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Xuemei Qian

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Hugh E. Lockhart
Major professor

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DISSOLUTION STABILITY FOR PACKAGING APPLICATION

By

Xuemei Qian

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ABSTRACT

DISSOLUTION STABILITY FOR PACKAGING APPLICATION

By

Xuemei Qian

The effect of moisture and heat on the dissolution stability of a capsule product was evaluated by storing the product, without any packaging protection, at three temperatures (18 °C, 28 °C and 38 °C) with nine relative humidities (12, 23, 33, 44, 50, 63, 75, 80, and 90%) for about 90 days. The findings will be used for selecting cost-effective packaging materials for the product for stability testing.

The study showed that the dissolution stability of the product was significantly affected by storage conditions (temperature and relative humidity), storage times, and all the interactions among them. High relative humidities (75-90%) caused significant decreases in the dissolution rate. At such conditions, the higher the temperature, the longer the storage time, the greater the loss of dissolution rate. The capsules stored at 12-63% RH were quite stable at all three temperatures tested. This indicated that a certain critical level of relative humidity higher than 63% was required for the initiation of dissolution changes. The package for the product could be chosen in such a way that it is able to keep the relative humidity level no more than 63% inside the package within the expected shelf life. Such packaged product should be able to pass the dissolution requirement during stability testing.

To my husband Guoquan

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CHAPTER 1. INTRODUCTION

The shelf life of a solid oral drug product could be indicated by many of its physical and chemical properties. Drug dissolution rate is an important indicator because of its association with drug bioavailability (Murthy and Ghebre-Sellassie 1993). A decrease in release rate of the drug is often reflected as an impaired absorption. Also changes in the bioavailability of a drug product during storage are always associated with or preceded by changes in the physicochemical properties of the dosage form, such as chemical decomposition or slow dissolution. Therefore, absence of change in drug dissolution provides some assurance that the bioavailability of the drug product is intact.

Dissolution has been accepted by the United States Pharmacopeial Convention as a stability indicating parameter for solid oral drug products. It is measured by a standard method published in the United States Pharmacopeia (U.S.P.) (1995), and dissolution limits are specified in the U.S.P. monographs for most solid oral products. The U.S. Food and Drug Administration (FDA) requires that any drug product on the market must at all times meet the requirements of its U.S.P. monograph; otherwise, it will be recalled from the market. During the year of 1994, for example, 16 recalls of solid oral drug products were listed in U.S.P. DI Update (1994) because of their failure to meet the U.S.P. dissolution requirements.

Factors influencing the dissolution stability of solid oral products include manufacturing processes, formulation variables, storage conditions, storage times, packaging and interactions among them (Murthy and Ghebre-Sellassie 1993, Chowhan 1994). For a specific product, the dissolution stability is determined by storage conditions, storage times, packaging and their interactions. When a product is exposed to high humidities at high temperatures, the dissolution rate can often be reduced substantially. Long times at such

conditions cause greater reduction than short times. However, the role of each of the three factors and the interactions among them are different for each drug product and need to be evaluated case by case.

Packages for drug products serve as barriers to moisture transfer and they protect from the deleterious effect of high humidities. The lower the moisture permeability of the package, the less the effect of high humidity on dissolution rate, the longer the dissolution shelf life of the drug product. Therefore, drug companies are spending a lot of money buying the best and most expensive barrier materials for manufacturing packages for drug products. Both the high cost and the risk of recall could be avoided if the relationship among a product, its package and its environment has been adequately described. Therefore, the objective of this research project is to investigate the dissolution stability of a capsule product under different storage conditions. The information will be used to develop a model for predicting dissolution shelf life of the product in future studies. The approach will be meaningful in providing an effective and efficient way for the industry to select the packages of good barrier and low cost for stability test.

This study was co-ordinated with the work of two other students, M. Kokitkar and S.S. Wu. Their results will be published in their master theses. The standard curve for determination of the nizatidine concentration by spectrophotometry was based on the data from the three workers for the purpose of increasing the precision.

CHAPTER 2. LITERATURE REVIEW

DISSOLUTION METHOD

It was in 1970 that the first dissolution method was officially adopted and dissolution tests became a part of the monographs in the National Formulary (NF) and U.S.P. (Hanson 1992). Since then dissolution technology has undergone a lot of development. Enormous efforts have been made to devise new dissolution methods for various drug products and improve the repeatability of the tests. Currently there are seven official dissolution methods, corresponding to seven different dissolution apparatuses (Hanson 1992). Apparatus 1 (Figure 1) and Apparatus 2 (Figure 2) are the most basic and widely used for testing immediate-release dosage forms (Murthy and Ghebre-Sellassie 1993).

In the monographs the requirements for amount of drug dissolved involve a minimum amount of drug to be in the solution at a specified time interval. Normally not less than 75% of the labeled amount of the drug should be dissolved in 45 minutes (typical range, 30-60 minutes). The specification is based on the premise that no known bioequivalence problems exist with a dosage form in which 75% dissolves in water in 45 minutes (Hanson 1992). For modified-release dosage forms, more than single point determinations are required. Multiple point dissolution data profiles are becoming necessary.

The selection and use of dissolution medium, apparatus, and specifications for dissolution testing are given in the individual monographs. Water is the recommended, preferred medium, followed by aqueous hydrochloric acid and buffer solutions in the pH 4-8 range (Murthy and Ghebre-Sellassie 1993). Enzymes are not used in the test fluids for analytical convenience. However, the exclusion of enzymes in dissolution medium and its

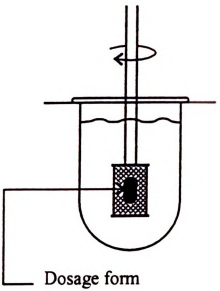

Figure 1. U.S.P. Dissolution Method -- Apparatus 1, rotating basket.

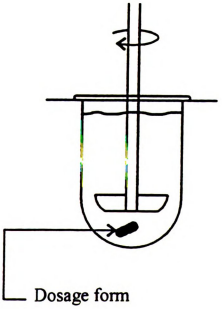

Figure 2. U.S.P. Dissolution Method -- Apparatus 2, rotating paddle.

relevance to the bioavailability and bioequivalence has been questioned, since the gastro-intestinal fluids almost invariably contain enzymes. Several studies examining the effect of using enzymes on dissolution and bioavailability have been reported (Dahl et al 1991, Dey et al 1994). According to Chowhan (1994), the working group on this issue representing industry associations have been meeting with the FDA internal task force and have made progress on the action steps.

The future development of dissolution technology includes expansion of dissolution studies into biotechnology products, self-regulating dosage forms, and a refinement of analytical methods and procedures with an emphasis on validation and correlation with bioavailability (Hanson 1992). To make dissolution tests cost-effective has also been on the agenda (Grady 1995).

TABLET PRODUCTS

The dissolution stability of a dosage form is affected by a number of factors including formulation, manufacturing method, processing variables, in-process controls, packaging, storage conditions, storage time and the interactions among them (Murthy and Ghebre-Sellassie 1993, Chowhan 1994). A lot of studies have been reported which examined the effects of these factors on the dissolution stabilities of tablet products.

The solubility, hygroscopicity, and thermal characteristics of the active component and excipient, including coating materials, are key parameters that have significant impact on the outcome of dissolution stability (Murthy and Ghebre-Sellassie 1993). Under high humidity and temperature, the active component of a tablet product may dissolve and recrystallize,

resulting in altered dissolution profiles of the tablets. Fillers or diluents in the formulations are normally considered as inert and noninteracting with the active ingredients and other components. However, under accelerated storage conditions specific interaction may occur between a filler and the active drug substance, resulting in decreased dissolution rate of the drug (Al-Meshal et al 1989).

