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REGULATION OF STABILITY OF MARKETED PHARMACEUTICALS

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ABSTRACT

The United States Pharmacopeia / National Formulary (USP/NF) sets the standards and maintains monographs for the evaluation of various dosage forms, especially during the storage and distribution channels. This document is compiled with the critical review of the stability testing of pharmaceutical products. In particular, it considers the progress toward globalization and harmonization, attention being directed to monitoring stability in the distribution channels. It is also focussed on the implications of Mean Kinetic Tempearature (MKT) concept and the effect of temperature spikes on MKT values, thus effecting the stability of drug products. The assignment of conformance period to the tablets were determined using the NIR stability indicating assay, both with the original data and the normalized. The stability of compounded cefazolin ophthalmic solution was studied for the various Arrhenius parameters and Beyond-use date assignment.

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PREFACE

This document was prepared in the format of the manuscript plan in accordance to section 11-3 of the Graduate Manual at the University of Rhode Island. This thesis is divided into three sections.

Section I contains a general introduction to the objectives of my research. Section II consists of the main body of this thesis and is composed of four manuscripts written in the format required for each scientific journal they have been or will be submitted to. Section III contains Appendices A, B & C, which include the list of manuscripts for publication, role of co-authors in papers, and additional information and experimental details useful for the clear understanding of the work in Manuscript III respectively. A summary of overall conclusions and bibliography for the entire thesis follows this section.

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INTRODUCTION

It has been known for many years that many drug products have the potential to degrade on storage. In some instances, instability problems are so acute as to result in the product becoming unfit for use (i.e. lacking in acceptable safety, efficacy or patient acceptability) in a quite short time - in extreme instances in only a few days (1).

In the United States, USP (The United States Pharmacopoeia) and FDA (Federal Food and Drug Administration) have, during the past thirty years, developed well-proven methods that ensure drug product stability when pharmaceuticals are maintained under the conditions of storage indicated on the label.

However, there is a good reason to believe that products in the channel of distribution between the manufacturer and the user are not always stored in full compliance with label instructions (2). It seems possibly that the growth of community pharmacist compounding and mail order pharmacy practice may further complicate drug stability. Thus, the stability of drug products in the channel of distribution is in urgent need of definition. It is known that both USP and FDA are concerned about this problem.

The advancement of technology and the availability of high performance liquid chromatography (HPLC) have been a boom in the field of pharmaceutical stability testing. In addition to the technology advancement, organizational and regulatory developments have also been of great significance in stability testing.

The acceptance of USP definition of Controlled Room Temperature (CRT) and Mean Kinetic Temperature (MKT) concept has gained the attention of regulators in both the European Union and the United States (3,4). In this particular document, some of the implications of MKT on the drug product stability and the effect of temperature

excursions on the shelf life of drug products were investigated. The assignment of conformance period to the tablets using the NIR stability-indicating assay is also given a berth. Also reported some preliminary studies of the chemical stability of compounded cefazolin sodium ophthalmic solution.

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OBJECTIVES

The objectives of this thesis are mentioned as four points, all of which are related to one another, basically relating to the drug stability and are as follows.

1) To study the theoretical aspects related to drug stability, the problems encountered during distribution and storage, the ways to calculate MKT, the concepts of compounding and beyond-use date. Attention is also to be given for the globalization and harmonization of stability testing of drug products.
2) To study some of the implications of the MKT concept and the effect of temperature excursions / temperature spikes on the drug product stability.
3) To investigate the Arrhenius parameters and assign the Beyond-use dates for the compounded Cefazolin ophthalmic solution.
4) To estimate the shelf life of the tablets using the NIR stability indicating assay.

SECTION II

MANUSCRIPT I

Trends in Stability testing with emphasis on stability during distribution and storage

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Abstract

This paper reviews contemporary trends in the stability testing of pharmaceutical products. In particular, it considers the progress toward globalization and harmonization and indicates stability problems, which probably will be the focus of attention for pharmaceutical scientists and regulators in the near future. Attention is specifically directed to monitoring stability in the channels of distribution.

INTRODUCTION

Within the past twenty-five years or so, the stability testing of pharmaceutical products has advanced dramatically from a somewhat haphazard exercise which showed dramatic variations in quality, both within and between various jurisdictions, to an operation based on sound scientific principles, which shows a significant degree of commonality in many parts of the world.

Although pharmaceutical scientists and regulators have known for many years that all drug delivery systems - to a varying degree - have a propensity to degrade and thus show a lower level of "fitness for use", it was only in the nineteen seventies that standardized approaches for the reliable quantification of the stability of pharmaceutical products began to emerge.

The stability of pharmaceutical products is a broad area encompassing many potential routes of degradation. Any change which occurs in a pharmaceutical product, subsequent to its preparation, that adversely affects any attribute of the quality of the product in terms of its fitness for use by a patient is, potentially at least, a matter of concern to pharmaceutical scientists and regulators involved in stability testing.

It is conventional and convenient to classify degradation of pharmaceutical products as being chemical, physical or biological. However, in many instances these distinctions are not complete. For example, oxidation in a condom (chemical) results in a loss of tensile strength (physical). Also, for many drugs or devices more than one mode of degradation may be possible. (1)

In general, we may classify the adverse effects of pharmaceutical product's instability as modifying efficacy, safety, or ease of use or patient acceptability. In terms

of efficacy the most obvious effect is loss of potency of the drug. Indeed, for many stability studies loss of potency is the key factor in the determination of the shelf life of the product. Usually we regard 90% of label claim as being the lowest acceptable value of potency. Thus, for many pharmaceutical products an estimation of the time, which will elapse (when the product is stored under specified conditions) before the potency, is less than 90% of label claim will be central to our stability studies.

Important, though loss of potency can be there, is now an increasing recognition that for some pharmaceutical products other effects of instability may be of equal or of greater importance than loss of potency. For example, if a degradation product is toxic it may be that the accumulation of the toxic degradation product is of more critical importance than loss of active. Although such occurrences are presently probably relatively rare, the increasing use of protein drugs, for which small changes in structure can have profound impact on immunogenicity, may result in this situation becoming more likely and therefore deserving of more attention.

In considering the stability of pharmaceutical products it is essential to consider the totality of the product: drug, excipients, pack and label. All of these elements can play an important role in the fitness for use of the drug delivery system. For example, if migration of a plasticizer from the plastic bottle into a label causes the ink to become blurred so that the legibility of the information on the label is impaired, this is a matter of concern.

A major factor in the improvement of pharmaceutical stability testing has been the development of analytical methods, which are suitable for use in stability indicating assay. In particular, the availability of high performance liquid chromatography (HPLC)

has been a real boon to stability testing. It is noteworthy that our definition of a stability-indicating assay has evolved from a method that would allow quantification of a drug in the presence of its degradation products and excipients to a method, which allow quantification not only of the drug but also major degradation products.

In addition to technical achievements, such as the emergence of HPLC for use in stability indicating assays, organizational and regulatory developments have also been of great significance in stability testing. During recent years the substantial number of corporate takeovers and mergers has increased the number of pharmaceutical companies, which operate in many areas of the world. For such transnational corporations there is an obvious attraction to using the same raw materials, equipment, production methods and quality control tests at all their plants throughout the world. Thus such companies have an especially strong interest in promoting compatibility in regulatory policies such as those which control stability testing.

STABILITY

Concepts

Stability testing is a routine procedure performed on drug substances and products. It is involved at various stages of a product's development. In early stages, accelerated stability testing (at relatively high temperatures and / or humidities) can be used for some drugs as a "worst case" evaluation to determine what types of degradation products may be found after long-term storage. Testing under less rigorous conditions (those recommended for long- term shelf storage), and slightly elevated temperatures, can be used to determine a product's shelf life and expiration dates (2). Stability testing is performed to ensure that drug products retain their fitness for use up to the end of their expiration dates. (3)

The raison d'être of pharmaceutical testing should be to provide reasonable assurance that the "fitness for use" of our products remains at an acceptable level throughout the period during which they are in the market place available for supply to the patient/consumer. It has been suggested by some that the above definition should be extended so that it covers the period until the patient uses the last unit of product. However, since we cannot control how patients store drugs and because we are aware that a significant proportion of patients store pharmaceuticals in a quite inappropriate manner, many pharmaceutical scientists believe this concept to be impracticable. The most likely method of improving storage of drug products by patients may well be in individual counseling by pharmacists

Stability of a pharmaceutical product may be defined as the capability of a particular formulation, in a specific container/closure system to remain within its

physical, chemical, microbiological, therapeutic, toxicological, protective and informational specifications. Although there are exceptions, 90% of labeled potency is generally recognized as the minimum acceptable potency level (4). Stability is also defined as the extent to which a product retains, within specified limits, and throughout its period of storage and use (i.e., its shelf life), the same properties and characteristics that it possessed at the time of its manufacture. The criteria for acceptable levels of stability have been reviewed in the form of a table. (5,6)

