg.	4.00	9.00	4.10	9.12
SD	0.000	0.000	0.017	0.000

Table 198 Dimensions (mm) of tablets stored for 180 days at 25°C/90%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.21	9.22	4.25	9.29
2	4.21	9.24	4.24	9.28
3	4.21	9.22	4.25	9.28
4	4.22	9.22	4.25	9.28
5	4.22	9.22	4.25	9.28
Avg.	4.214	9.224	4.248	9.282
SD	0.005	0.009	0.004	0.004

Table 199 Dimensions (mm) of tablets stored for 180 days at 25°C/75%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.06	9.07	4.16	9.19
2	4.04	9.06	4.20	9.20
3	4.07	9.07	4.16	9.17
4	4.06	9.08	4.17	9.19
5	4.07	9.08	4.17	9.19
Avg.	4.06	9.072	4.17	9.19
SD	0.012	0.008	0.016	0.011

Table 200 Dimensions (mm) of tablets stored for 180 days at 25°C/65%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.05	9.04	4.14	9.15
2	4.02	9.05	4.14	9.15
3	4.05	9.05	4.14	9.15
4	4.05	9.05	4.14	9.15
5	4.06	9.05	4.14	9.15
Avg.	4.046	9.048	4.14	9.15
SD	0.015	0.004	0.000	0.000

Table 201 Dimensions (mm) of tablets stored for 180 days at 25°C/50%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	4.02	9.05	4.09	9.10
2	4.02	9.06	4.10	9.09
3	3.99	9.05	4.07	9.09
4	4.02	9.05	4.06	9.10
5	4.02	9.05	4.11	9.09
Avg.	4.014	9.052	4.09	9.09
SD	0.013	0.004	0.021	0.005

Table 202 Dimensions (mm) of tablets stored for 180 days at 25°C/0%

	Uncoated		Coated	
	thickness	diameter	thickness	diameter
1	3.99	9.02	3.95	9.10
2	4.03	9.02	4.00	9.09
3	4.05	9.02	3.97	9.10
4	4.01	9.02	3.96	9.09
5	4.03	9.02	3.97	9.13
Avg.	4.022	9.02	3.97	9.10
SD	0.023	0.000	0.019	0.016

Appendix G

Hardness and Raw Data

In order to help explain the effect of intermolecular forces among ingredients in tablets, the hardness of tablets was measured at each condition for 190 days. Table 203 shows the average hardness of tablets measured for 190 days.

Table 203 Average hardness of drug X uncoated and coated tablets

		Hardness (kp)							
		Uncoated tablets							
		Storage time (days)							
Temp (°C)	RH (%)	0	6	18	70	100	130	170	190
25	90	8.9	2.2	1.6	1.6	1.7	1.9	1.7	1.8
	75	8.9	5.9	6.5	7.0	7.3	7.6	6.8	6.8
	65	8.9	6.9	7.4	8.3	8.5	8.7	8.4	8.1
	50	8.9	7.2	7.5	7.8	7.8	8.1	7.8	8.2
	0	8.9	7.4	7.1	7.4	7.1	7.3	7.1	7.1
40	90	8.9	2.5	2.6	2.6	3.0	2.7	3.0	3.1
	75	8.9	6.7	7.4	7.5	7.4	7.8	8.1	7.7
	65	8.9	8.0	8.5	8.9	8.8	8.9	9.7	9.5
	50	8.9	8.0	8.8	9.4	9.2	9.8	10.1	10.1
	0	8.9	7.1	7.5	7.4	7.2	7.3	7.0	7.4
		Uncoated tablets							
		Storage time (days)							
Temp (°C)	RH (%)	0	6	18	70	100	130	170	190
25	90	9.2	2.4	1.8	1.8	1.6	1.9	1.9	1.9
	75	9.2	7.6	7.3	8.0	7.5	7.9	7.9	8.4
	65	9.2	8.0	8.2	9.5	9.0	9.2	9.7	9.6
	50	9.2	8.2	8.2	8.8	9.0	9.3	9.2	9.2
	0	9.2	8.4	8.2	8.3	8.0	8.4	8.0	8.0
40	90	9.2	2.5	2.6	2.5	2.6	2.8	3.0	3.0
	75	9.2	7.5	8.0	8.4	8.7	9.0	9.2	9.3
	65	9.2	8.6	9.1	9.7	9.9	10.0	10.9	10.3
	50	9.2	8.9	10.2	10.6	10.3	10.8	11.2	11.2
	0	9.2	8.2	8.4	8.4	8.3	8.6	8.4	8.6

After 6 days storage time, the hardness of tablets obtained from all conditions decreased. The hardness of coated and uncoated tablets stored at 90% decreased a lot;

around 2.2-2.5 kp (kilopond) from 8.9-9.2 kp initial hardness. The hardness of tablets stored at 0% and 75% dropped to around 6-7 kp, then it increased a little as a function of storage time as shown in Figures 98-101. The hardness of tablets stored at 50% and 65% decreased a little (about 1-2 kp) from 9 kp to about 7-8 kp, then it increased as a function of storage time to a value higher than the initial hardness. The hardness values at the initial and 7 day storage times were analyzed statistically using t-tests (see Table 204).

Table 204 p-values from t-test between initial and 7 day aged tablet hardness

	p-value			p-value	
40°C	uncoated	coated	25°C	uncoated	coated
90%	4.1E-19	3.5E-20	90%	4.2E-19	2.3E-20
75%	1.8E-08	6.2E-06	75%	1.1E-11	2.7E-05
65%	6.4E-03	2.1E-02	65%	1.1E-05	2.1E-04
50%	3.9E-04	**9.0E-02**	50%	6.6E-08	3.1E-03
0%	2.6E-08	2.5E-05	0%	5.2E-08	2.1E-03

As shown in Table 204, the p-values are all less than 0.05 except for coated tablets stored at 40°C/50%. Therefore, it could be concluded that all hardness values from initial tablets to 6 day aged tablets changed significantly except for coated tablets stored at 40°C/50%. The hardness of coated tablets stored for 7 days at 40°C/50% is not significantly different statistically or visually in comparison with the hardness of initial coated tablets. It can be concluded that the hardness at 50% RH was not changed because it is close to the initial condition (42.6% RH).