The function of a binder in a tablet formulation is to provide the necessary adhesion and bonding between particles. Therefore, it is directly related to the dissolution property of a dosage form. The nature and level of the binder not only affect the dissolution of the dosage form at the time of manufacturing, but also the dissolution stability upon aging. Accelerated storage conditions may alter the properties of a binder and cause decreased dissolution rate (Asker et al 1981).

Disintegrants are used to facilitate the breakup of the tablet mass, increase the surface area and promote dissolution. However, moisture sorption may reduce the efficacy of the disintegrant in the tablet when exposed to high humidity conditions, which results in the reduced dissolution rate of the drug (Gordon et al 1993).

In case of coated tablet products (film-coated, sugar-coated, or enteric-coated tablets), additional variables need to be considered. Moisture and heat may greatly influence the integrity of the coating and thus affect the dissolution stability. Sugar coatings can dissolve under high humidity and recrystallize and harden when reverted to ambient conditions, resulting in slow release of the drug from the dosage form (Romero et al 1988). Polymer coatings may undergo "thermal gelation", hydrolysis, or cross-linking under accelerated conditions, which can change the dissolution profiles substantially (Murthy and

Ghebre-Sellassie 1993). Gelatin coatings may become insoluble under stressed storage conditions and delay the dissolution of the tablets (Dahl et al 1991).

CAPSULE PRODUCTS

Capsule products can be divided into hard gelatin capsules and soft gelatin capsules. Since the latter usually have no compendial dissolution requirements, the following literature review is focused on hard gelatin capsules.

The dissolution stability of a capsule product relies on the stabilities of the gelatin shell and the capsule content. During storage gelatin may become insoluble and hinder the release of the capsule contents. On the other hand, since gelatin is a poor moisture barrier, water vapor can be transmitted through the shell and the contents may become moist or even form a cake. Significant retardation of dissolution of ampicillin trihydrate capsules was noted that was attributed to the agglomeration and subsequent caking of the capsules' contents due to moisture transfer from the shell (Georgarakis et al 1988).

Gelatin is a mixture of polypeptides extracted from animal skin or bone. It is water-soluble at temperatures above 35°C. It can form thermally reversible gels when warm aqueous suspensions of the polypeptides are cooled. The gelation mechanism involves formation of ionic crosslinks and hydrogen bonding (Kester and Fennema 1986). Under certain conditions gelatin may become partially or totally insoluble.

Marks and co-workers (1968) studied the factors influencing gelatin solubility by storing prepared gelatin in a closed system at 75°C for a week. They found that the rate of insolubilization depended upon: (1) the gelatin fraction obtained in the gelatin manufacturing

procedure, and (2) the moisture content of the gelatin. Higher moisture content led to increasing degrees of insolubility. For example, for the first-extract gelatin (usually used for making capsule shells), at 12% moisture level, only 1% insolubles formed. However, at 16% moisture level, about 52% insolubles formed. The authors suggested that insolubilization was a polymerization of gelatin molecules, possibly involving cross-linking and hydrogen bonding. The insolubilization could be accelerated by prolonged heating and the addition of specific reagents, such as aldehydes, aromatic sulfonates, and oxidizing substances. On the other hand, the insolubilization could be retarded by various nitrogen compounds, such as semicarbazide, hydroxylamine, and certain heterocyclic carbo-nitrogen ring compounds.

Insolubility of gelatin shells of aged capsule products has been reported in several studies. Murthy and co-workers (1989) evaluated the effect of exaggerated storage conditions on the dissolution characteristics of capsule preparations. Three drug formulations were used with five kinds of capsule shells, each of which contained a different combination of certified colorants. The filled capsules were exposed to 80% relative humidity (RH) and high-intensity fluorescent light or UV light. Some aged capsules showed big decreases in dissolution rate and the gelatin shells were observed swelling and forming a rubbery matrix which enveloped the encapsuled powder during the dissolution tests. Release of the powder through this gelatin matrix became rate-limiting for the dissolution process. Formation of insoluble gelatin film resulted in not only a slower average rate of drug dissolution, but also a large intercapsule variation in release. It was suggested that the insolubility of gelatin resulting from storing under stress conditions was probably caused by the polymerization process involving cross-linking and hydrogen bonding. The cross-linking was promoted by

the interaction between gelatin and the dyes, UV or visible irradiation.

Chafez and co-workers (1984) noticed that gemfibrozil capsules showed a significant decrease in dissolution rate with time of storage and exposure to high humidity. During the dissolution tests the capsule contents were held by a thin, tough, water-insoluble film, the disruption of which was seen to be the dissolution rate-limiting factor for the drug product. They found that the film formation was due to denaturation of the inner surface of the capsules by formaldehyde, formed by trace autoxidation of the polysorbate 80 used as an excipient in the product. The bioavailability study showed that these capsules were still bioequivalent to the readily dissolving product.

Hartauer and co-workers (1993) found that rayon coiler, which was used as a space-filler, might cause decrease in the dissolution profile of a capsule product. It was due to the reaction between the volatile component of rayon coiler, 2-furaldehyde, and the gelatin protein, which resulted in altered disintegration of the capsule shell.

Khalil and co-workers (1974) studied the influence of storage time and relative humidity on dissolution of chloramphenicol capsules at room temperature. At 49% and 66% RH no apparent change in drug dissolution occurred upon storage for up to 32 weeks. However, storage at 80% RH for two weeks resulted in almost total loss of dissolution due to the failure of the gelatin shell to disintegrate. The gelatin shell exhibited a considerable swelling and failed to disintegrate within one hour. The phenomenon was also observed for empty gelatin capsules upon storage under the same condition. However, at 100% RH drug release was slightly increased and the gelatin shells were rubbery, soft and difficult to handle.

Another study by Khalil and co-workers (1991) indicated that two brands of

amoxycillin capsules showed minor changes in the extent of dissolution after storage at room temperature for up to four weeks at 76%, 80% and 92% RH. Longer periods of storage resulted in dissolution reduction for one brand. There was no disintegration of the gelatin shells of the product after storing at 80% RH for 12 weeks, while there was incomplete disintegration of the gelatin shells of the product after storing at 92% RH for the same period of time. It was also noted that the red caps of capsules of both brands failed to disintegrate when stored at 92% RH, while the white colored body of the capsules disintegrated readily. It illustrated that the dyes also affected the disintegration of capsule shells.

Based on these reported studies, it could be concluded that, for capsule products, changes in the dissolution properties may result from either a change in the solubility of the capsule shells and/or changes in the properties of the capsule contents. Insolubilization of capsule shells is a function of storage conditions, storage times, compositions of capsule shells and contents, space-fillers, and interactions among them. Insolubilization of capsule shells not only result in delayed dissolution, but also large intercapsule variation.

PACKAGING

Packaging plays an important role in maintaining the dissolution stability of a dosage form. Packages with low water vapor permeability limit the humidity levels inside the packages and thus protect the products from the effects of moisture. Packages also protect the products from the effects of light and oxygen. Desiccants in the packaged containers absorb the moisture and reduce the humidity in the headspace.

The effect of packaging on the dissolution stability of a sustained-release tablet

product was reported by Murthy and Ghebre-Sellassie (1993). The tablets were stored in three types of packages and exposed to 37°C/75% RH for three months. It turned out that the tablets stored in HDPE bottles and foil/foil blisters were well protected, but samples packaged in laminated PVC/PE/Saran blisters showed marked retardation in dissolution rate. The moisture permeabilities of the packages were not reported. The study showed the sensitivity of the in vitro release pattern of the product to moisture effects and the moisture-barrier properties of packages.