Factors affecting Product Stability

Many factors affect the stability of a pharmaceutical product, including the stability of the active ingredient(s), the potential interaction between active and so-called inactive ingredients, the manufacturing process, the dosage form, the container closure system, the environmental conditions encountered during shipment, storage, handling, and length of time between manufacture and usage. Environmental properties such as heat, light, and moisture as well as chemical factors like, oxidation, reduction, hydrolysis, or racemization, can all play vital roles in pharmaceutical stability. Degradation reactions in pharmaceutical formulations may depend on such conditions as concentration of reactants, pH, radiation, temperature and catalysts etc (7). A number of other factors are listed in the literature. Of all the many environmental factors, which can be involved in drug degradation, temperature is the most important one, which cannot be controlled by package selection.(4)

The stability of a drug product depends on the raw materials used, warehouse and transport facilities, patient/consumer storage and in-vivo stability. The effects of drug product instability include loss of active drug (e.g., nitroglycerin tablets), increase in

concentration of active ingredient (e.g., lidocaine gel), change in biological activity (e.g., tablet aging), loss of content uniformity (e.g., flocculation and impaction in suspensions), presence of pathological microorganisms (e.g., contamination of a multi use cream), loss of pharmaceutical elegance (e.g., yellowing of direct compression lactose tablets containing an amine drug), production of toxic decomposition products (e.g., conversion of tetracycline to epianhydrotetracycline) and other factors changing fitness for use (e.g., adhesion aging of transdermals). (8)

Expiration Date / Shelf life

An Expiration date is defined as the time up to which the preparation will remain stable when stored under recommended conditions. Thus, an *expiration date* is the date beyond which it is predicted that the product may no longer retain fitness for use. If the product is not stored in accordance with the manufacturer's instructions, then the product may be expected to degrade more rapidly. Strict adherence to the storage requirements specified in the product labeling will help ensure product stability through to the manufacturer's labeled expiration date. The manufacturer's expiration date only applies if these storage requirements are met from the time the product leaves the manufacturer until it is supplied to the user. (9)

Shelf life is the time during which we have reason to believe that the product, if stored appropriately, will retain fitness for use (>90% of label claim of potency) (10). The *expiration date* is also defined as the date placed on the container/labels of a drug product designating the time during which a batch of the product is expected to remain within the approved shelf-life specification if stored under defined conditions, and after which it may not be used (11). The use of kinetic and predictive studies for establishing credible

expiration dates for pharmaceutical products are now accepted worldwide. However, prior to about 1950 only qualitative or semi-quantitative methods and procedures were commonly used in pharmaceutical studies. Stability study requirements and protocol designs were covered in detail in the standard professional literature. (10-13)

Although shelf life may be in some instances be estimated by accelerated stability testing protocols, real time product stability testing is necessary to validate stability claims (14). Additional data pertinent to shelf life may be obtained using the retained samples, from market challenge tests and test distributed samples, and from returned samples. (8)

STABILITY TESTING METHODS

Real -Time Stability Testing

In real-time testing, the duration of the test period should normally be long enough to allow significant product degradation under recommended storage conditions. Alternatively, if a product is essentially stable the test should be conducted for a long enough period to clearly indicate that no measurable degradation is occurring. At the least, the testing protocol must permit one to distinguish degradation from inter assay variation. For example, data may be collected at an appropriate frequency such that a trend analysis may discern instability form day-to-day imprecision. The reliability of data interpretation can be increased by including in each assay a single lot of reference material with established stability characteristics. Sample recovery between assays can be thereby normalized to this reference, minimizing the impact of systematic drift and inter assay imprecision. Frequently, however, an appropriate reference material is not available for use as a control. When one measures the stability of a reference material, imprecision may be introduced by changes in both reagents and instrumentation. Ideally, reagents should be sufficiently stable that a single lot provides unchanging performance throughout the stability study and instrument performance should remain constant. However, one must monitor system performance and control for drift and discontinuity resulting from changes in both reagents and instrumentation. (14)

The time at which the 90% two sided lower confidence bound intersects at 90% potency level on the stability plot (percent of label claim against time) is best termed the Conformance period. This length of time must always be greater than the actual shelf life that is assigned to the product. The Conformance period may, of course, be any time

interval e.g., 21.3 months, 38.7 months or 69.5 months. The shelf life is rounded down from the Conformance period to give a convenient value e.g., 18 months, 3 years or 5 years. Full details of the method of calculation are given in the FDA Guidelines (12).

Accelerated Stability Testing

Accelerated stability testing refers to methods by which product stability may be estimated by storage of the product under conditions that accelerate degradation commonly by an increase in temperature. Stress conditions that accelerate change fall under the general headings of temperature, light, moisture, agitation, gravity, pH, packaging, and method of manufacture. This method is often used to provide an early indication of product shelf life and thereby shorten the development schedule. This may permit in some circumstances the prediction of the stability of the product at ordinary shelf temperature from data obtained by stress testing. A reasonable statistical treatment in accelerated stability projections based on the Arrhenius equation normally requires that at least four stress temperatures be used. Many accelerated stability-testing models are based on the Arrhenius equation. (15-18)

$$k = A\, e^{-Ea/RT}$$

where k is a rate constant at temperature T (in degree Kelvin), Ea is the activation energy, and R is the gas constant. This equation describes the relationship between storage temperature and degradation rate. Use of the Arrhenius equation permits a projection of stability from the degradation rates observed at high temperatures for some degradation processes. (19) When the activation energy is known, the degradation rate at low temperatures may be projected from those observed at "stress" temperatures.

Bracket Tables

The bracket table technique assumes that, for a given analyte, the activation energy is between two limits, e.g., between 10 and 20 kcal. As a result, a table may be constructed showing "days of stress" at various stress temperatures. Readers are requested to view the table from (14). The use of a 10 to 20 kcal bracket table is reasonable, because broad experience indicates the most analytes and reagents of interest in pharmaceutical; and clinical laboratories have activation energies in this range. (23,24)

For analytes with high activation energies, both bracket tables and the Q rule provide useful information when they are applied conservatively. Use of published or experimentally derived activation energy values can significantly lower the risks inherent in projecting product shelf life.

The Q rule and the Bracket tables were used in the past by some in the pharmaceutical for the prediction of shelf life of the product. These methods are not official either in the ICH or FDA Stability Guidelines.

Retained Sample Stability Testing

One of the most important elements in most stability testing of marketed pharmaceutical product is evaluation of retained stability samples. The usual practice for such studies is that for every marketed product, for which stability data is required, the manufacturer selects stability samples form retained storage for at least one batch a year. If the number of batches marketed exceeds 50 it is probably desirable to take stability samples from two batches. Often when a new product is first introduced on to the market the manufacturer may decide to take stability samples of every batch. Later as increased confidence is gained in the stability of the product the number of batches kept on stability

testing is likely to be progressively reduced so that only two to five percent of marketed batches are designated as stability sample batches. (8)

Stability samples are tested at predetermined intervals. Thus, if a product has a five-year shelf life, it is conventional to test at 3,6,9,12,18,24,36,48,and 60 months. This conventional method of obtaining stability data on retained storage samples was termed as "Constant Interval Method" by Carstensen and Rhodes (8) who pointed out some disadvantages of this method earlier. (25,26). These authors have proposed use of the first, the **Fixed Date method** of stability sample testing, which uses a modified form the conventional retained sample testing. They also proposed a much more radical change and termed this method as "**Stability Testing by Evaluation of Market Samples**". This method involves taking samples already in the marketplace and evaluating stability attributes (27-29). This type of testing is inherently more realistic since it challenges the product not just in the idealized retained sample storage conditions, but also in the actual market place.

6. Cyclic-Temperature Stress Testing

This method, as explained by Carstensen and Rhodes, (30) may provide evidence about the instability not available from isothermal tests. This type of testing is a very useful component in the gamut of tests available to the pharmaceutical scientist for stability testing (1,29), used in development or trouble shooting but not for routine testing of marketed product. The cyclic temperature stress tests should be designed based on knowledge of the product, so as to mimic likely conditions in market place storage. The period of the cycle mostly favored is as 24 hours since the diurnal rhythm on earth is 24

hours and thus marketed pharmaceuticals are most likely to experience such a cycle during storage. (31,32)

Carstensen and Rhodes (32) derived an equation relating temperature change to time based on a sine wave, function. It was proposed that the maximum and minimum temperatures for the cyclic stress testing should be selected on product by product basis and taking into account such factors as recommended storage temperatures for the product and specific chemical and physical degradation properties. It was also recommended that the test should normally have about twenty cycles.

MEAN KINETIC TEMPERATURE (MKT)

Concepts

For an *USP/NF* product it is expected that, when properly stored, the product can meet monograph specifications at any time during its shelf life. From time to time, health care practitioners have expressed concerns about the environmental stresses to which drug products are exposed throughout the product's lifetime and about whether the exposure will effect the articles' integrity. The concerns include transportation and storage of drug products by manufacturers, wholesalers, and pharmacies. Thus, the stability of the pharmaceutical article is an attribute that must be known. The *USP/NF* recognized that storage temperature affects stability and thus defined the storage conditions.