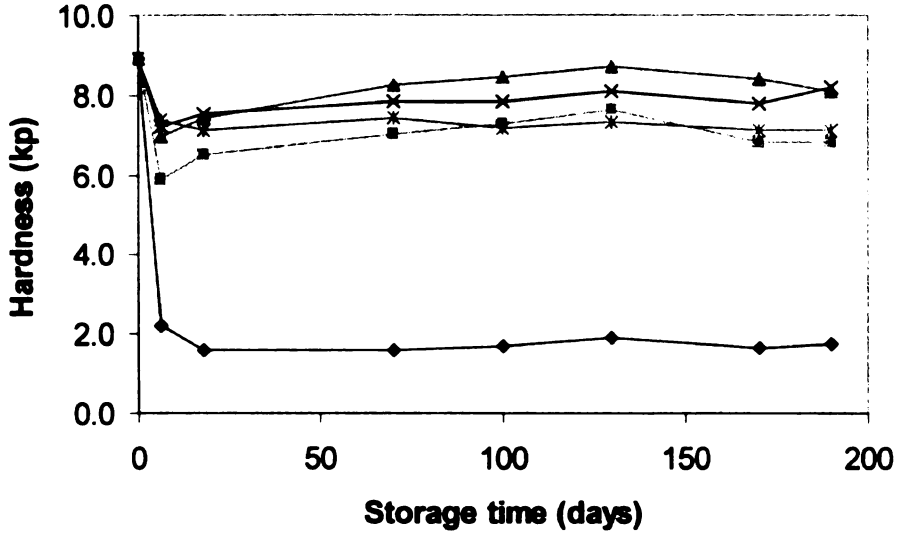
Second, the hardness values from 7 days to 190 days were analyzed statistically using ANOVA. Table 205 shows the p-values from ANOVA.

Table 205 p-values from ANOVA between 7 to 190 day aged tablet hardness

	p-value			p-value	
40°C	uncoated	coated	25°C	uncoated	coated
90%	1.1E-03	1.0E-09	90%	1.4E-11	8.3E-20
75%	2.6E-05	6.1E-04	75%	9.1E-05	1.5E-02
65%	2.1E-08	8.1E-07	65%	5.3E-08	2.8E-06
50%	1.2E-12	1.3E-11	50%	1.2E-06	2.2E-05
0%	**1.0E-02**	**3.2E-01**	0%	**2.8E-01**	**2.6E-01**

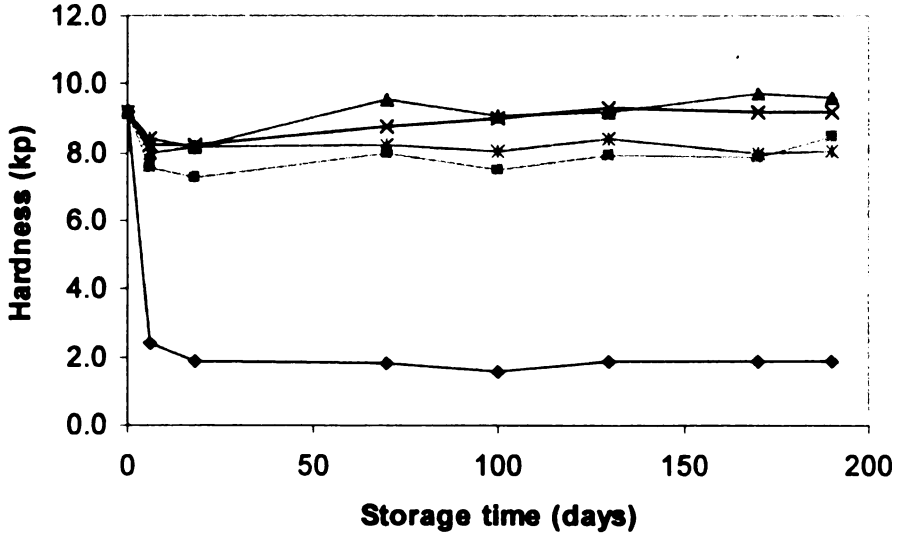
As shown in Table 205, p-values of coated/uncoated tablets stored at 40°C, 25°C/0% are greater than 0.05. Therefore, they are not significantly different for 7 to 190 days. However, the hardness of tablets stored at other conditions is significantly different for 7 to 190 days because the p-values are less than 0.05. This can also be recognized by inspecting Figures 98-105.

When tablets were stored at higher RH, the hardness decreased quickly. It can also be explained by the swelling property. The swollen croscarmellose make boundary strength among excipients weak. Therefore, the hardness of tablets decreases quickly at a high relative humidity.



◆ 90% RH ■ 75% RH ▲ 65% RH × 50% RH ✳ 0% RH

Figure 98 Hardness of drug X uncoated tablets stored at 25°C as a function of storage time (each point is average value for 10 tablets)



◆ 90% RH ■ 75% RH ▲ 65% RH × 50% RH ✳ 0% RH

Figure 99 Hardness of drug X coated tablets stored at 25°C as a function of storage time (each point is average value for 10 tablets)

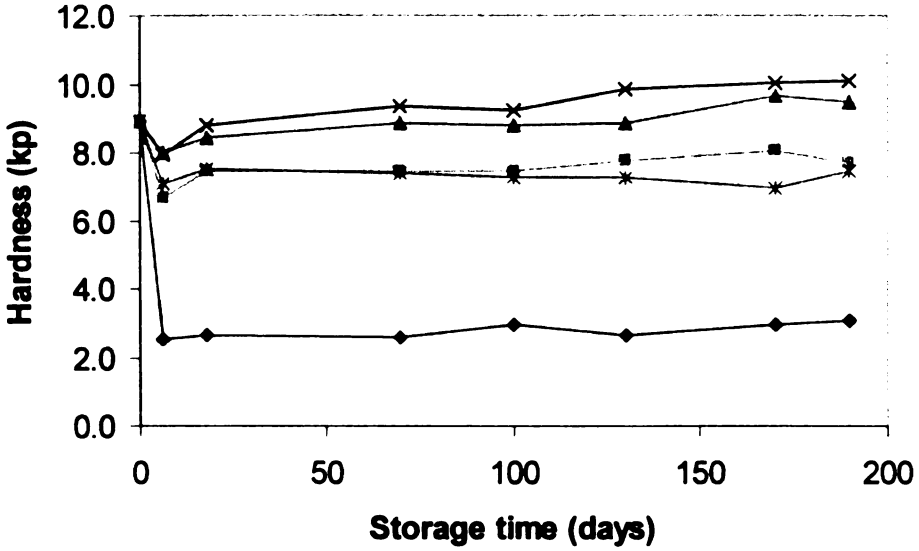


Figure 100 Hardness of drug X uncoated tablets stored at 40°C as a function of storage time (each point is average value for 10 tablets)