Khalil and co-workers (1991) studied the effects of package type on in-vitro release and chemical stability of amoxycillin capsules. A typical PVC/foil blister package and a nitrocellulose lacquer/foil/PE laminated package were used for the study. The product was stored both in- and outside the blister or laminated packages at 76%, 80% and 92% RH at room temperature. Storage at 92% RH without package resulted in a significant loss of dissolution rate after 8 weeks, while only minor change occurred in the dissolution rate of packaged capsules. The laminated-type package afforded better protection compared with the PVC/foil blister package in terms of amoxycillin potency.

The relationship between packaging variables and the dissolution stability of model prednisone tablets was illustrated in the studies by Taborsky-Urdinola and co-workers (1981). Two types of multiple-unit vials and six types of unit-dose containers were employed in the experiment. The multiple-unit vials were PP vials and PS vials. The unit-dose containers were PS-MDPE/foil strips, polyester/foil strips, PE bags, foil/foil strips, Bartuf/foil strips, and PVC-Saran cup/foil. The packaged product was stored at 40°C/85% RH, 37°C/75% RH, and 22°C/75% RH for three to six months. It was shown that, at 40°C/85% RH, the 30 minutes

dissolution values of the tablets decreased with time, except those packaged in the foil/foil strips which were impermeable to moisture transmission. The rate of decrease depended on the moisture permeation rate of the package. The higher the moisture transmission rate, the greater the decrease in the dissolution rate. When stored at 22 °C/75% RH, little change in the dissolution rate occurred in any packaged tablets. It was concluded that packaging and storage conditions affected tablet dissolution stability markedly. The conditions of high heat and humidity caused the greatest change in dissolution rate. At such conditions, the higher the moisture transmission rate of the package, the longer the storage time, the greater the loss of dissolution rate.

Hoblitzell and co-workers (1985) investigated the effect of packaging on the dissolution stability of enteric-coated aspirin tablets. The product was stored in five kinds of packages and exposed to 33 °C/60% RH or 33 °C /60% RH and 25 °C/10% RH cyclic condition. The packages were an open petri dish, a two-ounce amber glass bottle with a child-resistant closure, a U.S.P. class A strip pack, and one of two U.S.P. class B strip packs. It was indicated that there were statistically significant differences in dissolution among packages, storage conditions, and storage periods. However, the rate of decrease in dissolution rate did not correspond to the package moisture-protection characteristics, which implied that temperature was the primary factor. The dissolution stability also showed a quadratic trend with time. It could be suggested that there were interactions among storage conditions, storage times and packages, that were ignored in the statistical analysis.

From these reported studies, it could be concluded that, for a dosage form which is greatly affected by moisture in the drug dissolution rate, packaging with low moisture

permeability can protect from the deleterious effect of humidity and maintain the dissolution stability. On the other hand, if the dissolution of a dosage form is only or mainly affected by temperature rather than moisture, the role of packaging in maintaining the dissolution stability is very small, since packaging cannot shield the product from the effect of heat. Therefore, it is necessary to characterize a product before determining what kind of packages to use for the product.

DATA TREATMENT

In the literature several kinds of treatment of dissolution data were employed for describing the dissolution stability:

1). Present the dissolution profiles of a product before and after aging. Conclusions were made based on the observed differences between the dissolution profiles. No statistical analysis was performed in such studies.

2). Choose a time point in the dissolution profile for dissolution value and compare the values obtained under different storage conditions and periods.

This second approach was used in many studies. But again no statistical analysis was performed for comparisons in these studies. Also there have been no mathematical relationships built between a single dissolution value and the factors influencing the dissolution stability to predict the dissolution change.

3). Determine a dissolution efficiency from a dissolution graph by expressing the area under the experimentally determined dissolution curve as a percentage of a defined rectangle. This method was employed in the dissolution stability studies reported by Habilitzell and co-

workers (1985). An ANOVA indicated significant differences in dissolution efficiencies among packages, temperature, relative humidity, and storage periods. No quantitative relationships were given between the dissolution efficiency and the above four factors for the purpose of prediction.

4). Establish a general mathematical expression for the entire dissolution curve in terms of meaningful parameters and determine the effects of aging on these parameters.

a. log-normal type

$\ln\{C_s/(C_s-C_t)\} = k^* t'$

where

t' = dissolution time;

C_s = the whole content of the drug in a tablet;

C_t = the whole content of the drug at time t' in the test solution;

k = constant which is a function of storage time, moisture content and temperature.

According to Nakabayashi and his co-workers, the above equation fit the dissolution curves in their study. They successfully developed, by a multiple regression analysis, the mathematical relationship between the k value and the storage time, t, moisture content,m , and storage temperature, T:

$\ln(k/k_0) = - K^*t$

$\ln K = 4.5241 + 3.4936^*\ln m - 4556.049^*(1/T)$

Based on the above relationships, they predicted changes in the dissolution rate of a packaged tablet kept under various temperature-humidity conditions. There were good agreements between the predicted values and the observed data. However, the log-normal

expression can only describe a few dissolution curves.

b. Weibull distribution

$$\log [-\ln (1- C/C_\infty)] = b \log (t - T_i) - b \log T_d.$$

where

C = the concentration in solution at time t;

C_∞ = the concentration in solution at time t_∞;

t = dissolution time;

b = shape parameter which characterizes the curve;

T_i = location parameter which represents the time lag before the actual onset of the dissolution process;

T_d = the time interval necessary to dissolve 63.2% of the material.

The equation was considered to be able to describe all common types of dissolution curves (Langenbucher 1976). The expression was employed by Rubino and co-workers for their dissolution stability studies (1985). An ANOVA indicated that C_∞ was significantly affected by the excipient to drug ratio, humidity, storage time and the interaction between the later two factors. T_d was significantly affected by excipient to drug ratio and the interaction between the type of excipient and storage time. However, no mathematical relationships were developed to calculate the values of those parameters under different storage conditions.

There are some difficulties in using this expression. For the four parameters, b and T_d can be obtained in a straightforward linearized manner, but T_i and C_∞ have to be determined by trial-and-error. This requires a lot of data points and enormous work. Possibly this is one of the reasons why the expression has not been widely used. The data

treatment discussed above will be examined carefully for applicability to this study.

STABILITY TESTS AND DISSOLUTION SHELF LIFE PREDICTION

In the pharmaceutical industry every drug product needs to have stability testing before being introduced to the market place. It is required by regulation. At 21 Code of Federal Regulations (CFR) 211.166, the FDA says:

"There will be a written testing program designed to assess the stability characteristics of drug products. The results of such stability testing shall be used to determine proper storage conditions and expiration dates. The written program shall be followed and shall include:

(1) sample size and test intervals based on statistical criteria for each attribute examined to assure valid estimates of stability;

(2) storage conditions for samples retained for testing;

(3) reliable, meaningful and specific test methods;

(4) testing of the drug product in the same container-closure system as that in which the drug product is marketed;

(5) testing of drug products for reconstitution at the time of dispensing."

The procedures for stability testing used to vary widely among drug companies. However, with the development of the tripartite guideline by the Expert Working Group (Quality) of the International Conference on Harmonization, stability testing procedures are becoming uniform and standardized. The following storage conditions and minimum storage time for stability test prior to submission of the regulatory document are recommended:

Condition		*Minimum time period at submission*
Long-term testing	*25 ± 2°C/60 ± 5% RH*	*12 months*
Accelerated testing	*40 ± 2°C/75 ± 5% RH*	*6 months*

If the drug product fails the accelerated testing, additional testing at an intermediate condition (30°C, 60% RH) should be conducted for a period of 12 months. Data from the first six months can be submitted in place of the accelerated testing data.