The amendment of the USP definition of Controlled Room Temperature in November 1993 includes a requirement for "a mean kinetic temperature calculated at not more than 25 ^{0}C". The definition of Controlled room temperature is as follows:

"A temperature maintained thermostatically that encompasses the usual and customary working environment of 20 ^{0}C to 25 ^{0}C that results in a mean kinetic temperature calculated to be not more than 25 ^{0}C; and that allows for excursions between 15 ^{0}C and 30 ^{0}C that are experienced in pharmacies, hospitals, and warehouses. Articles may be labeled for storage at "controlled room temperature" or at " up to 25 ^{0}C", or other wording based on the same mean kinetic temperature". (33,34)

The relationship between CRT ant MKT for storage and distribution of pharmaceutical articles is given special attention in official publications. (11,35)

Since degradation rate constants are temperature-dependent, the amount of degradation varies with the temperature during a storage period. The use of Mean Kinetic temperature (MKT) originally proposed by Grimm (36) has become generally accepted as a convenient method of quantifying storage temperatures as they relate to degradation.

The equation for the determination of MKT is derived from Arrhenius equation, relating the degradation rate constants at different temperatures to the activation energy and is known as Haynes formula (37). The MKT concept can be applied to many areas of pharmaceutical distribution, namely, to manufacturers, warehouses, shippers, hospitals and community pharmacies, emergency vehicles, sales representatives' vehicles, etc.

Mean Kinetic Temperature is the single calculated temperature at which the total amount of degradation over a particular period is equal to the sum of the individual degradations that would occur at various temperatures. Thus, the mean kinetic temperature may be considered as an isothermal storage temperature that simulates the nonisothermal effects of storage temperature variation (38,39). It is not a simple arithmetic mean. It is always higher than the arithmetic mean temperature. (39)

Calculation of MKT

Although there is general recognition in North America, the European Union and Japan of the utility of the MKT concept, there is still some debate about the exact method by which this value should be calculated, although in many instances the differences in mode of calculation will have little significant effect on numerical value obtained.

USP Method

The USP method of calculation (40) is shown below. The mean kinetic temperature is calculated from the average storage temperatures recorded over a one year

period and running average calculated from the average of weekly high and low temperatures recorded over the preceding 52 weeks. If the exposure of the pharmaceuticals is for a lesser period (as in doctor's cars, patient's cars, sales representatives' cars etc.), then it is advised to calculate the MKT with frequent recording of the temperature profile.

The mean kinetic temperature is calculated by the Haynes' equation:

$$MKT = \frac{\Delta H/R}{-\ln\left(\left(e^{-\Delta H/RT1} + e^{-\Delta H/RT2} + \ldots\ldots + e^{-\Delta H/RTn}\right) / n\right)}$$

Where MKT is the mean kinetic temperature; ΔH is the heat of activation, 83.144 kJ/mole; R is the universal gas constant 0.0083144 kJ/mole/degree; T_1 is the arithmetic mean of the highest and lowest temperatures recorded during the first time period, e.g., the first week; T_2 is the arithmetic mean of the highest and lowest temperatures recorded during the second time period, e.g., second week; T_n is the arithmetic mean of the highest and lowest temperatures recorded during the nth time period, e.g., nth week, n being the total number of average storage temperatures recorded (52) during the annual observation period; and all temperatures, (T) being absolute temperatures in degrees Kelvin (K).

In reality, of course, not all pharmaceutical products are characterized by degradation energy of activation as 83kJ/mole. This is the average value based on work by Grimm (36) and Kennon (24). Ideally, the value of activation energy, ΔH, to be used in the calculation should be determined experimentally for any given product. Among various pharmaceutical dosage forms, the activation energy may vary from 5-240

kJ/mole. The change in MKT that results from this variation of activation energies is probably relatively small in many instances (39).

FDA method

FDA recommends the method of entering both the individual highest and the lowest temperatures (rather than averages) in the equation for the calculation of MKT. This results in entering 104 data points in contrast to USP's 52 points (13). Bailey and Medwick (40) have discussed the characteristics of methods used to calculate MKT.

The USP and the FDA methods of calculation of MKT were compared by the authors, taking into consideration, the different values for the activation energy. (41)

If temperatures are electronically recorded at many times during a day and all the values used in the calculation of MKT then there is no difference between the USP and FDA methods.

Mail Order Temperature Excursions

Factors that may affect the stability of a drug product during shipment include the specific nature of the product, the types of packaging, and variations in environmental conditions during transport. Since many pharmaceutical products are distributed through United States postal service, a study was performed by Black and Layloff (42) which revealed the interior temperature of a black mail-box was 58 ^{0}C in an ambient temperature of 38 ^{0}C at St.Louis, Missouri. This result indicates that pharmaceutical products distributed through the postal service may be exposed to temperatures that significantly exceed those normally specified in stability standards. This is especially likely to be a problem for temperature sensitive (labile) products.

In order to observe the effects experienced by the packaged pharmaceuticals during the shipment and distribution, the USP recorded the temperatures and humidities experienced by packages during mail-order distribution by packaging temperature and humidity monitoring devices and shipping to different parts of the country. On return of the packages, the MKT was calculated. Results of the study have shown that only 8.4% of the packages experienced temperature variations within the excursions allowable under the CRT. The remaining packages were exposed to temperatures significantly above the accepted excursion range. While 65.5% of the packages experienced warm conditions (30^0C – 40 ^{0}C) during the shipment, the remaining 26.1% experienced excessive heat (>40 ^{0}C) conditions. Additionally, MKT calculations have shown that 31.1% of the packages had MKT values above 25 ^{0}C for periods of 19 to 21 days. Significant spikes in relative humidity experienced were also reported. (43)

The USP team of scientists also studied to determine the extent of physical and chemical changes experienced by the pharmaceutical preparations exposed to typical shipping conditions. Monitoring devices were used for the study. Results of temperature and humidity variations during shipment indicated about 40% of the articles experiencing MKT greater than 25 ^{0}C (44). The data presented agreed with previous findings, demonstrating that the pharmaceuticals experience significant fluctuations in temperature and humidity during shipment.

Recognizing that some products will especially be sensitive to temperature change, USP proposed a definition of "Labile" preparations and the shipping and the labeling requirements for such preparations (45).

The data profile of the temperatures experienced during the shipment and distribution can be obtained using electronic indicators as TempTale 3, TempTale H, and Cox Lynx and chemical indicators as Time temperature indicator (TTI) and Monitor Mark. The functioning of the indicators were dealt by C.C.Okeke *et.al* (43). It has also been reported by Carstensen that MKT in Sudan is in excess of that stipulated for the "dry, hot" climate zone. (46)

STORAGE CONDITIONS

Concepts

USP compendial monographs specify storage requirements that are to be maintained throughout the shelf life, shipment, distribution, and storage of the article. USP storage requirements fall into two major categories, specific and non-specific (33,47). Many monographs include specific storage conditions, such as "Store in a cool place". A survey conducted by the USP revealed that there exist products, which do not have any specific storage conditions (48). The USP General Notices section addresses these types of compendial monographs in Storage under non-specific conditions.

The storage conditions under the specific requirements are defined using the terms: freezer, cold, cool, Room temperature, Controlled room temperature, warm, excessive heat, and protection from freezing. The storage under non-specific conditions states that for articles, regardless of quantity, where no specific storage directions or limitations are provided in the individual monograph, it is to be understood that conditions of storage and distribution (including the shipment of articles to the consumer) include protection from moisture, storage at controlled room temperature, and, where necessary, protection from light. (33)

The length of the stability studies and the storage conditions should be sufficient to cover storage, shipment, and subsequent use (e.g., reconstitution or dilution as recommended in the labeling). The accelerated and long-term storage conditions and the minimum time period at submission are listed below.

Conditions	Minimum time period at Submission
Long-term testing 25 ^{0}C +/- 2 ^{0}C / 60 +/- 5% RH	12 months
Accelerated testing 40 ^{0}C +/- 2 ^{0}C / 75 +/- 5%RH	6 months

Where "significant change" occurs due to accelerated testing, additional testing at an intermediate condition, e.g., 30 ^{0}C +/-2 ^{0}C / 60+/- 5% RH may be used (49). The data (from accelerated testing or from testing at an intermediate condition) may be used to evaluate the impact of short-term excursions outside the label storage conditions such as might occur during shipping.

Testing under the defined long-term conditions will normally be every three months during the first year, every six months during the second year, and then annually. The long-term testing should be continued for a sufficient period beyond 12 months to cover shelf life at appropriate test periods. The further accumulated data should then be submitted to the authorities during the assessment period of the Registration application. The containers to be used in the long-term, real time stability evaluation should be the same or as simulate the actual packaging used for storage and distribution.

Heat sensitive products should be stored under an alternative lower temperature condition, which will eventually become the designated long-term storage temperature. Where a lower temperature storage condition is used, the six months accelerated testing should be carried out at 15 ^{0}C above its designated long-term storage temperature. For example, if a product is to be stored long term under refrigerated conditions, accelerated testing should be conducted at 25 ^{0}C +/- 2 ^{0}C/60% +/- 5% RH. The designated long-term

testing conditions will be reflected in the labeling and expiration date. A storage temperature range indicated on the label may be used in accordance with relevant national/regional requirements.

For products where water loss may be important, such as liquids or semi-solids in plastic containers, it may be more appropriate to replace the high RH conditions by lower RH, such as 10-20%. (11)

Temperature and humidity determines the climatic and storage conditions. Both factors greatly affect the stability of a drug product. Since the temperature and humidity however constantly change – day and night alteration, seasonal variations-, considerations regarding the sorption behavior of the drug and the permeability of packaging materials must also be included (50). There are a several of studies reporting the changes in characteristics of tablets (51-57) and other dosage forms upon storage.