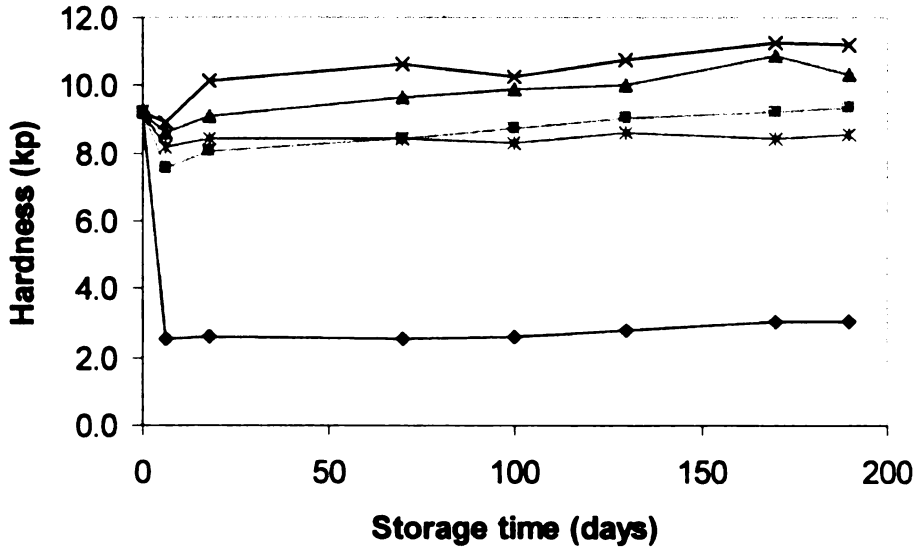
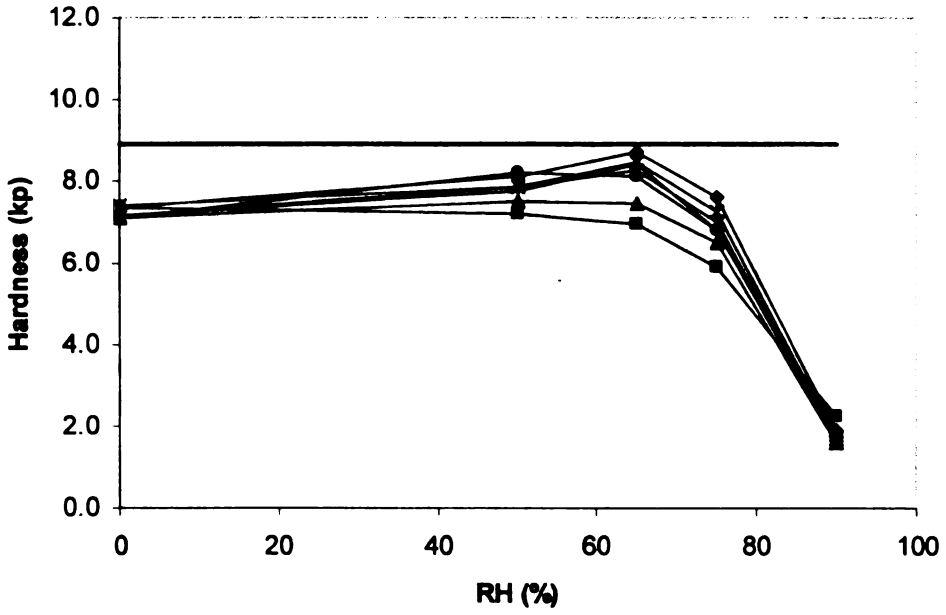


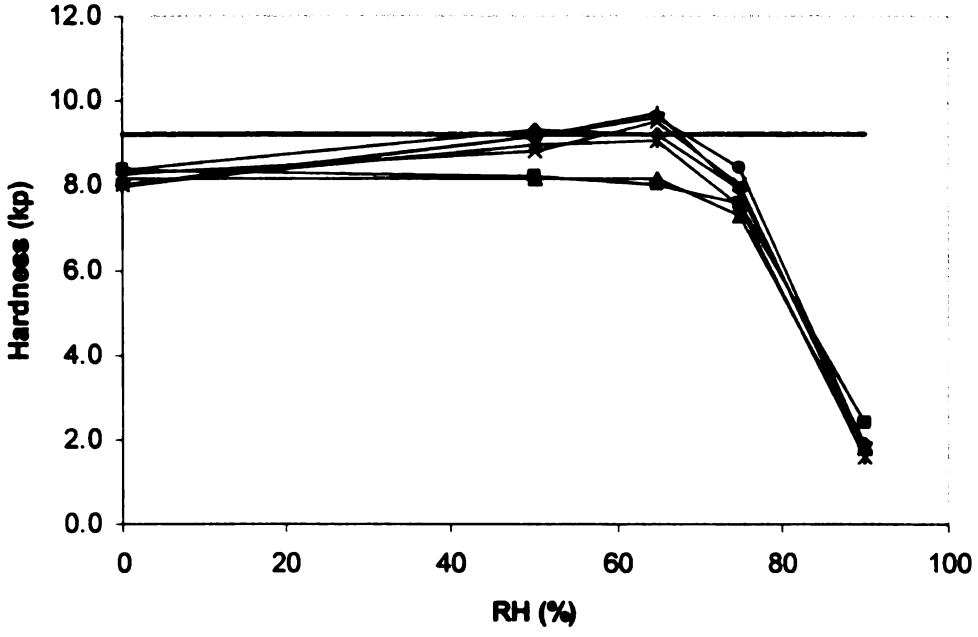
Figure 101 Hardness of drug X coated tablets stored at 40°C as a function of storage time (each point is average value for 10 tablets)

Also, there is evidence for differences in tablet hardness at different temperatures. Figures 102 and 104, and 103 and105 show the hardness values of tablets stored at 40°C are higher than those of tablets stored at 25°C, and they also show the hardness increased as a function of storage time, as concluded before. The tablets stored around 50-65% RH have the greatest hardness.