Since stability testing is very expensive and time-consuming, estimation techniques are highly desirable to minimize experimentation. Attempts have been made to estimate the dissolution shelf-life of a product under ambient storage conditions based on accelerated testing over a short time span or simulation modeling. Absence of changes under short-term exaggerated storage conditions can be suggestive of dissolution stability of the product under long-term ambient storage conditions. However, if changes are observed, it may not be predictive of dissolution instability at ambient conditions. According to Murthy and Ghebre-Sellassie (1993), in many instances, a certain critical moisture and/or temperature level of the product is usually required for the initiation of dissolution changes. Attainment of this minimum level is dependent on the product and packaging characteristics, environmental conditions, and time of storage. A general relationship is not available between the data obtained under an accelerated condition and those under ordinary conditions.

Compared to accelerated testing, the simulation modeling technique is becoming popular because it considers the entire system and combines expressions for product sensitivity, package effectiveness, and environmental severity into a model. In the literature there is only one model reported for predicting the dissolution shelf life of a packaged drug product (Nakabayashi et al 1981). The model was based on establishing a linear relationship between the dissolution and humidity at any given temperature and determination of the amount of water permeated through the packaging at a certain time point. Good agreements were obtained between the predicted stability data and the actual ones. However, the model is not applied to drug products which require minimum moisture and/or temperature level for the initiation of dissolution changes. Dissolution changes of these products are not linearly

related to the moisture content of the products in the humidity and temperature range used in the ambient and accelerated storage testing (Murthy and Ghebre-Sellassie 1993).

The literature review presented above indicated that the dissolution rate of a solid dosage form is a function of temperature, relative humidity, storage time, packaging, and their interactions. High relative humidities and/or high temperatures often cause big decreases in drug dissolution, while packaging may help maintain the dissolution stability by limiting the relative humidity in the package. In order to determine the needed protection from a package for a dosage form, it is necessary to evaluate the effect of moisture and heat on the dissolution stability of the product by exposing it to various storage conditions. Previous studies employed accelerated conditions for testing. They are of limited value in predicting the dissolution stabilities under ambient conditions. Also statistical analysis was not used in most such studies. This limited the interpretation of the experiment results. Therefore, the present study was designed to investigate the dissolution stability of a capsule product by exposing it to a wide range of storage conditions without any packaging protection. Statistical methods will be used for data analysis. The information will be used to choose cost-effective packages for the product and minimize the experimentation of stability testing.

CHAPTER 3. MATERIALS AND METHODS

PRODUCT

A hard gelatin capsule product, AXID (Eli Lilly and Company, Indianapolis, IN), was selected for this study. Each capsule contains 150-mg nizatidine as the active ingredient. Capsules from the same lot were used for the entire study.

DISSOLUTION METHOD

Dissolution Test

The dissolution tests in this study were performed according to the specifications in the U.S.P. monograph for nizatidine capsules. The dissolution equipment was a Vankel 6 vessel Dissolution Prep Center VK 6010 (Vankel Industries, Inc., Edison, NJ). The dissolution medium (water) was sampled at 5, 10, 20, 30, 40, and 50 minutes. The sampling tool was a 5-ml plastic syringe to which a piece of plastic tubing was attached. A piece of cotton was inserted into the end of the tubing near the syringe as a filter to remove undissolved particles (Appendix 1). Each time 2-3 ml were withdrawn, and from this 0.4 ml was exactly measured with a calibrated Pipetman P-1000 (Rainin Instrument Co., Inc., Woburn, MA) and stored in a disposable glass tube. The remaining sample was returned to the vessel.

Assay of Dissolution Medium

The 0.4 ml samples were diluted 20-fold with water and then placed in 1 cm quartz cuvettes. The absorbance of each sample was then measured at 314 nm on a Perkin-Elmer

Lambda 3B UV/Vis spectrophotometer (Perkin-Elmer Corp., Analytical Instruments, Norwalk, CT) within one hour after each dissolution test. The data were converted to percentage dissolved using the following equation:

$$\% \text{ dissolved} = (\text{Absorbance}/s) * n * V/W * 100$$

where s ---- slope of the calibration curve for nizatidine, 48.96 ml/mg;

n ---- dilution fold of the sample, 20;

V ---- volume of the dissolution medium in the vessel, 900 ml;

W ---- the amount of the nizatidine in each capsule, 150 mg.

STORAGE STUDIES

Capsules were stored at three temperatures (18°C, 28°C, and 38°C) with nine relative humidities (12, 23, 33, 44, 50, 63, 75, 80, and 90%) for about 90 days. At 6-30 day intervals, a representative number of samples (3) were removed from storage, and the dissolution rate of the product was determined based on triplicate runs.

Storage Conditions Set-up

For each temperature, a series of nine humidity buckets were used and placed in a chamber which was maintained at the constant temperature. The desired relative humidities were obtained by placing appropriate salt solutions into these tightly closed 5-gal plastic buckets. The following saturated salt solutions were used: Lithium Chloride (12%), Potassium Acetate (23%), Magnesium Chloride (33%), Potassium Carbonate (44%), Magnesium Nitrate (50%), Sodium Nitrite (63%), Sodium Chloride (75%), Ammonium

Sulfate (80%), and Potassium Nitrate (90%). The relative humidity inside each bucket was verified by a corresponding Hygrosensor (Newport Scientific, Inc., Jessup, MD).

Storage Plan

The storage plan is shown in Table 1. For each temperature the storage tests at different levels of humidities were initiated at the same time except 63% and 80% RH. These two conditions were added later after noticing the big change in the dissolution rate at 28°C and 75% RH. Because of the availability problem of the dissolution apparatus, the intended dissolution tests at 6 days were prolonged to some extent. Therefore, 6 days level was not included in the statistical analysis later.

TREATMENT OF DATA

The 30 minutes dissolution data at each storage condition was used for analysis. The decision was made based on two facts. First, the 30 minutes dissolution is required by the U.S.P. for this product. Second, the two kinds of mathematical treatment discussed before were tried but were not successful. The log-normal type did not fit the data. For the Weibull function, since t_0 and C_∞ were unknown, it was very difficult to apply the equation. Dissolution isotherms were obtained by plotting 30 minutes dissolution value versus relative humidity at each temperature studied.

A three-way analysis of variance (ANOVA) was applied to the data to determine whether there were any statistically significant differences among storage conditions and storage time. The three factors and their corresponding levels used were:

temperature -- 18°C, 28°C, and 38°C;

RH -- 33, 50, 63, 75, 80, and 90%;

time -- 0, 30, 60, and 90 days.

Following ANOVA, contrasts were performed to determine if there were significant differences between the data of the capsules after aging under various storage conditions and storage times and the data of the capsules as manufactured. A contrast is a specialized type of hypothesis test which compares the means of selected levels of a factor, or combination of factors. The contrast was used in this study to help understand the relationships among the various levels of the experimental factors. Significance level of 0.05 was used for all statistical analysis. ANOVA and contrasts were performed using Super ANOVA software (Abacus Concepts, Inc., Berkeley, CA).

Table 1. Storage plan of nizatidine capsules. The storage conditions at which the samples were taken are checked.