Climatic zones

For convenience in assigning shelf life stability experts have divided the world into four climatic zones (Table I) (58) based on their MKTs and relative humidities. The zones are characterized as follow with the corresponding storage conditions (59). The criteria and guide values for assignment of a city to the correct climatic zones are listed in Table II. (60,61)

The basis of the derived storage conditions were climatic values, measured in the open. They covered an average time span of 20 years and are therefore taken as representative for each place. These climatic values were then corrected, because drugs are not stored in the open. The average values for temperature and partial pressure of water vapor so obtained were provided with a safety factor. (61)

Storage conditions for Zones I and II

About 85% of the trade in pharmaceutical products in the world is undertaken within the areas of the EU, Japan and the USA. Therefore, it was obviously useful to have one storage condition, which could cover all these territories.

Uniform storage conditions are a basic requirement. In the EU most of the population live in climatic zone I or II, in Japan 99% and in the USA 94%. Since climatic zone II is a worst case situation for the EU and most of Japan and the US a MKT of 25 ^{0}C covers all those areas. The measured conditions in many warehouses are well below the storage conditions for climatic zone II, giving an indication of the safety margin.
All areas in climatic zones I and II in the three areas can be covered by one storage condition (thereby naturally including zone I as well) 25 ^{0}C /60%RH.

Thus, it can be concluded that stability testing in the EU, Japan and the USA (zones I & II) can normally be performed applying the same storage conditions, 25 ^{0}C / 60%RH for long term testing and 40 ^{0}C / 75%RH for high temperatures contain a safety margin, meaning that the derived shelf lives also have a built-in safety margin. (3)

Storage conditions for zones III and IV

If a drug substance is to be marketed in climatic zone III, then samples are stored at 30 ^{0}C / 35%RH; if the product is used in climatic zone IV, samples are stored at 30 ^{0}C / 70%RH. (62)

COMPOUNDING

Definition

Compounding is the process by which a pharmacist combines, mixes or alters ingredients to produce a medication for a patient, acting in accordance, or in reasonable anticipation of, a prescription issued by a physician, nurse practitioner, dentist or some other duly authorized person. Compounding can be as simple as adding a liquid to a manufactured drug powder, which has been formulated to produce a solution or a suspension, and as complex as the extemporaneous creation of a novel preparation.

During the past decade there has been a significant increase in the number of pharmacists in the United States devoting a substantial part of their activities to compounding prescription, in some instances for a wide variety of drugs and drug delivery systems (63).

FDA Modernization Act of 1997

The FDA Modernization Act of 1997 (64), added a new section (503A) on Pharmacy Compounding to the Federal, Food, Drug and Cosmetic Act (FDC Act). This act also requires FDA to establish an Expert Advisory Committee on compounding which will assist FDA in preparing a list of non USP drugs which may be used in compounding.

The legislation helps to delineate legal aspects of compounding. Specifically, the new section 503A: (1) recognizes the triad relationship (viz. patient, physician, pharmacist) as the basis for the practice of compounding; (2) allows for anticipatory compounding; (3) sets criteria for the drug substances to be used in compounding; (4) describes the development of a memorandum of understanding between states and FDA to address interstate distribution of compounded drugs; and (5) limits advertising and

promotion of compounding services. Section 503A, subsection (b) of FDA Modernization Act of 1997 specifies the compounding of drugs by the licensed pharmacist and licensed physicians.

The FDA has limited authority, to regulate pharmacists legitimately engaged in compounding. (65)

Stability of compounded products

With the increase in recent years in compounded prescriptions, the question most frequently asked is "What is the stability of this product after it is prepared?" In repackaging, diluting or mixing a product, the pharmacist should have concern about stability. Assurance of sterility of compounded injections or opthalmics is obviously of great importance. The pharmacist is responsible for the HSDs (Sterile Drug Products for Home Use) dispensed which are of commercially available type or compounded product right from dispensing to the patient till the stage of consumer's use passing through the phases of distribution and storage (66).

As a final step in meeting responsibility for the stability of drugs compounded or dispensed, the pharmacist is obligated to inform the patient regarding the proper storage conditions (for example, in a cool dry place ---- not in the bath room), for both prescription and non-prescription products, and to provide a reasonable estimate of the time after which the medication should be discarded. When expiration dates are applied, the pharmacist should emphasize to the patient that the dates are applicable only when proper storage conditions are used. Patients should be encouraged to clean out their drug storage cabinets periodically. (5)

Compounded products pose a new set of concerns, because the pharmacist does not always have extensive stability data. Trissel has proposed some stability monographs of a number of compounded drug products (67). The stability of compounded products is defined to be the same as that of manufactured products, officially in USP (35). Compounded preparations should be packaged in containers meeting USP standards. The information regarding the containers for packaging is dealt in detail in Sections <661> and <671> of USP 23.

The safety, efficacy, and other quality attributes of compounded preparations depend on correct ingredients and calculations, accurate and precise measurements, appropriate formulation conditions and procedures, and prudent pharmaceutical judgement. The pharmacist should review each procedure in the compounding process to ensure accuracy and completeness, the pharmacist should be prepared to conduct such tests as may be necessary for any given product (68).

Beyond-use-date

The ICH Stability Guidelines (1993) provides uniform test conditions of temperature and humidity for stability testing of drug substances and products (69,70). With the establishment of these uniform test conditions of temperature and humidity for stability testing, a re-examination of beyond-use dating proposals from 1991 had taken place and the revised form was published in 1996. (71)

The beyond-use date is a means of making available to pharmacists some reliable information for indicating to patients the date after which a prescribed medication should not be used. The beyond-use date applies to all the medications which are not directly from manufacturers such as repackaged and/or compounded and dispensed by the

pharmacist. Because compounded preparations are intended for administration immediately or following short term storage, their beyond-use dates may be assigned based on criteria which are not always identical to those used in assigning expiration dates for manufactured drug products. Beyond-use dates should be assigned conservatively.

The pharmacist is responsible to allot a justifiable beyond-use date for the compounded / dispensed product based on reliable information such as that available from pharmaceutical manufacturers or literature on the compounded product's stability or from USP. All stability data must be carefully interpreted in relation to the actual compounded formulation. In addition to using all available stability information, the pharmacist will also use his or her pharmaceutical education and experience in allotting the beyond-use date for the compounded formulations.

Bailey and Medwick reported the available methods of securing data on which to base a beyond-use date (72,73). The manufacturers may conduct the "open dish" studies (apart from other stability studies) to obtain the data needed to provide the pharmacist with the information on dispensing container selection and beyond-use date recommendations for solid dosage forms. The open dish study is a study in which the dosage forms are exposed to 60%RH at 25 ^{0}C for 30 days without any container protection: three samples of 30-unit doses from one lot are analyzed at 0 and 30 days. A detailed procedure for conducting the open-dish studies was published in PF. (74)

In the absence of stability information that is applicable to a specific drug preparation, it is recommended that for non-sterile non-aqueous liquids and solid formulations that maximum beyond-use date not later than 25% of the time remaining

until the product's expiration date or 6 months, whichever is earlier (when packed in tight, light resistant containers and stored at CRT unless otherwise indicated). For non-aqueous formulations, a maximum period of 14 days is recommended as beyond-use date when stored at cold temperatures.

Federal law requires that the label on the container or package of an official compounded preparation must bear a beyond-use date. Good pharmacy practice dictates beyond-use labeling for all compounded preparations.

CONCLUSION

Pharmaceutical scientists and regulators may justifiably fed a sense of achievement when they review the progress which has been made in stability testing in recent decades. The increasing attention now being given to the possible effects of storage and transport on the stability of pharmaceutical products (manufactured or compounded) is well-deserved and will, hopefully, lead to a improved level of confidence about the quality of drug products when such items are supplied to patients.

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Table I: World climatic zones based on their MKTs and relative humidities.

Climatic zone		Definition	Storage condition
Zone1	N.Europe	Temperate	21 ^{0}C /45%RH
Zone2	S.Europe, Japan,US	Mediterranean	25 ^{0}C /60%RH
Zone3	Sahara	Hot and dry	30 ^{0}C/35%RH
Zone4	Central Africa,Indonesia etc.	Hot and wet	30 ^{0}C/70%RH

Table II: Criteria and guide values for assignment of a city to the correct climatic zones

Criteria	Guide values for Individual climatic zone			
	I	II	III	IV
Mean annual temperature measured in the open air	Up to 15 ^{0}C	>15-22 ^{0}C	>22 ^{0}C	>22 ^{0}C
Calculated mean annual temperature (<19 ^{0}C)	Up to 20.5 ^{0}C	>20.5-24 ^{0}C	>24 ^{0}C	>24 ^{0}C
Mean annual water vapor partial pressure	Up to 11 mbar	>11-18 mbar	Up to 15 mbar	>15 mbar

MANUSCRIPT II

Effects of Temperature Spikes on Mean Kinetic Temperature and Shelf Life

❋ Submitted for publication in *Pharmacopeial Forum*

Abstract

The international acceptance of the definition of Controlled Room Temperature (CRT) has given additional impetus to the use of Mean Kinetic Temperature (MKT) as a method of quantifying temperatures during transport and storage and consequent possible effects on drug product stability. The present paper explores some of the implications of the MKT concept and considers the effect of temperature spikes on MKT values and hence on stability of drug products.