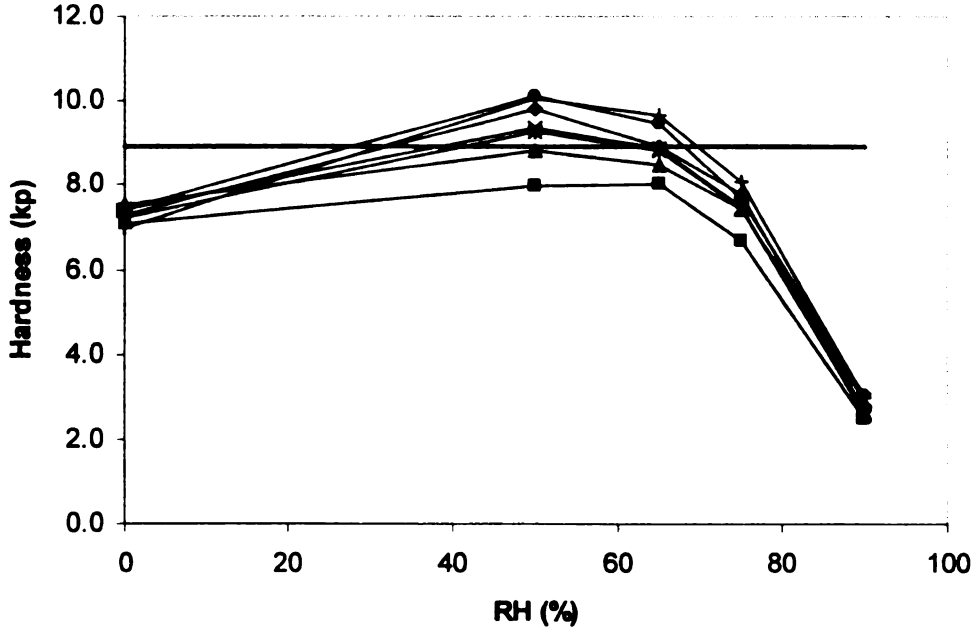
— initial tablets ■t = 6 days ▲t = 18 days ×t = 70 days ✱t = 100 days ◆t = 130 days +t = 170 days ●t = 190 days

Figure 102 Hardness of drug X uncoated tablets at 25°C as a function of RH (%) (each point is average value for 10 tablets)



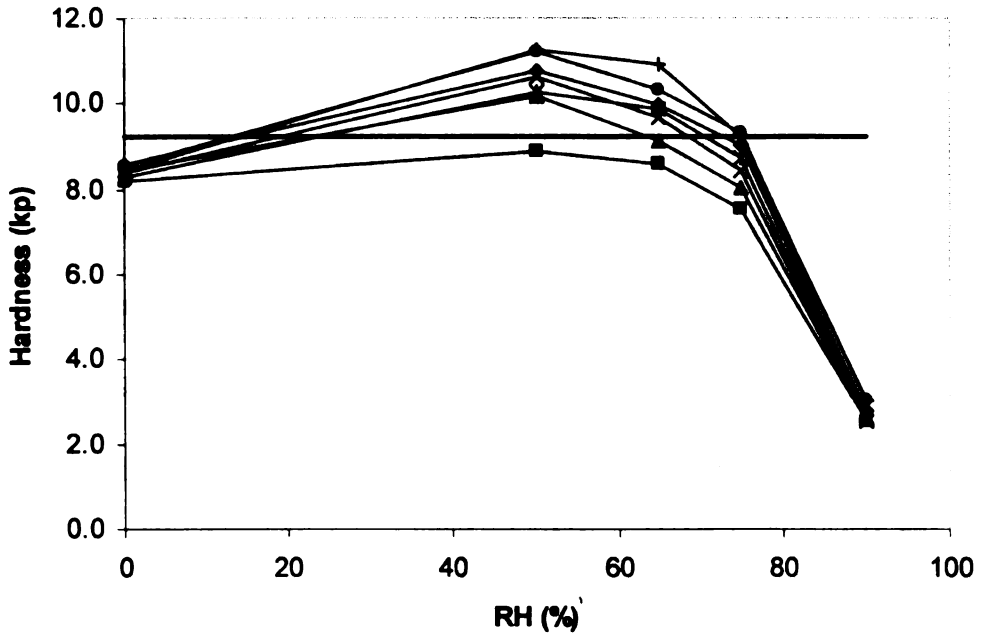
— initial tablets ■t = 6 days ▲t = 18 days ×t = 70 days ✱t = 100 days ◆t = 130 days +t = 170 days ●t = 190 days

Figure 103 Hardness of drug X coated tablets at 25°C as a function of RH (%) (each point is average value for 10 tablets)



— initial tablets ■t = 6 days ▲t = 18 days ×t = 70 days ✱t = 100 days ◆t = 130 days +t = 170 days ●t = 190 days

Figure 104 Hardness of drug X uncoated tablets at 40°C as a function of RH (%) (each point is average value for 10 tablets)



— initial tablets ■t = 6 days ▲t = 18 days ×t = 70 days ✱t = 100 days ◆t = 130 days +t = 170 days ●t = 190 days

Figure 105 Hardness of drug X coated tablets at 40°C as a function of RH (%) (each point is average value for 10 tablets)

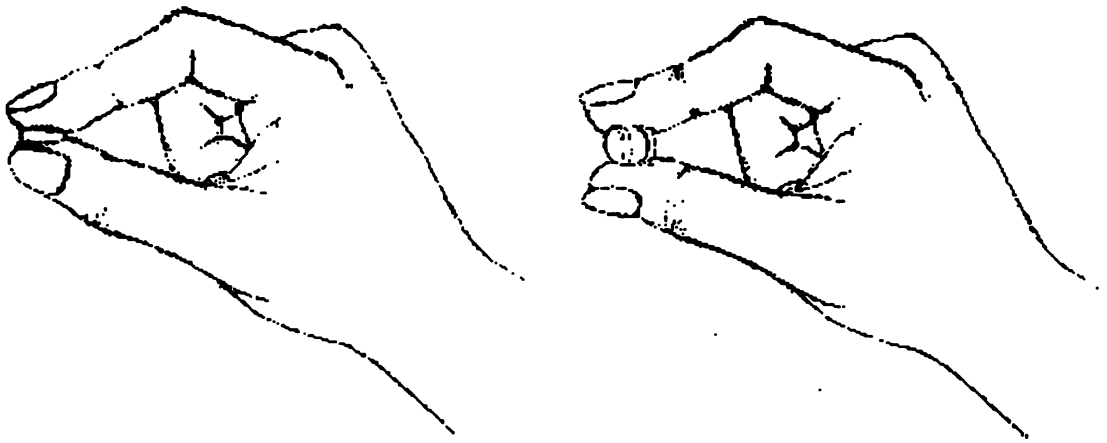
Inspection of Figures 102-105 shows that the hardness of tablets stored at 40°C was greater than those stored at 25°C. Table 206 shows p-values from t-test analysis.