Temp., °C	Time, day	RH, %								
		12	23	33	44	50	63	75	80	90
18	6	x	x	x	x	x	x	x	x	x
	30	x	x	x	x	x	x	x	x	x
	45								x	x
	60	x	x	x	x	x	x	x	x	x
	75								x	x
	90	x	x	x	x	x	x	x	x	x
	117			x		x		x		x
28	6	x	x	x	x	x	x	x	x	x
	30			x		x	x	x	x	x
	45								x	x
	60			x		x	x	x	x	x
	75								x	x
	90			x		x	x	x	x	x
38	6	x	x	x	x	x	x	x	x	x
	30	x	x	x	x	x	x	x	x	x
	45						x	x	x	x
	60	x	x	x	x	x	x	x	x	x
	75						x	x	x	x
	90	x	x	x	x	x	x	x	x	x

CHAPTER 4. RESULTS AND DISCUSSION

DATA AND OBSERVATIONS

Figure 3 illustrates two representative dissolution profiles, one of which is the typical profile for the product as manufactured, and for any time during its life when no deleterious changes have taken place; the other is an altered dissolution profile of the product after aging at 38°C/75% RH for 45 days. As can be seen, the 30 minutes dissolution value decreased from 98.7% to 83.6%. The U.S.P. requires 75% dissolved, so the product was headed for a shelf life problem and recall.

Figure 4 shows the dissolution isotherms at 18°C at different time intervals. The 30 minutes dissolution value remained almost constant over the whole testing range of relative humidities within 90 days storage. The tabulated data are shown in Appendix 2. All the 30 minutes dissolution values passed the U.S.P. requirement. No apparent delay of the disintegration of the capsule shells was observed.

Figure 5 shows the dissolution isotherms at 28°C at different time intervals. Decrease in dissolution can be seen at high relative humidities after 60 days storage. At the end of 90 days storage, the 30 minutes dissolution values went back to normal. The tabulated data are shown in Appendix 2. All the 30 minutes dissolution values passed the U.S.P. requirement. The disintegration of the capsule shells were delayed for the samples stored at 90% RH after 60 days.

Figure 6 shows the dissolution isotherms at 38°C at different time intervals. Big reduction in dissolution could be observed at relative humidities above 63%. The tabulated data are shown in Appendix 2. The biggest decrease happened at 75% RH after 60 days storage due to impaired disintegration of the capsule shell. During the dissolution tests, it was

observed that, in contact with the dissolution medium, the gelatin shell exhibited a considerable swelling and formed a matrix . It took more than five minutes for the gelatin matrix to be broken. No drug was released into the dissolution medium before the gelatin matrix was broken. The 30 minutes dissolution value of the product was reduced substantially and failed the U.S.P. requirement. The capsules also exhibited large intercapsule variations in dissolution (Appendix 3). Insoluble capsule shells were also observed for the samples stored at 80% and 90% RH. In addition the capsules stored at 90% RH were soft and difficult to handle. At the end of 90 days storage, all the 30 minutes dissolution values had increased. The rate of increase was dependent on the relative humidity level. It should be pointed out that the return to adequate release did not make the capsules usable. They were still failed drugs based on the FDA requirements and subject to recall. However, the information is useful for research purposes.

The 30 minutes dissolution value at various storage times was also plotted versus moisture content of the product based on the published moisture isotherms at 28 ^{0}C and 38 ^{0}C (Lockhart et al 1995). The profiles were very similar to the dissolution isotherms at these two temperatures.

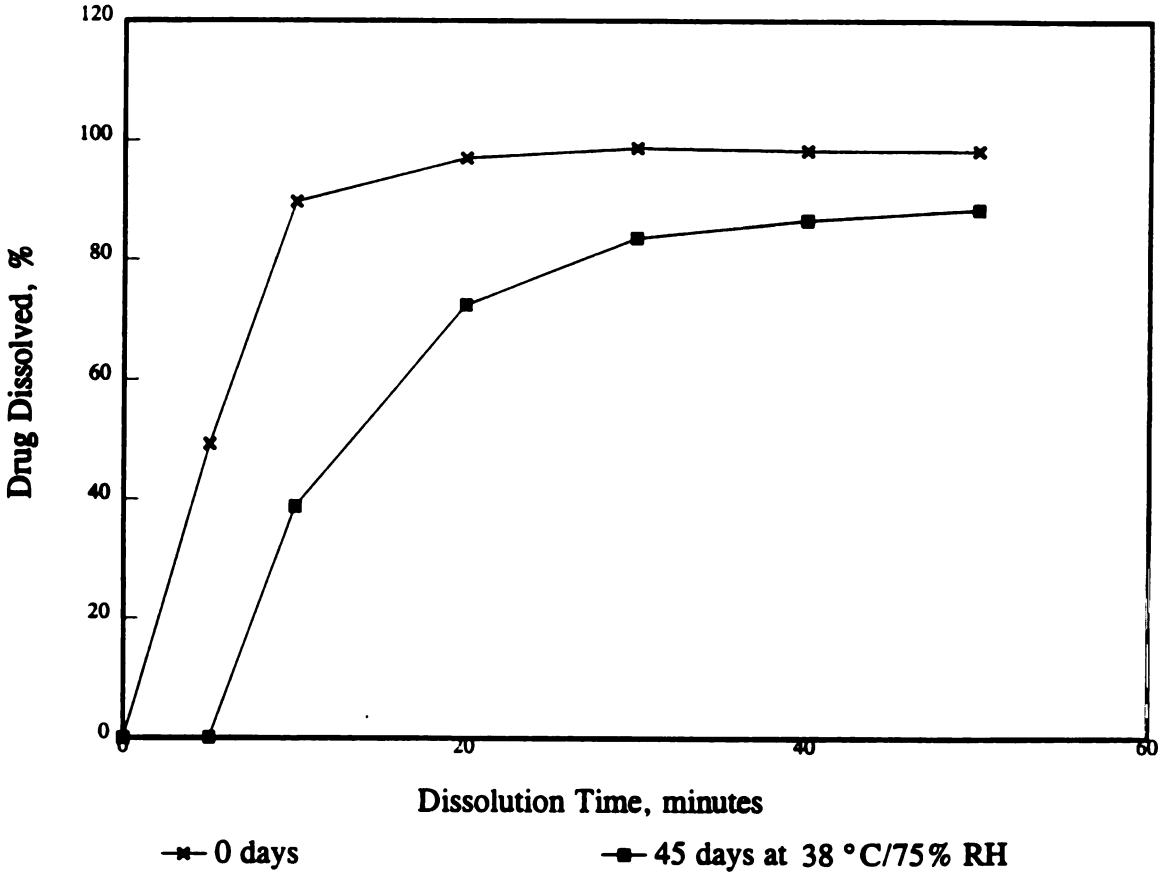

Figure 3. Representative dissolution profiles of Axid at 0 storage time, and after 45 days storage at 38 °C and 75% RH.