INTRODUCTION

The USP definition of Controlled Room Temperature, CRT, is: "A temperature maintained thermostatically that encompasses the usual and customary working environment of 20 ^{0}C to 25 ^{0}C that results in a Mean Kinetic Temperature calculated to be not more than 25 ^{0}C, and that allows for excursions between 15 ^{0}C and 30 ^{0}C that are experienced in pharmacies, hospitals, and warehouses."

MKT (1) is defined as the isothermal temperature that corresponds to the kinetic effects of a time-temperature distribution and determined using Haynes' formula (2) into which temperature data obtained at defined intervals are entered. The MKT equation is shown as follows:

$$MKT = (\Delta H/R)/ (-\ln ((e^{-\Delta H/RT1} + e^{-\Delta H/RT2} + \ldots\ldots + e^{-\Delta H/RTn}) / n))$$

USP has proposed a method of calculating MKT, which enters the 52 weekly arithmetic means of the highest and lowest temperatures recorded over the preceding 52 weeks for the calculation of a yearly MKT (3). The FDA recommends that, for manufacturers, repackagers, and warehouses, all data points obtained be inserted directly into the equation. A minimum of 104 weekly high and low readings recorded over the preceding 52 weeks would be inserted into the MKT equation to calculate a yearly MKT (4,5,6,7)

In the present paper we consider some of the implications of MKT for the stability of drug products. In particular, we explore the effect of temperature "excursions" or temperature spikes on the shelf life of drug products.

THEORY

The USP definition of CRT is most useful. However, one question that has been raised by a number of persons, including some of the participants at the 4 June 1998 USP Open conference on Packaging, Storage and Distribution, is: "How long in time can the excursions in temperature up to 30 ^{0}C be before it is likely that there will be a serious adverse effect on drug product stability?" In particular: "Is it likely that for some products the total effect of a number of temperature excursions will be such as to invalidate a previously assigned expiration date or beyond-use date?" Further: "What are the factors which may make some pharmaceutical products more sensitive than others to the adverse effects of temperature spikes of up to 30 ^{0}C?"

The form of the Arrhenius equation used by Grimm (6) in his calculation of MKT assigns an Energy of Activation of 83kJ/mole. This value was obtained by Grimm from a survey which he made of literature reports the Energy of Activation for a variety of drugs as being a mode or average value. Obviously, products with energies of activation which are significantly different from the Grimm average will show differing susceptibilities to changes in temperature such as are qualified by MKT determinations.

Where solvolysis is the route of degradation the Grimm value is probably more than reasonable and, of course, hydrolysis is a very common mode of degradation. However, for drug products for which oxidation is the primary route of degradation the energy of activation will be significantly less, values of the region of about 20 to 50 kJ/mole are not unlikely. Drug products, which have, lower than average energies of activation will be less sensitive to temperature stress than the Grimm average.

Conversely, there are drug products which degrade by mechanisms characterized by energies of activation substantially greater than 83kJ/mole. Such products will be more sensitive than the Grimm average to temperature stress.

The normal conventional method of determining a shelf life (SL) for a pharmaceutical product is to determine the intersection of the 95% confidence bound for the isothermal (storage temperature) regression line with the 90% potency value. The time given by such an exercise is the *maximum, which* can be assigned as the shelf life. In practice this period determined (termed by A.J. Smith) as the conformance period (CP) is often substantially greater than the shelf life. Thus suppose we determined that conformance periods were 1.1, 12.2, and 38.0 months, for three different products, it is likely that the respective shelf lives would be 1, 12 and 36 months. The difference between the conformance period and the assigned shelf life, in effect, provides an additional safety margin with respect to stability. Of course, since conformance periods are not normally publicly available it is not east to quantify the extent of this extra margin of safety for any given product.

METHODS

The data used in this paper were computer generated. In the studies of the effect of temperature spikes on MKT and hence shelf life we used idealized square wave spikes such that temperature is deemed to rise instantaneously (Fig.1). (Some limitations of this model are considered in a later part of this paper). For example, for a one month spike we select a virtual product stored isothermally at exactly 25 ^{0}C and cause the temperature to instantaneously increase to 30 ^{0}C. At the end of one month the temperature is required to revert instantaneously to the former value of 25 ^{0}C. Knowledge of the time for which the product was subjected to 30 ^{0}C allows us to calculate the MKT for products with different energies of activation, shelf lives or conformance periods. With the new calculated MKT we are able to determine whether or not the new MKT has adversely affected the shelf life of the product, assuming a first order degradation process.

RESULTS AND DISCUSSIONS

Table I shows the effect of a one month 30 ^{0}C spike on MKT values of systems all of which have a baseline storage temperature of 25 ^{0}C and an activation energy of 83 kJ/mole. As can be seen if the conformance period is slightly greater than the assigned shelf life the spike stress is not sufficient to invalidate the shelf life. However, when the shelf life is exactly equal to the conformance period the MKT (calculated to include the effect of the spike) is in excess of 25 ^{0}C and thus assigned shelf life is now invalid.

Table II shows the effect of varying energy of activation on spike effects for two sets of system, one with SL of 1 month and the second with SL values of 12 months. It can be seen that the spike effects on MKT are indeed somewhat dependent on the value of activation energy. Thus, for systems with a SL of 12 months the effect of the spike on the MKT is 0.45 ^{0}C for products with an energy of activation of 55kJ/mole. This effect is not large and thus suggests that in most cases the use of the Grimm average for the energy of activation is unlikely to lead to major error.

Table III shows the effect of increasing spike stress from 0.01 months (i.e. about 7 hours) at 30 ^{0}C to 2 months at 30 ^{0}C. As can be seen for the smallest spike the effect on MKT values is almost negligible even for products which only have a shelf life of 1 month. As the length of the spike is increased the effect on MKT values, especially for the systems with short shelf lives, becomes, increasingly significant.

The data presented in Tables I, II and III is all derived for systems with a baseline storage temperature of 25 ^{0}C. This is, of course, a worst case scenario. Table IV shows results for various spike stress, and shelf lives when the baseline temperature is 22.5 ^{0}C (i.e. in the middle of the 20-25 ^{0}C range). As can be seen, with the exception of two one

month shelf life systems, the MKT values all remain under 25 ^{0}C even with a 2 month 30^{0}C spike.

Table V shows comparable data for a best case scenario for systems with a baseline storage temperature of 20 ^{0}C. As would be expected such systems are especially resistant to the adverse effect of spike stress although even in this case some of the one-month shelf life products are adversely affected by the longer spikes.

In all the calculations presented in this paper we have assumed that the degradation process was governed by first order kinetics. Calculations have shown that using zero order degradation kinetics does not affect the conclusions reported in this paper.

Obviously, the square wave model used for the calculations reported in this paper is not likely to exist in actuality. However, it is suggested that, although the model has limitations, conclusions drawn from the use of this model are highly likely to be applicable to real storage conditions. In Fig.1 we show a square wave and a non-square wave spike which have the same amount of energy input (i.e. area under the temperature time curve from the baseline). Because of the logarithmic nature of the Arrhenius relationship the MKT of the square wave is slightly higher than that of the spike for the period Ts. However, the effect is small and thus it is legitimate to use the square wave model for studies of this type. Certainly, for investigations designed to elucidate the relative effects of such values as conformance periods, shelf lives or energies of activation as described in this paper this model is valid.

It is recognized that temperatures recorded in a storage area, at some detector location, will not always necessarily reflect the actual temperature of pharmaceutical

products stored in the area. Depending on the nature of the heating/air conditioning system and airflow efficiency in the area there may be cold spots or hot spots. Certainly, if a storage area is overcrowded with packages airflow will probably be seriously impaired. Thus, it is important that all warehouses or other storage areas used for pharmaceutical products should not be overloaded and should allow a free flow of air in all parts of the unit. The thermodetector used as the temperature probe for a warehouse or other unit should be placed at a location which may reasonably be regarded as representative of the average temperature. When there is any doubt on this point a conservative approach should be used. Thus, place the detector higher in the room rather than closer to the floor.

When continuous monitoring of temperature is obtained, as for example, with chart recorders there may be some quite transient spikes-caused perhaps by leaving a door open - which may have very little effect on the temperature of drug products stored in the area. All products have a finite thermal capacity and thus, for example, a liter glass bottle of aqueous injection has a specific heat of about 5 kJ per ^{0}C. A current of warm air at 30 ^{0}C flowing over this bottle, even if it does not have an overwrap or other pack, would have little effect on the temperature of the product if the exposure to the warm air was for a short period.

A question that naturally comes to mind when we consider the effect of temperature spikes on drug product stability is: Do n 30 ^{0}C, 1 hour spikes have the same adverse effect on drug product stability as one 30 ^{0}C, n hour spike? Using the model developed in this paper the answer is: Probably yes, at least in a semi-quantitative way for chemical degradation. However, for some physical changes e.g. loosening of a plastic

cap the answer to the question No. Cap loosening and some other adverse physical changes are more affected by temperature change *per se* rather than MKT.