Table 206 p-values from t-test between hardness of tablets stored at 25°C and 40°C (p-values greater than 0.05 are bold-faced)

		p-values from t-test					
RH (%)		1 month	2 months	3 months	4 months	5 months	6 months
90	uncoated	1.3E-08	4.0E-07	1.7E-09	4.6E-09	1.1E-10	1.2E-10
	coated	2.8E-08	1.2E-12	5.2E-11	2.6E-11	3.8E-12	2.0E-11
75	uncoated	1.0E-02	**1.7E-01**	**6.6E-01**	**3.7E-01**	3.3E-03	2.5E-03
	coated	1.1E-02	**2.2E-01**	2.4E-03	1.2E-02	4.0E-03	**5.2E-02**
65	uncoated	1.8E-05	4.0E-03	**2.3E-01**	**3.4E-01**	2.2E-04	7.5E-06
	coated	1.0E-03	**6.9E-01**	1.9E-02	4.0E-05	4.3E-02	**1.0E-01**
50	uncoated	7.2E-09	5.0E-06	1.3E-05	1.4E-07	8.3E-11	8.2E-10
	coated	5.0E-06	8.0E-07	4.8E-06	3.0E-04	4.3E-07	2.2E-08
0	uncoated	**1.5E-01**	**9.5E-01**	**5.5E-01**	**7.4E-01**	**3.1E-01**	**7.8E-02**
	coated	**7.8E-02**	**4.1E-01**	**2.7E-01**	**4.2E-01**	**6.3E-02**	5.5E-03

The hardness at 0% RH is not significantly different between 25°C and 40°C because the p-values are greater than 0.05 during most of the storage time. The hardness at 50% and 90% is significantly different between 25°C and 40°C because the p-values are less than 0.05 at all storage times. Five p-values at 75% and four p-values at 65% are greater than 0.05, but more p-values are less than 0.05. Figures 102-105 show that the hardness of tablets stored at 40°C/75% and 65% is greater than hardness of those stored at 25°C/75% and 65%. Therefore, it can be concluded that the hardness of tablets stored at 40°C is greater than those stored at 25°C, except for 0% RH. This may explain why the dissolution of tablets stored at 40°C decreased a lot more quickly than for tablets stored at 25°C. See Chapter 4.4. Proposed theory of dissolution retardation as a function of relative humidity for a more detailed explanation.

The hardness of tablets is decreased by moisture absorption. The hardness at 25°C/90% and 40°C/90% changed to 2 kp from 9 kp. The tablets at those conditions are still hard if they are squeezed as shown in Figure 106. However, if they are bent as shown in Figure 107, they can be broken very easily in comparison to initial tablets.



(a) Squeeze in the thickness direction (b) Squeeze in the diameter direction

Figure 106 Graphical representation of the tablet squeezing in the thickness and diameter directions by fingers

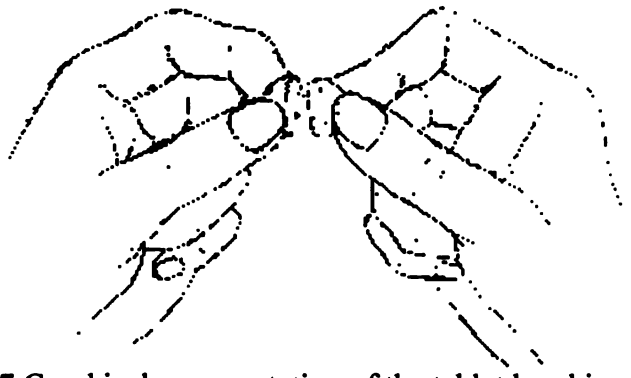


Figure 107 Graphical representation of the tablet breaking by fingers

Tablets will soften in a short time if they are packaged in PVC blisters and stored at a high relative humidity. Therefore, pharmaceutical companies may not want to use PVC blisters for solid dosage forms even if dissolution is high enough for a long time. It must be determined whether 2 kp hardness is enough for use of blister packages or not. Tablets obtained from the open dish study (0%, 50%, 65%, 75%, 90% at 25/40°C) were packaged in PVC blisters by using a blister thermoform heat sealing machine. The thickness of PVC film was 10 mil, and the thickness of the backing film (paper/Al laminate) was 1.9 mil.

As shown in Table 207, some of the tablets from 90% RH were broken when the blister packages were opened. Therefore, the hardness of tablets stored at 90% RH was not enough for the blister packaging. Though the hardness also decreased at the other conditions, the tablets were still hard enough to be used with the blisters since none of them broke, as shown in Table 207.

Table 207 The results of PVC blister opening tests (the number of broken tablets/the number of trials)

Temp.		RH(%)				
		0%	50%	65%	75%	90%
25°C	Hardness of uncoated tablets (kp)	7.12	7.51	7.43	6.48	1.59
	Opening test with PVC blisters	**0/10**	**0/10**	**0/10**	**0/10**	**6/10**
	Hardness of coated tablets (kp)	8.18	8.19	8.16	7.25	1.83
	Opening test with PVC blisters	**0/10**	**0/10**	**0/10**	**0/10**	**2/10**
40°C	Hardness of uncoated tablets (kp)	7.51	8.81	8.45	7.44	2.63
	Opening test with PVC blisters	**0/10**	**0/10**	**0/10**	**0/10**	**2/10**
	Hardness of coated tablets (kp)	8.44	10.17	9.1	8.02	2.6
	Opening test with PVC blisters	**0/10**	**0/10**	**0/10**	**0/10**	**0/10**

Table 208 shows the hardness of the initial tablets and Tables 209-218 show the hardness of tablets stored at 25/40°C, 0%, 50%, 65%, 75%, 90% RH for 190 days.