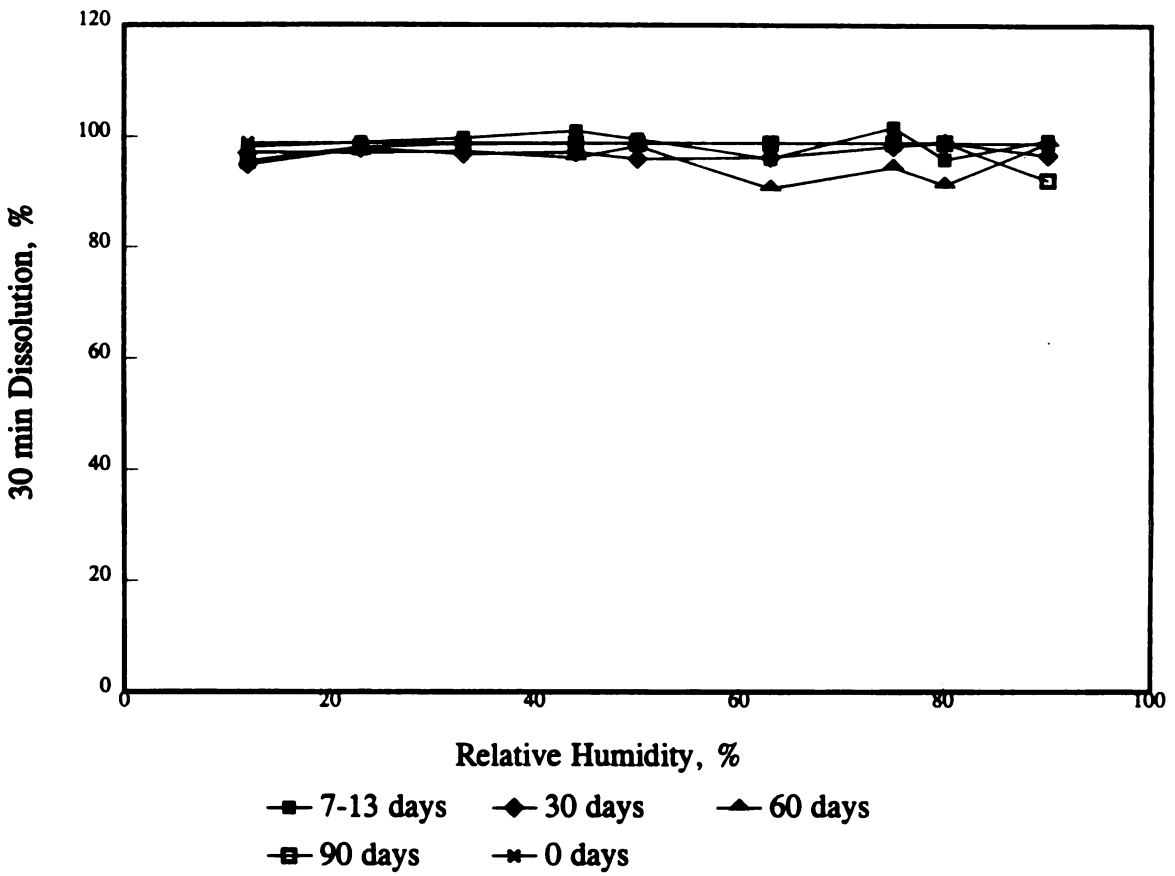

Figure 4. 30 minutes dissolution isotherms of Axid stored at 18 °C at various storage times.

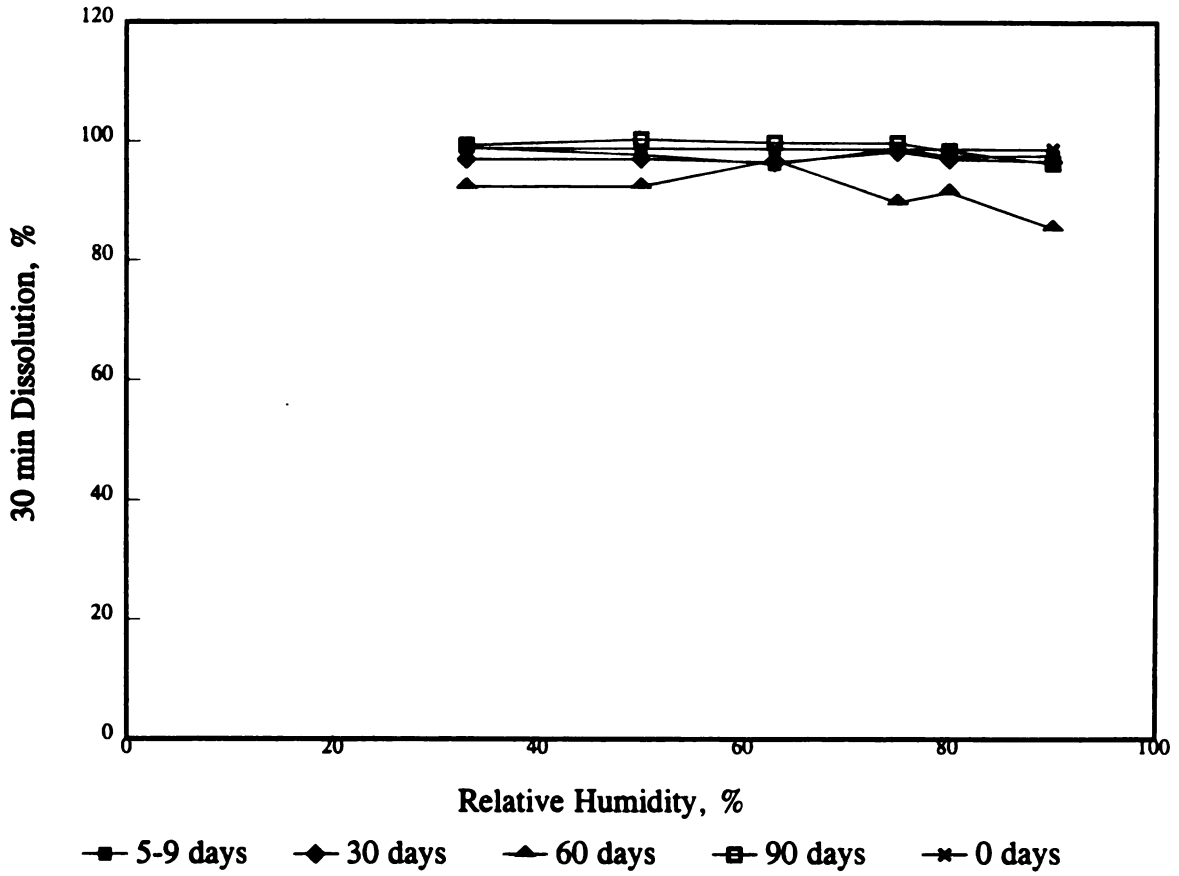

Figure 5. 30 minutes dissolution isotherms of Axid stored at 28 °C at various storage times.