CONCLUSION

The effect of temperature spikes on MKT has been evaluated. It appears that for systems with a baseline storage temperature of 22.5 ^{0}C total spikes equivalent to 2 months at 30 ^{0}C may be tolerated if he shelf life is 12 months or more. If the baseline storage temperature is more than 22.5 ^{0}C or the shelf life is less than 12 months then adverse affects on the validity of the assigned shelf life are more likely. It is highly improbable that a single 30 ^{0}C spike of seven hours or less would adversely affect the shelf life of any otherwise normal product.

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Table I: **Effect of a 1 month 30 ^{0}C spike on the Shelf life of drug products all of which have an activation energy of 83 kJ/mole.**

Conformance Period (CP) (months)	*Shelf life (SL) (months)*	*MKT including spike (^{0}C)*	*New CP (months)*	*Is Shelf life still acceptable?*
1.000	1.000	30.000	0.575	✗
12.00	12.00	25.532	11.31	✗
24.00	24.00	25.270	23.37	✗
28.00	24.00	25.232	27.29	✓
36.00	36.00	25.181	35.28	✗
39.00	36.00	25.167	38.21	✓
41.00	36.00	25.159	40.28	✓
62.00	60.00	25.105	61.28	✓
65.00	60.00	25.100	64.28	✓

✗ - SL is not valid after spike

✓ - SL is still acceptable

Table II: **Effect of activation energy on the Shelf life of products subjected to a one month 30 ^{0}C spike.**

Activation energy (ΔH) (kJ/mole)	*MKT including spike (^{0}C)*	*New CP (months)*	*Is Shelf life (SL) still acceptable?*
System with 1.0 month SL and CP of 1. 1 month.			
55	29.608	0.785	✗
70	29.625	0.715	✗
95	29.650	0.611	✗
110	29.665	0.555	✗
120	29.674	0.521	✗
System with 12.0 months SL and CP of 13.0 months.			
55	25.450	12.57	✔
70	25.472	12.43	✔
95	25.511	12.17	✔
110	25.537	12.00	✔
120	25.554	11.88	✗

✗ - SL is not valid after spike

✔ - SL is still acceptable

Table III: **Effect of spike duration on Shelf life for products with an activation energy of 83 kJ/mole with a baseline at 25 ^{0}C**

Conformance Period (CP) (months)	*Shelf life (SL) (months)*	*MKT including spike (^{0}C)*	*New CP (months)*	*Is Shelf life still acceptable?*
Spike for 0.01 month at 30 ^{0}C				
1	1	25.065	0.993	✗
12	12	25.005	11.99	✗
24	24	25.003	23.99	✗
36	36	25.002	35.99	✗
Spike for 0.1 month at 30 ^{0}C				
1	1	25.635	0.931	✗
12	12	25.055	11.93	✗
24	24	25.027	23.93	✗
36	36	25.018	35.93	✗
Spike for 0.5 month at 30 ^{0}C				
1	1	27.820	0.731	✗
12	12	25.270	11.64	✗
24	24	25.136	23.64	✗
36	36	25.091	35.64	✗
Spike for 1 month at 30 ^{0}C				
1	1	30.000	0.576	✗
12	12	25.532	11.31	✗
24	24	25.270	23.29	✗
36	36	25.181	35.28	✗
Spike for 2 months at 30 ^{0}C				
12	12	26.035	10.69	✗
24	24	25.532	22.61	✗
36	36	25.358	34.59	✗

✗ - SL is not valid after spike

✔ - SL is still acceptable

Table IV: **Effect of spike duration on Shelf life for products with an activation energy of 83 kJ/mole with a baseline at 22.5 ^{0}C**

Conformance Period (CP) (months)	*Shelf life (SL) (months)*	*MKT including spike (^{0}C)*	*New CP (months)*	*Is Shelf life still acceptable?*
Spike for 0.01 month at 30 ^{0}C				
1	1	22.614	1.310	✔
12	12	22.510	15.91	✔
24	24	22.505	31.84	✔
36	36	22.503	47.77	✔
Spike for 0.1 month at 30 ^{0}C				
1	1	23.578	1.174	✔
12	12	22.595	15.76	✔
24	24	22.548	31.68	✔
36	36	22.532	47.61	✔
Spike for 0.5 month at 30 ^{0}C				
1	1	26.966	0.803	✘
12	12	22.965	15.11	✔
24	24	22.735	31.01	✔
36	36	22.657	46.94	✔
Spike for 1 month at 30 ^{0}C				
1	1	30.000	0.576	✘
12	12	23.407	14.37	✔
24	24	22.965	30.21	✔
36	36	22.812	46.11	✔
Spike for 2 months at 30 ^{0}C				
12	12	24.234	13.08	✔
24	24	23.407	28.73	✔
36	36	23.114	44.56	✔

✘ - SL is not valid after spike

✔ - SL is still acceptable

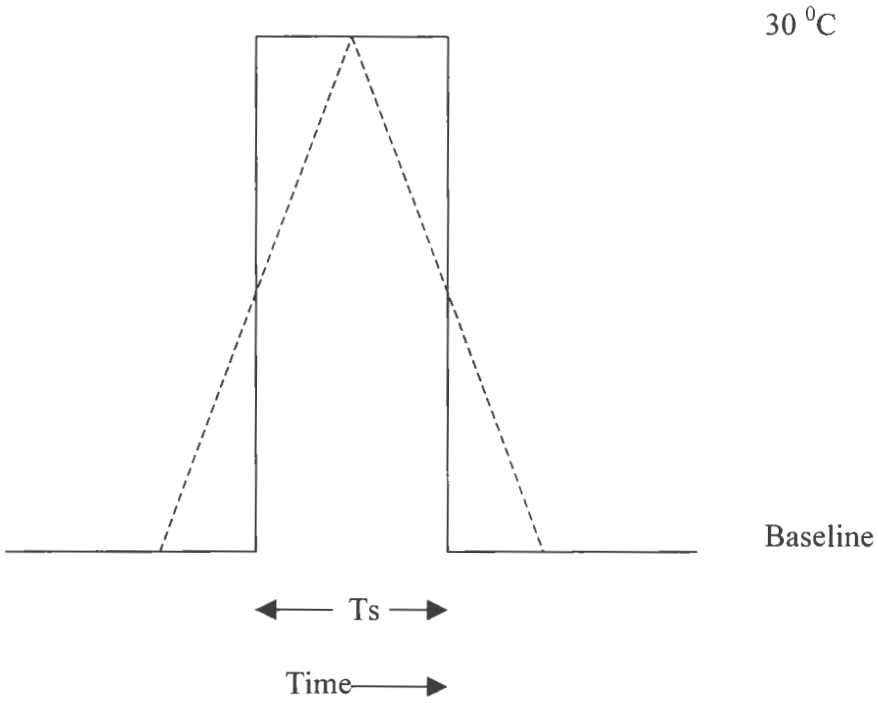
Table V: **Effect of spike duration on Shelf life for products with an activation energy of 83 kJ/mole with a baseline at 20 ^{0}C**

Conformance Period (CP) (months)	*Shelf life (SL) (months)*	*MKT including spike (^{0}C)*	*New CP (months)*	*Is Shelf life still acceptable?*
Spike for 0.01 month at 30 ^{0}C				
1	1	20.177	1.734	✔
12	12	20.015	21.21	✔
24	24	20.007	42.45	✔
36	36	20.005	63.69	✔
Spike for 0.1 month at 30 ^{0}C				
1	1	21.632	1.466	✔
12	12	20.148	20.88	✔
24	24	20.074	42.12	✔
36	36	20.050	63.36	✔
Spike for 0.5 month at 30 ^{0}C				
1	1	26.258	0.869	✘
12	12	20.716	19.55	✔
24	24	20.365	40.73	✔
36	36	20.245	61.94	✔
Spike for 1 month at 30 ^{0}C				
1	1	30.000	0.576	✘
12	12	21.379	18.11	✔
24	24	20.716	39.10	✔
36	36	20.483	60.26	✔
Spike for 2 months at 30 ^{0}C				
12	12	22.579	15.79	✔
24	24	21.380	36.22	✔
36	36	20.942	57.15	✔

✘ - SL is not valid after spike.

✔ - SL is still acceptable.

Fig 1. Variation of temperature with time for a spike.



Key:

Solid line - square wave
Dotted line - spike

MANUSCRIPT III

Some Studies of the Stability of Compounded Cefazolin Ophthalmic Solution

* Accepted for publication in *International Journal of Pharmaceutical Compounding*

Abstract

The chemical stability of three compounded batches of Cefazolin Ophthalmic Solution was monitored by a stability-indicating HPLC assay. The degradation was governed by first-order kinetics, and the effect of temperature on reaction rate was in accordance with the Arrhenius equation at and above 17 ^{0}C. Although the stability of all the three batches was essentially the same, buffering the formulations may be useful. Even using a most cautious and conservative approach to the assignment of Beyond-use date for this type of product, it appears that if the product is stored at Controlled Room Temperature a Beyond-use date of six days would be fully justifiable. If the product is stored in a refrigerator, then a Beyond-use date of fourteen days could be assigned.