Table 208 Hardness (kp) of initial tablets

	1	2	3	4	5	6	7	8	9	10	avg.	SD
uncoated	9.8	9	9.2	8.4	8.6	8.7	8.9	9.5	8.6	8.3	8.9	0.48
coated	9.1	8.6	9.7	9.7	9.5	9.2	9.7	8.6	9.1	8.9	9.21	0.43

Table 209 Hardness (kp) of tablets stored at 40°C/90% as a function of storage time

	Uncoated							Coated						
	7	21	70	100	130	170	190	7	21	70	100	130	170	190
1	2.8	2.8	2.9	2.8	2.8	2.7	2.9	2.5	2.7	2.4	2.6	2.7	3.2	2.8
2	2.5	2.6	2.5	2.6	2.8	2.7	2.6	2.4	2.9	2.6	2.5	2.7	2.9	3.4
3	2.5	2.8	3.2	2.7	2.9	2.9	3.1	2.7	2.9	2.5	2.8	2.8	3.2	2.9
4	2.4	3.3	2.8	3.0	2.9	2.8	3.2	2.5	2.8	2.7	3.0	2.9	2.9	3.1
5	2.5	2.5	2.8	2.7	2.5	3.0	2.7	2.6	2.6	2.6	2.5	2.7	3.0	2.8
6	2.5	2.5	3.2	3.2	2.6	3.1	3.1	2.2	2.4	2.6	2.6	2.8	3.2	2.8
7	2.4	2.4	2.0	3.5	2.5	3.0	3.1	2.6	2.6	2.4	2.8	2.9	3.2	3.1
8	2.5	2.5	2.8	2.8	2.8	2.7	3.3	2.6	2.3	2.5	2.6	2.9	3.1	3.1
9	2.6	2.7	2.0	2.7	2.4	3.5	3.4	2.7	2.6	2.5	2.6	2.4	2.8	3.0
10	2.3	2.2	2.8	3.2	3.0	2.9	2.8	2.5	2.2	2.4	2.2	3.0	2.7	3.3
Avg.	2.5	2.6	2.6	3.0	2.7	3.0	3.1	2.5	2.6	2.5	2.6	2.8	3.0	3.0
SD	0.2	0.3	0.4	0.3	0.2	0.2	0.3	0.1	0.2	0.1	0.2	0.2	0.2	0.2

Table 210 Hardness (kp) of tablets stored at 40°C/75% as a function of storage time

	Uncoated							Coated						
	8	21	70	100	130	170	190	8	21	70	100	130	170	190
1	6.3	7.3	6.8	7.3	7.6	7.4	7.8	7.7	9.6	9.0	9.0	8.5	7.9	8.4
2	6.1	7.1	8.5	7.4	7.4	8.2	7.6	6.9	8.4	7.6	9.4	8.4	10.2	7.9
3	7.1	8.9	7.1	8.5	8.5	8.1	7.7	7.8	7.4	8.1	9.0	8.3	10.0	9.9
4	6.6	7.5	7.5	7.1	7.8	7.9	7.3	7.6	8.5	9.2	7.6	10.8	8.6	9.9
5	6.6	6.9	7.6	7.2	7.3	8.4	8.3	6.7	7.6	7.9	7.9	10.4	11.0	8.4
6	6.3	7.4	7.0	8.2	7.4	8.1	7.5	7.5	7.7	8.3	9.5	9.0	9.1	9.3
7	6.9	8.8	7.5	7.3	7.6	8.1	7.5	6.8	8.2	10.2	7.4	8.1	10.3	8.4
8	6.4	6.8	7.7	7.2	7.8	7.0	7.6	7.1	7.8	7.4	8.7	8.5	8.4	9.3
9	8.0	6.8	7.5	6.9	8.3	9.9	7.4	9.0	7.2	7.6	9.9	8.1	8.0	10.5
10	6.2	6.9	7.3	7.1	8.0	7.8	8.0	8.3	7.8	8.8	8.9	10.0	8.5	11.3
Avg.	6.7	7.4	7.5	7.4	7.8	8.1	7.7	7.5	8.0	8.4	8.7	9.0	9.2	9.3
SD	0.6	0.8	0.5	0.5	0.4	0.8	0.3	0.7	0.7	0.9	0.8	1.0	1.1	1.1

Table 211 Hardness (kp) of tablets stored at 40°C/65% as a function of storage time

	Uncoated							Coated						
	6	19	70	100	130	170	190	6	19	70	100	130	170	190
1	8.1	8.7	8.5	8.1	9.1	9.1	9.9	8.7	9.1	9.8	9.4	9.6	13.8	9.6
2	7.6	8.0	8.3	8.4	9.0	9.6	8.9	9.4	8.8	9.6	11.0	10.1	10.0	10.6
3	8.3	8.9	9.3	8.7	8.8	9.3	9.7	8.3	8.2	9.5	9.3	10.0	11.1	10.4
4	8.0	8.1	9.5	8.4	9.1	9.7	9.1	9.8	8.4	9.0	10.2	9.6	9.5	10.3
5	7.3	8.5	8.7	9.5	8.2	11.5	9.7	8.6	9.4	9.6	11.4	10.0	9.8	10.4
6	9.9	8.3	9.1	9.3	9.2	9.7	9.4	7.6	8.8	9.8	8.5	10.7	9.6	9.5
7	7.4	8.6	8.3	9.2	9.3	9.8	9.5	8.8	9.2	9.4	9.8	10.4	10.0	10.7
8	7.2	8.7	8.8	8.8	8.8	9.1	9.5	8.0	9.1	9.0	9.1	9.7	11.1	9.8
9	7.8	7.8	9.4	8.9	8.9	9.5	9.0	8.6	10.6	11.8	9.7	10.4	12.0	10.1
10	8.4	8.9	8.6	9.0	8.5	9.2	9.8	7.9	9.4	9.3	10.4	9.4	12.1	11.6
Avg.	8.0	8.5	8.9	8.8	8.9	9.7	9.5	8.6	9.1	9.7	9.9	10.0	10.9	10.3
SD	0.8	0.4	0.4	0.4	0.3	0.7	0.3	0.7	0.7	0.8	0.9	0.4	1.4	0.6

Table 212 Hardness (kp) of tablets stored at 40°C/50% as a function of storage time