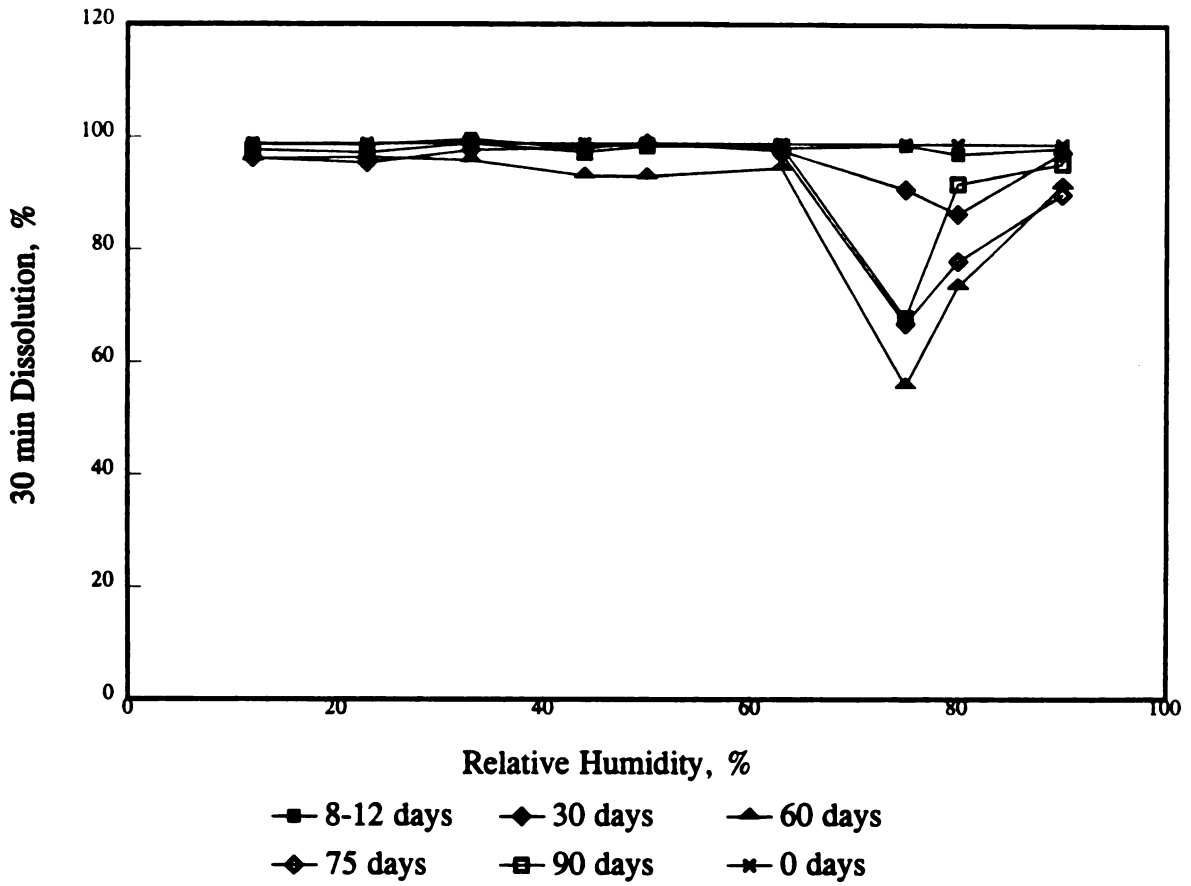

Figure 6. 30 minutes dissolution isotherms of Axid stored at 38 °C at various storage times.

STATISTICAL ANALYSIS AND DISCUSSION

The 3-way ANOVA results are present in Table 2. As can be seen, the stability of 30 minutes dissolution value of the product was significantly affected by temperature, relative humidity, storage time, and the interactions among them.

The contrasts results are presented in Table 3. Only P-values less than 0.05 are given in the table. Comparisons were made between the 30 minutes dissolution values of the capsules aged under various storage conditions and storage times and the values of the capsules as manufactured. At 28°C and 38 °C, there was no significant change in dissolution at 30%, 50%, and 63% RH during 90 days storage. Since the 30 minutes dissolution values at 12, 22, and 44% RH were very close to the initial one at 38°C at different time intervals (Figure 6), it could be deduced that there was no significant change in dissolution of the product stored at temperature up to 38°C and relative humidity of 12-63% during 90 days .

The contrasts results for 30 minutes dissolution values at 18°C are not quite comparable to those at 28°C and 38°C. The dissolution value at 18 °C/63% RH/60 days was significantly different from the initial value, while there was no significant difference at 18 °C/75% RH/60 days. Since the RH level generated by a saturated salt solution will increase if the temperature is decreased, so the RH level of the sodium nitrite solution at 18 °C was actually slightly higher than those at 28 °C and 38 °C. This may have been the threshold where the dissolution started to change.

High relative humidities resulted in significant decreases in dissolution. In the range of 75-90% RH, significant decreases in dissolution were observed at all three temperatures. Higher temperature resulted in greater and faster decrease in dissolution. Significant

reduction in dissolution at 75% RH appeared after 30 days at 38°C, while there was no significant reduction in dissolution at 75% RH after 30 days at 28°C. The biggest decrease was observed at 38°C/75% RH/60 days.

Based on the literature review and experimental observations, it could be suggested that the decrease in dissolution of the product was caused by insolubilization of the capsule shell. Accelerated storage conditions resulted in altered solubility of the gelatin shell through the effects of moisture and heat. The degree of insolubilization determined the rate of decrease in dissolution. It seemed that the equilibrium relative humidity level of 75% favored the gelatin insolubilization most. Higher levels not only resulted in the gelatin insolubilization, but also in the swelling of the gelatin structure. According to Lockhart and co-workers (1995), the moisture content of the capsule shell at 80% and 90% RH at 38°C is 22% and 30%, respectively. Such high moisture content levels might result in loosening the gelatin structure. Similar results were reported in the studies by Khalil and co-workers (1974). They found that storage at 80% RH resulted in total loss of dissolution because of impaired disintegration of the gelatin shell, but storage at 100% even resulted slightly increase in dissolution.

It also could be suggested that the capsule contents might be quite stable under accelerated conditions and have no contribution to the decrease in the drug dissolution in this case. One evidence was that the equilibrium moisture content of the capsule contents only changed from 3% to 10% when the relative humidity was raised from 12% to 90% (Lockhart et al 1995). Another evidence was that even though the 30 minutes dissolution value of the product decreased with time at first, it increased at the end of 90 days storage at 90% RH

almost to its initial value. In the literature several studies also showed that certain capsules with insoluble gelatin shell were still bioequivalent to the readily dissolving capsules, which indicated that the capsule contents were stable under accelerated conditions (Dey et al 1993, Chafetz et al 1984).

Table 2. Three-way ANOVA for 30 minutes dissolution value.

Source	df	Sum of squares	Mean square	F-value	P-value
Temperature	2	1021.539	510.769	31.652	0.0001
Time	3	2133.573	711.191	44.072	0.0001
RH	5	1261.004	252.201	15.629	0.0001
Temperature*Time	6	748.100	124.683	7.726	0.0001
Temperature*RH	10	2574.847	257.485	15.956	0.0001
Time*RH	15	1203.244	80.216	4.971	0.0001
Temperature*Time*RH	30	1958.966	65.299	4.046	0.0001
Residual	144	2323.753	16.137		

Table 3. Comparisons of the 30 minutes dissolution values of aged capsules to the initial value by contrasts. The results are presented in P-values and only those less than 0.05 are listed below.

Temp., °C	Time, day	RH, %					
		33	50	63	75	80	90
18	30	-	-	-	-	-	-
	60	-	-	0.0147	-	0.0262	-
	90	-	-	-	-	-	0.0450
28	30	-	-	-	-	-	-
	60	-	-	-	0.0075	0.0313	0.0001
	90	-	-	-	-	-	-
38	30	-	-	-	0.0155	0.0020	-
	60	-	-	-	0.0001	0.0001	0.0305
	90	-	-	-	0.0001	0.0329	-

CHAPTER 5. CONCLUSIONS

The effect of moisture and heat on the dissolution stability of the capsule product was evaluated by exposing the product to various storage conditions without any packaging protection. It showed that the dissolution stability was significantly affected by storage conditions (temperature and relative humidity), storage time, and all the interactions among them. High relative humidities (75-90%) caused significant decrease in the dissolution rate. At such conditions, the higher the temperature, the longer the storage time, the greater the loss of dissolution rate. The capsules stored at 12-63% RH were quite stable at all three temperatures tested. It indicated that certain critical level of relative humidity higher than 63% was required for the initiation of dissolution changes.

The above findings are very important in selecting packaging for the product. Since the dissolution stability of the product is reduced by moisture, the moisture barrier property of the packaging material and the using of desiccant need to be considered when selecting the packages. The packages should be able to protect the product from the effect of moisture. The package for the product could be chosen in such way that it is able to keep the relative humidity level no more than 63% inside the package within the expected shelf life. If the product is packaged in bottles, the requirement is very easy to achieve by using high moisture barrier materials, such as HDPE, and placing desiccant inside the bottles. However, if the product is packaged in blisters (blister packaging is becoming popular), it is not so easy to achieve because of the exclusion of desiccant. The moisture barrier property and thickness of the blister material need to be carefully selected. The packaged product based on the above considerations should be able to pass the dissolution requirement during stability testing.

CHAPTER 6. RECOMMENDATIONS

Recommendations for furture research are as follows:

1. To establish a mathematical relationship among the dissolution stability of the product, environment relative humidity and storage time at the three temperatures based on the collected data.
2. To predict the dissolution shelf life of the product in a variety of packages by using the mathematical relationship and determining the amount of moisture permeated through each of the packages.
3. To determine dissolution shelf life for additional products.
4. To generalize the results to basic principles for determining drug dissolution shelf life.