I. INTRODUCTION

The recent resurgence in compounding activities by a substantial number of US pharmacists (1) and the passage by the Congress of the 1997 Food and Drug Administration Modernization Act have been factors, that have increased the attention being given to the stability of pharmacist compounded (as distinct from manufactured) pharmaceutical products. Concurrent with these developments is an increased concern about the suitability of storage and packaging during distribution. Thus, the use of the concept of Mean Kinetic Temperature as a means to monitor pharmaceutical warehouses has gained the attention of regulators in both the European Union and the United States (2,3). Many pharmaceutical scientists recognize that success in assuring the quality of many pharmaceutical products at the time of preparation means that it is now appropriate to devote more attention to the quality of products during storage and distribution (4). Cefazolin sodium is a broad-spectrum β-lactam anti-bacterial drug closely related to penicillin (5). Cefazolin sodium is often administered topically to the eye to treat ocular and peri-ocular infections (6,7). Although the ointment form of cefazolin sodium would provide longer contact with ocular tissues, the solution form can be more conveniently used. However, a potential problem of stability of cefazolin sodium in aqueous solution exists. Cefazolin stability is influenced primarily by pH and temperature (8). Formulation is accomplished by reconstituting Cefazolin sodium in 0.9% sodium chloride solution (9) without pH adjustment or buffering.

In the present paper we report preliminary studies of the chemical stability of Cefazolin Sodium Ophthalmic Solution. Three batches were prepared and samples were stored isothermally at 7^{0}, 17^{0}, 25^{0} and 40^{0}. A specific HPLC stability-indicating assay

was used to determine the potency of the samples, and the raw experimental data were transformed using conventional kinetic and statistical methods so that estimates of Beyond-use-date could be made.

II. EXPERIMENTAL

Chemicals: USP Cefazolin RS Lot J; cefazolin sodium, Ancef®, SmithKline Beecham; 0.9% sodium chloride injection, USP, Abbott Laboratories; thimerosal [Mercury,ethyl(2-mercaptobenzoato-S)-,sodium salt], USP/NF, Gallipot; sodium phosphate dibasic anhydrous, Ultrapure Bioreagent grade, J.T.Baker; citric acid monohydrate, ACS reagent grade, J.T.Baker; potassium phosphate monobasic, Sorensen grade, Fisher Scientific; acetonitrile, high purity solvent, Burdick and Jackson; Milli-Q® water, Millipore.

Equipment: Spectra Physics Model 8800 ternary pump using a gradient mobile phase pumping program; Waters Model 991 photodiode array HPLC detector; Waters Millenium Software version 2.10; Waters Model 717 Plus autosampler with temperature of 4 ^{0}C and 10-µl injection; Waters µBondapak C18 column, 10-µm, 30-cm X 3.9-mm; Scientific Resources Inc. Model 83099Rc column temperature controller set at a temperature of 25 ^{0}C; Millipore HVLP 0.45-µm filters used for buffer preparation; Sterile Dropper bottles.

Formulation Preparation: The preparation of the ophthalmic solution followed the procedure in the preview of a new pharmacy compounding monograph of Cefazolin Ophthalmic Solution (9). The preparation steps are as follows:

Diluent: A 2-mg portion of Thimerosal was added to a 100-mL bottle of 0.9% sodium chloride injection and mixed well.

Cefazolin Ophthalmic Solution (COS): The COS formulation specifies that 10 mL of a 50mg/mL solution of cefazolin sodium in *Diluent* be made. Dissolve 500mg of Cefazolin sodium (Ancef®) in 10 mL of *Diluent.* A 7.0-mL aliquot of this solution is then diluted to 100 mL (3.5mg/mL) with *Diluent.* The solution is then transferred to the sterile

ophthalmic dropper bottles (3 mL) and stored at four different temperatures (7^0, 17^0, 25^0 and 40 ^{0}).

Solutions for Gradient HPLC assay procedure:

pH 3.6 Buffer: A 0.9 g portion of anhydrous sodium phosphate dibasic and 1.298 g of citric acid monohydrate were dissolved and diluted to 1000 mL with water. This solution was filtered through a Millipore HVLP 0.45-μm membrane filter.

pH 7.0 Buffer: A 5.68 g portion of anhydrous sodium phosphate dibasic and 3.63 g portion of potassium phosphate monobasic were dissolved and diluted to 1000 mL with water. This solution was filtered through a Millipore HVLP 0.45-μm membrane filter.

Standard preparation: A 35-mg portion, accurately weighed, of USP Cefazolin Reference Standard was transferred to a 10.0-mL low actinic volumetric flask and dissolved and then diluted to volume with pH 7.0 Buffer. A 1.0-mL portion of this solution was transferred to a 10.0-mL low-actinic volumetric flask and diluted to volume with pH 7.0 Buffer.

Assay preparation: A 1.0mL aliquot of the COS preparation was transferred to a 10.0mL low-actinic volumetric flask and diluted to volume with pH 7.0 Buffer for all the 3 batches. All injections were performed in triplicate.

Pump gradient program: The flow rate was maintained at 2.0 mL per minute throughout the run. The column was equilibrated with pH 3.6 Buffer. After the injection, the gradient change to acetonitrile is completed in 15 minutes. The column is then equilibrated back to pH 3.6 Buffer for 10 minutes before the next injection.

Pump Gradient Program Table:

Time (min)	pH 3.6 Buffer (%v/v)	Acetonitrile(%v/v)
0.0	90	10
15.0	20	80
15.1	90	10
25.0	90	10

III. RESULTS AND DISCUSSION

Fig.1 shows some typical plots of percentage drug remaining as a function of time. The results for all three batches at all four temperatures appeared similar. The correlation coefficients for the three batches A, B and C were 0.84, 0.84, & 0.70 at 7^0, 0.94, 0.96, & 0.81 at 17^0, 0.99, 0.99, & 0.96 at 25^0, and 0.99, 0.99 & 0.99 at 40^0, the degrees of freedom being six. The high correlation of percentage remaining and time at 17^0, 25^0, and 40^0 provided strong evidence that the degradation was governed by first-order kinetics. (The relatively low r values at 7^0 and 17^0 reflected the low extent of reaction during the brief study period: the percentage of drug remaining was almost independent of time. The correlation coefficient approaches zero, as the y value becomes less dependent on the x value, in this case time. The analysis was further confounded by the possibility of a competing reaction (vide infra).)

Table I records the calculated first-order rate constants for the three batches. The scatter in the apparent rates may reflect the unbuffered nature of the formulation. The drug substance is a β-lactam, which should be susceptible to alkaline hydrolysis. Cefazolin sodium is also an aliphatic carboxylate salt, a simple solution of which would be poorly poised with respect to pH. The alkaline nature of this salt would make the product solution susceptible to partial neutralization due to absorption of atmospheric carbondioxide and thus to significant interbatch variation in pH. Such variation in hydroxyl-ion activity would alter the hydrolytic degradation rate. This suggests the desirability of buffering this type of formulation. Fig. 2 depicts the corresponding Arrhenius plots. While the correlation coefficients for these plots were close to unity, the residuals clearly showed that the linear model failed at 7^0. This suggests that a different

decomposition mechanism predominated at the lowest temperature. (10) Without the 7^{0} data, the correlation coefficients for the three batches A, B, and C were 0.99, 0.99, and 0.99 (two degrees of freedom), which provided strong evidence that the effect of temperature on the degradation was in accordance with the Arrhenius equation. Table II lists the values of Arrhenius parameters for the three batches. Although the activation energies (Ea) were not detected as being statistically different at the 95% confidence level, further work would be necessary to demonstrate this conclusively. Using the data obtained at 7^{0} and 25^{0} estimates have been made from the lower 90%confidence bounds of the conformance periods for all three batches (Irrespective of mechanism the 7^{0} data are reliable). Table III presents the results of this statistical evaluation, and Fig. 3(a) & Fig. 3(b) show the example of the type of plot that was obtained. (The conformance period is defined as the time at which the 90% lower confidence bound intersects with potency value of 90% of label claim).

Since at 7^{0}, the degradation proceeded so slowly that the loss of potency never reached 10%, we cannot estimate the precise value of the conformance period. For all three batches it is clearly significantly in excess of fifteen days, which might therefore be a reasonable Beyond-use-date for products stored in a refrigerator. At 25^{0} a Beyond-use-date of six days might well be regarded as acceptable.

IV. CONCLUSION

The data reported in this paper are limited, pertaining only to three batches made at the same site. Nevertheless, it does appear that if this product were stored in a refrigerator, a Beyond-use-date of two weeks would be judiciously conservative.

Acknowledgements : One of the authors, Brahmaiah Kommanaboyina thanks USP for the award of Summer Fellowship. We thank Dr. P.White, Dr.J.Krasowski, Mr.A.Manna, Mrs.B.Voigt and Mrs.Y.Johnson, who developed and validated the stability-indicating assay for Cefazolin in the Drug Research and Testing Laboratory of the United States Pharmacopeial Convention, Inc.

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4. Carstensen, J.T. and Rhodes, C.T., *Clinical Research and Drug Regulatory Affairs*, 10: 177-185 (1993).
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9. Cefazolin Ophthalmic Solution. *Pharmacopeial Forum*. 23(3), 6188, May-June 1998.
10. Woolfe, A.J. and Worthington, H.E.C., *Drug Develop. Commun.*, 1: 185 (1974).