	Uncoated							Coated						
	6	19	70	100	130	170	190	6	19	70	100	130	170	190
1	8.2	8.4	9.4	8.1	9.4	10.5	10.0	9.0	9.3	9.7	10.0	9.9	11.4	11.0
2	7.2	8.7	10.4	10.3	9.4	10.8	9.1	9.0	10.6	11.2	10.5	12.4	12.4	11.6
3	7.8	9.0	9.9	8.9	10.2	9.6	10.4	8.3	9.8	10.0	10.6	11.6	11.1	11.0
4	7.1	9.2	9.0	9.2	9.4	10.6	10.4	9.2	10.4	10.9	10.1	10.5	10.7	10.9
5	8.6	8.8	10.0	9.4	9.8	9.8	10.4	8.4	10.4	10.5	9.6	10.3	10.5	11.3
6	8.2	8.8	9.5	10.0	9.8	10.0	10.3	9.5	10.5	11.4	10.2	11.4	10.8	11.1
7	8.1	8.4	8.6	9.1	10.0	10.0	10.4	8.6	9.2	10.9	10.7	10.2	12.4	11.4
8	8.2	8.8	9.0	8.8	10.4	10.0	9.5	8.8	9.9	10.1	10.1	10.8	11.3	10.7
9	7.7	9.4	9.4	9.4	9.3	9.1	10.5	8.7	12.1	11.2	10.3	11.2	11.6	10.8
10	8.4	8.6	8.5	9.2	10.6	10.2	9.9	9.3	9.5	10.2	10.7	9.5	10.2	12.2
Avg.	8.0	8.8	9.4	9.2	9.8	10.1	10.1	8.9	10.2	10.6	10.3	10.8	11.2	11.2
SD	0.5	0.3	0.6	0.6	0.5	0.5	0.5	0.4	0.8	0.6	0.4	0.9	0.7	0.4

Table 213 Hardness (kp) of tablets stored at 40°C/0% as a function of storage time

	Uncoated							Coated						
	5	18	70	100	130	170	190	5	18	70	100	130	170	190
1	6.8	7.4	7.8	7.1	6.9	7.1	7.6	7.9	8.7	8.8	7.5	8.5	8.1	8.0
2	7.9	7.1	7.2	7.8	7.2	7.4	7.1	8.1	8.2	8.6	8.4	8.6	8.4	8.8
3	7.2	8.1	7.4	7.3	7.6	6.4	7.8	8.2	8.1	8.6	8.2	8.8	9.6	8.6
4	6.7	7.1	7.4	7.5	8.0	6.8	7.7	8.4	8.3	7.6	8.6	8.1	8.6	8.1
5	7.1	7.6	6.5	6.6	7.3	7.3	7.3	8.1	8.5	8.9	9.2	8.6	8.4	8.6
6	7.2	9.3	7.8	7.3	6.9	6.7	7.1	8.4	8.9	8.3	8.7	8.6	8.4	8.4
7	7.4	7.0	7.6	7.3	7.1	7.3	6.8	8.6	8.0	8.7	8.1	9.1	7.7	9.4
8	7.0	7.3	7.3	6.8	7.4	6.6	7.9	7.8	8.0	8.2	7.8	8.5	8.4	8.9
9	6.6	7.2	7.6	6.7	7.4	7.2	7.5	8.8	9.0	8.2	8.1	8.5	7.9	8.5
10	6.7	7.0	7.5	8.0	6.9	6.8	7.4	7.5	8.7	8.0	8.0	8.4	8.6	8.2
Avg.	7.1	7.5	7.4	7.2	7.3	7.0	7.4	8.2	8.4	8.4	8.3	8.6	8.4	8.6
SD	0.4	0.7	0.4	0.5	0.4	0.3	0.3	0.4	0.4	0.4	0.5	0.3	0.5	0.4

Table 214 Hardness (kp) of tablets stored at 25°C/90% as a function of storage time

	Uncoated							Coated						
	7	20	70	100	130	170	190	7	20	70	100	130	170	190
1	2.2	1.7	1.5	1.6	1.9	1.9	1.5	2.4	1.9	1.8	1.6	2.0	1.9	1.9
2	2.1	1.5	1.7	2.1	1.9	1.6	1.7	2.6	1.9	1.8	1.5	1.8	1.8	2.0
3	2.6	1.4	1.6	1.7	1.8	1.6	1.9	2.2	1.9	1.8	1.7	1.7	2.0	1.7
4	2.5	1.9	1.8	1.8	1.6	1.6	1.8	2.3	1.8	1.6	1.8	1.9	1.9	1.6
5	2.4	1.8	1.6	1.6	2.0	1.7	1.6	2.4	1.8	1.8	1.6	2.0	1.9	1.9
6	2.1	1.5	1.8	1.7	1.8	1.8	1.8	2.5	2.0	1.9	1.5	1.9	2.1	1.9
7	2.2	1.5	1.6	1.8	2.1	2.0	2.0	2.5	1.8	1.9	1.6	2.0	1.9	1.8
8	2.1	1.5	1.5	1.5	1.9	1.5	1.9	2.5	1.8	1.8	1.5	1.8	1.7	2.1
9	2.1	1.6	1.7	1.8	2.0	1.5	1.7	2.2	1.8	1.8	1.5	1.9	1.7	1.8
10	2.0	1.5	1.4	1.5	2.0	1.5	1.8	2.2	1.6	1.8	1.5	1.8	1.8	1.8
Avg.	2.2	1.6	1.6	1.7	1.9	1.7	1.8	2.4	1.8	1.8	1.6	1.9	1.9	1.9
SD	0.2	0.2	0.1	0.2	0.1	0.2	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 215 Hardness (kp) of tablets stored at 25°C/75% as a function of storage time

	Uncoated							Coated						
	7	20	70	100	130	170	190	7	20	70	100	130	170	190
1	5.6	5.8	7.0	9.1	7.6	8.9	7.2	8.4	7.1	7.5	7.7	8.0	7.7	8.9
2	6.6	6.4	7.1	6.8	7.3	6.4	7.5	7.6	7.5	8.2	6.8	7.3	7.8	8.6
3	6.3	5.8	7.2	6.7	7.6	6.5	6.4	8.0	6.9	7.8	7.7	8.7	7.1	9.6
4	5.6	6.0	6.0	6.6	7.4	6.6	6.9	8.0	6.8	7.6	8.3	7.7	8.6	7.7
5	6.2	6.5	8.3	6.7	7.7	6.4	6.1	6.5	7.2	7.3	7.6	8.4	8.8	8.8
6	6.1	7.6	6.3	9.2	8.6	6.1	8.4	6.8	8.2	8.1	8.2	7.2	8.1	8.3
7	5.7	5.5	6.4	6.8	7.8	8.0	6.3	6.5	7.3	8.5	6.4	9.1	6.7	6.9
8	5.4	6.9	6.8	6.9	7.4	6.5	6.4	7.5	7.5	9.0	7.7	8.5	8.5	8.5
9	5.4	6.9	6.4	6.9	7.4	6.8	6.5	9.0	6.4	8.2	8.2	7.3	8.0	7.6
10	5.9	7.4	8.6	6.9	7.3	5.9	6.5	7.5	7.6	7.8	6.5	6.9	7.3	9.4
Avg.	5.9	6.5	7.0	7.3	7.6	6.8	6.8	7.6	7.3	8.0	7.5	7.9	7.9	8.4
SD	0.4	0.7	0.9	1.0	0.4	0.9	0.7	0.8	0.5	0.5	0.7	0.7	0.7	0.8