APPENDICES

APPENDIX 1

DEVELOPMENT OF A DISSOLUTION PROCEDURE FOR AXID

The general dissolution procedure is described in the U.S.P. and several parameters are well defined, such as paddle rotating speed and sampling position, etc.. However, preparation of the sampling tool is not addressed. Therefore, a sampling tool was specially designed for this study. It was a 5-ml disposable plastic syringe to which a piece of plastic tubing had been attached. A piece of cotton was inserted into the end of the tubing near the syringe as a filter to remove undissolved particles. The cotton was tightly packed in the tubing and the length it covered was about one cm. After each experiment, the syringe and cotton were removed and discarded.

Several filtering materials were compared: glass wool, cotton, and Millipore sterile 0.45um filter (Millipore Products Division, Bedford, MA). The following experiment was used for comparison.

Standard nizatidine solution was prepared and the absorbance of the solution at 314 nm was determined by spectrophotometry. About 4 ml standard solution was filled into a disposable syringe. Then the syringe was attached to a piece of tubing with one of the filtering materials. The solution was forced to run through the tubing and the filter, and collected for UV spectrophotometer determination again.

The results are shown in Table 4. Single population t-test (Burgess 1995) showed that Millipore filter absorbed the active ingredient significantly, while glass wool and cotton did not. Since glass wool may cause temporary skin and upper respiratory irritation, cotton

was chosen for the filtering material.

Table 4. Selection of the filtering material for the sampling tool.

Filtering material	Absorbance of the original standard solution at 314 nm	Absorbance of the standard solution after running through the tubing and the filter at 314 nm		t value
		Tool 1	Tool 2	
Glass wool	0.463	0.464	0.463	2.02
Cotton	0.466	0.466	0.467	2.02
Millipore filter	0.824	0.792	0.793	62.6

t (0.05, 1) = 6.314, 62.6>6.314, so significantly different.

APPENDIX 2

30 Minutes Dissolution Value of AXID at Different Storage Conditions and Times

The 30 minutes dissolution value of AXID at different storage conditions and times is shown in Table 5. The data were based on triplicate runs.

Table 5. 30 minutes dissolution value of AXID at different storage conditions and times.

Temp., °C	Time, day	RH, %								
		12	23	33	44	50	63	75	80	90
18	6	98.1	98.9	99.6	100.9	99.4	96	101.6	95.9	99.3
	30	94.9	97.7	96.8	97.1	95.9	96.2	98.2	98.9	96.7
	45								97.1	95.1
	60	97.1	97	97.2	96.1	98.2	90.6	94.4	91.3	98.8
	75								98.9	96.2
	90	95.6	98	98.5	98.6	98.6	98.7	98.9	98.9	92.1
	117			97.6		98.3		98.6		98.8
28	6	98.3	99.1	98.8	98	97.7	96.2	98.9	97.5	97.7
	30			96.9		97	96.5	98.3	97.1	96.7
	45								97.6	92.3
	60			92.3		92.4	96.9	89.8	91.6	85.5
	75								96.6	90
	90			99.2		100.3	99.8	99.8	98.4	96.4
38	6	98.6	98.5	99.5	98	98.9	98	98.5	97	98.1
	30	96.2	95.3	97.5	98.1	98.8	97.5	90.7	86.4	97.3
	45						95.8	83.6	83.5	91.9
	60	96.1	96.3	95.8	93	92.9	94.5	55.7	73.4	91.5
	75						97.1	66.8	77.9	89.9
	90	97.6	97.1	98.7	97.2	98.3	98.3	67.8	91.7	95.3

APPENDIX 3

Dissolution Profiles of Individual Capsules Sampled at Two Different Storage Conditions and Storage Times

Figure 7 shows the dissolution profiles of individual capsules sampled at two different storage conditions and storage times. The capsules at 18°C/33% RH/30 days dissolved readily and variations in the 30 minutes dissolution value are small. However, at 38°C/75% RH/60 days, insoluble gelatin shells were observed for the capsules, and the 30 minutes dissolution values not only decreased substantially but also varied greatly.

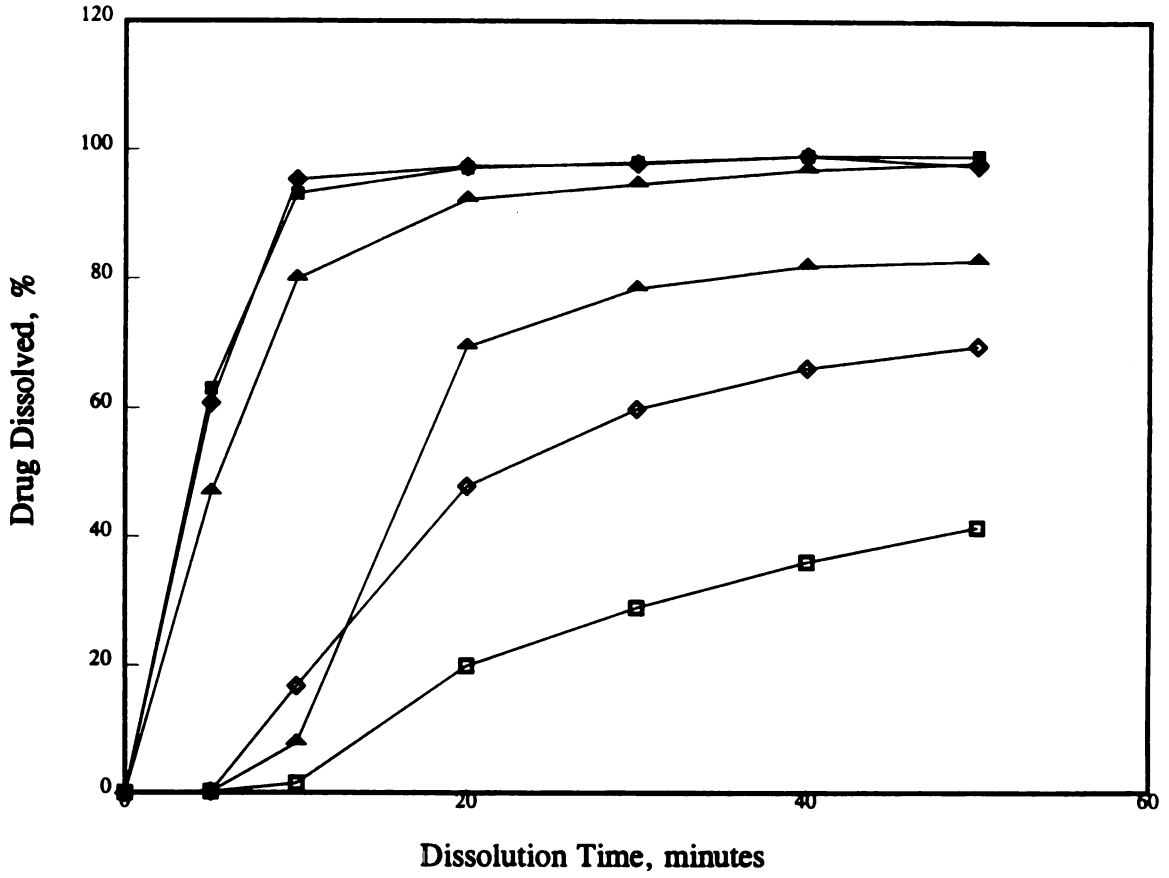

Figure 7. The dissolution profiles of individual capsules sampled at two different storage conditions and storage times. The top three profiles are for the capsules at 18 °C/33% RH/30 days, and the bottom three are for the capsules at 38 °C/75% RH/60 days.

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