Table 216 Hardness (kp) of tablets stored at 25°C/65% as a function of storage time

	Uncoated							Coated						
	5	19	70	100	130	170	190	5	19	70	100	130	170	190
1	6.9	6.8	7.8	8.2	8.4	9.5	8.5	7.7	7.7	9.0	8.7	9.4	10.2	8.3
2	6.5	8.0	8.2	8.9	8.6	8.3	8.1	8.0	8.6	8.5	8.8	9.4	9.3	8.5
3	7.1	7.5	8.6	7.2	8.0	7.9	8.2	7.6	8.1	8.9	8.6	9.0	11.0	10.5
4	6.5	7.3	8.2	8.2	7.8	8.4	7.7	9.4	7.8	8.7	9.6	8.9	8.5	12.0
5	6.5	7.6	8.3	8.0	8.9	8.3	6.8	8.3	8.7	9.8	8.7	9.4	8.4	10.0
6	6.7	7.8	7.9	10.4	8.8	8.1	7.6	8.9	8.2	10.5	9.2	9.0	8.6	9.6
7	6.3	7.2	8.4	8.3	8.8	8.5	8.2	7.3	8.0	8.5	8.6	9.2	10.0	9.1
8	6.4	7.9	7.8	8.1	9.1	8.5	8.6	7.3	7.9	9.6	10.0	9.4	9.4	9.8
9	9.4	7.3	8.7	9.0	9.2	7.9	8.8	8.1	8.7	11.1	8.6	9.1	10.7	9.5
10	7.1	6.9	8.7	8.3	9.4	8.8	8.5	7.4	7.9	10.6	9.6	9.2	11.0	9.0
Avg.	6.9	7.4	8.3	8.5	8.7	8.4	8.1	8.0	8.2	9.5	9.0	9.2	9.7	9.6
SD	0.9	0.4	0.3	0.8	0.5	0.5	0.6	0.7	0.4	0.9	0.5	0.2	1.0	1.1

Table 217 Hardness (kp) of tablets stored at 25°C/50% as a function of storage time

	Uncoated							Coated						
	5	19	70	100	130	170	190	5	19	70	100	130	170	190
1	7.3	7.3	8.5	7.9	8.4	7.7	8.3	9.7	7.4	8.2	8.7	10.2	8.8	8.6
2	6.7	7.3	7.2	7.7	7.2	8.0	8.1	7.0	7.7	8.6	8.5	9.9	9.2	8.9
3	7.5	7.9	7.5	7.9	8.5	7.5	7.7	8.1	7.7	9.6	9.4	8.7	9.4	8.4
4	7.0	7.6	8.0	8.0	8.2	7.7	8.1	8.0	8.7	8.4	8.9	8.8	8.7	8.8
5	7.0	7.7	7.4	7.1	8.6	7.5	8.3	7.7	7.9	8.1	10.1	9.4	8.7	9.5
6	8.0	7.4	7.5	8.5	7.7	8.0	8.4	8.8	8.2	8.5	8.6	9.1	9.3	10.0
7	6.9	7.7	7.9	7.8	7.4	8.1	8.0	8.4	8.6	9.2	8.7	9.1	9.3	9.4
8	7.3	7.4	8.1	7.8	8.4	7.7	8.3	7.5	8.8	9.1	8.4	8.6	9.1	9.1
9	7.4	7.7	7.7	7.3	8.2	7.7	8.4	8.0	8.5	9.4	9.5	10.0	9.1	9.8
10	7.0	7.1	8.5	8.4	8.2	7.7	8.3	9.1	8.4	8.8	9.0	9.3	10.1	9.2
Avg.	7.2	7.5	7.8	7.8	8.1	7.8	8.2	8.2	8.2	8.8	9.0	9.3	9.2	9.2
SD	0.4	0.2	0.4	0.4	0.5	0.2	0.2	0.8	0.5	0.5	0.5	0.6	0.4	0.5

Table 218 Hardness (kp) of tablets stored at 25°C/0% as a function of storage time

	Uncoated							Coated						
	5	18	70	100	130	170	190	5	18	70	100	130	170	190
1	7.4	7.0	7.1	7.3	7.8	7.2	7.8	8.5	8.0	7.7	7.4	8.6	8.4	8.4
2	7.2	7.4	6.7	6.9	8.1	7.8	6.8	8.5	8.0	8.4	7.6	7.9	8.8	7.6
3	7.3	6.8	7.3	7.3	7.4	7.3	7.3	8.6	8.0	7.9	8.4	8.2	7.9	8.2
4	7.4	6.5	7.8	7.0	7.1	7.3	7.4	7.9	8.2	8.5	8.0	8.1	7.5	7.9
5	7.5	7.1	7.5	6.8	7.2	7.3	7.3	7.9	8.1	8.5	7.9	7.9	7.8	8.2
6	7.9	6.7	7.3	7.0	6.6	6.6	6.9	7.7	8.0	8.6	8.6	7.9	7.8	7.9
7	7.2	7.8	7.5	7.6	7.6	7.1	6.8	7.7	8.6	8.7	8.1	8.7	8.5	7.8
8	7.6	7.3	8.0	7.1	7.4	6.5	7.4	9.5	8.1	8.0	7.9	9.3	7.9	8.0
9	7.1	7.2	7.1	7.2	6.9	7.3	6.6	8.3	8.6	8.2	8.0	7.7	7.5	8.6
10	7.1	7.4	7.7	7.2	7.2	6.9	6.9	9.1	8.2	8.0	8.5	9.6	7.8	7.6
Avg.	7.4	7.1	7.4	7.1	7.3	7.1	7.1	8.4	8.2	8.3	8.0	8.4	8.0	8.0
SD	0.2	0.4	0.4	0.2	0.4	0.4	0.4	0.6	0.2	0.3	0.4	0.6	0.4	0.3

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