TableI: Degradation rate constants ($hr^{-1} *10^3$)

Batch	7 ^{0}C	17 ^{0}C	25 ^{0}C	40 ^{0}C
A	0.115	0.207	0.461	3.224
B	0.138	0.207	0.461	3.224
C	0.092	0.138	0.690	3.450

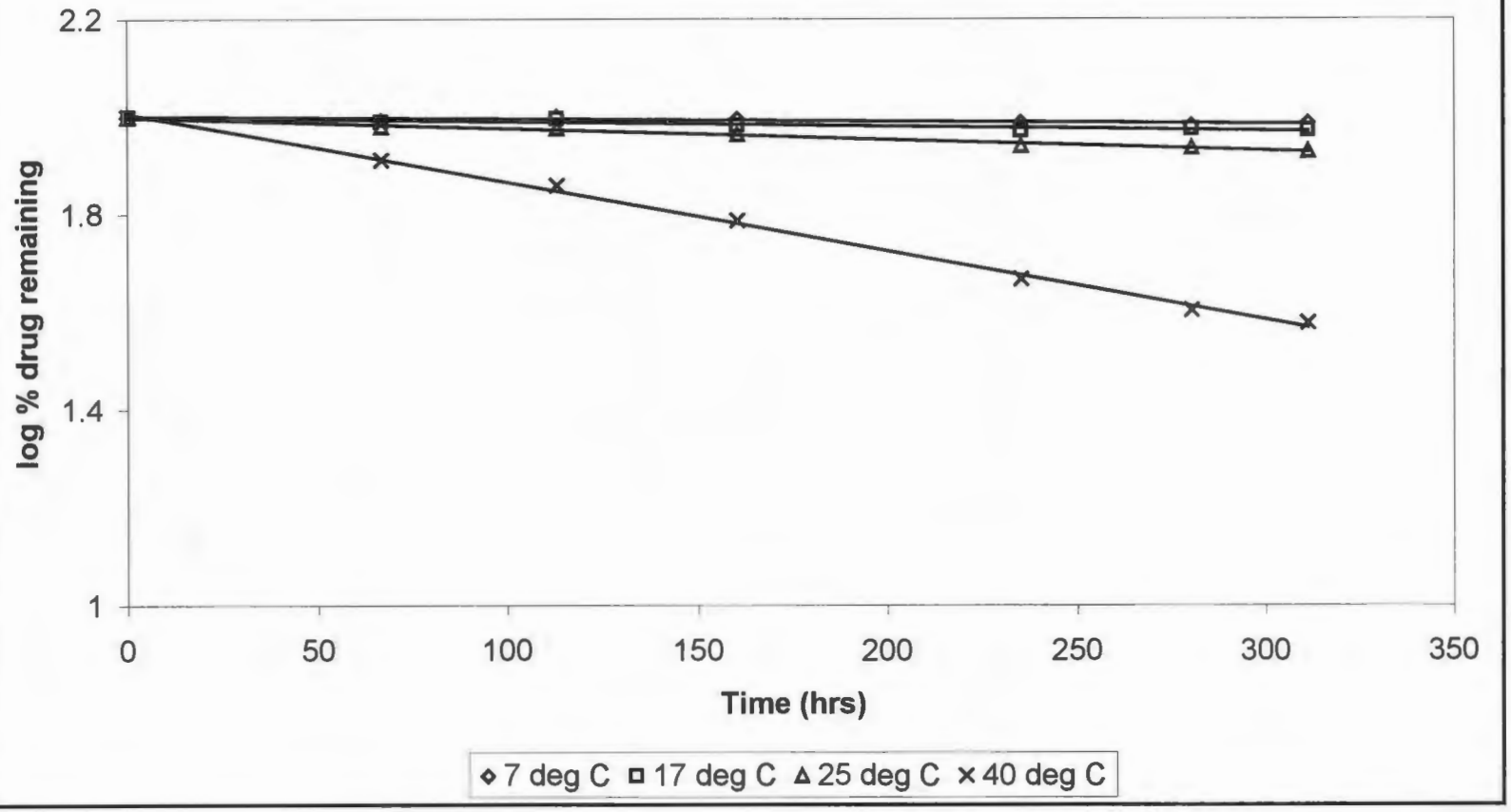
Table II: Values of Arrhenius parameters

	A	B	C
Activation energy (kJ/mole)	91.5	91.5	103
Frequency factor (/hrs)	5.28E+12	5.28E+12	6.28E+14

Table III: Conformance periods in days

Temperature	Batch A	Batch B	Batch C
7 ^{0}C	15+	15+	15+
25 ^{0}C	7.7	7.3	7.7

Figure 1: Plot of the log % drug remaining as a function of time at 7, 17, 25 & 40 deg C for batch A



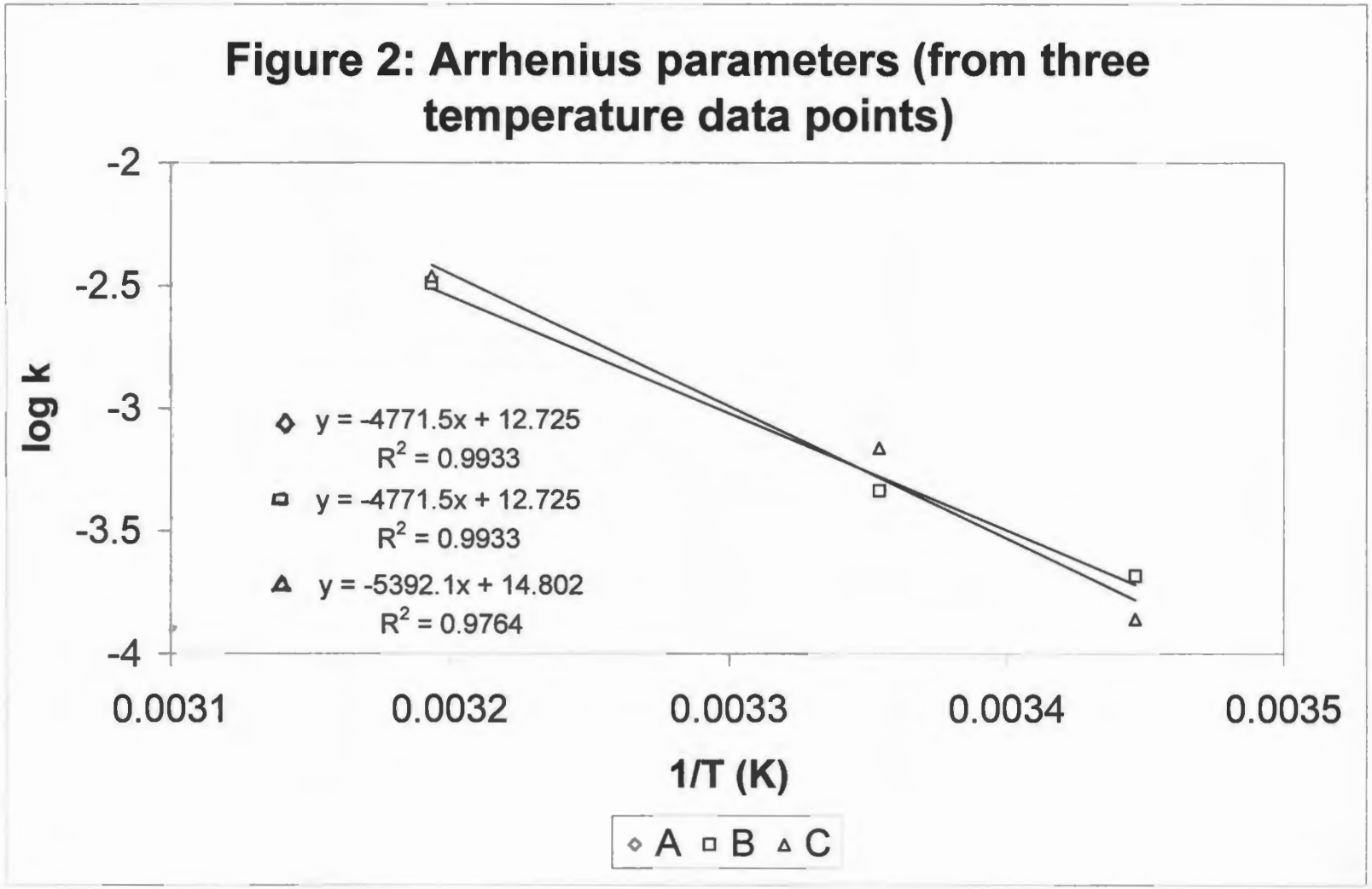


Figure 2: Arrhenius parameters (from three temperature data points)
-2
-2.5
-3
-3.5
-4
log k
y = -4771.5x + 12.725
R2 = 0.9933
y = -4771.5x + 12.725
R2 = 0.9933
y = -5392.1x + 14.802
R2 = 0.9764
0.0031
0.0032
0.0033
0.0034
0.0035
1/T (K)
A B C

Figure 3(a): Prediction of Beyond-use date at 7 deg C for batch A

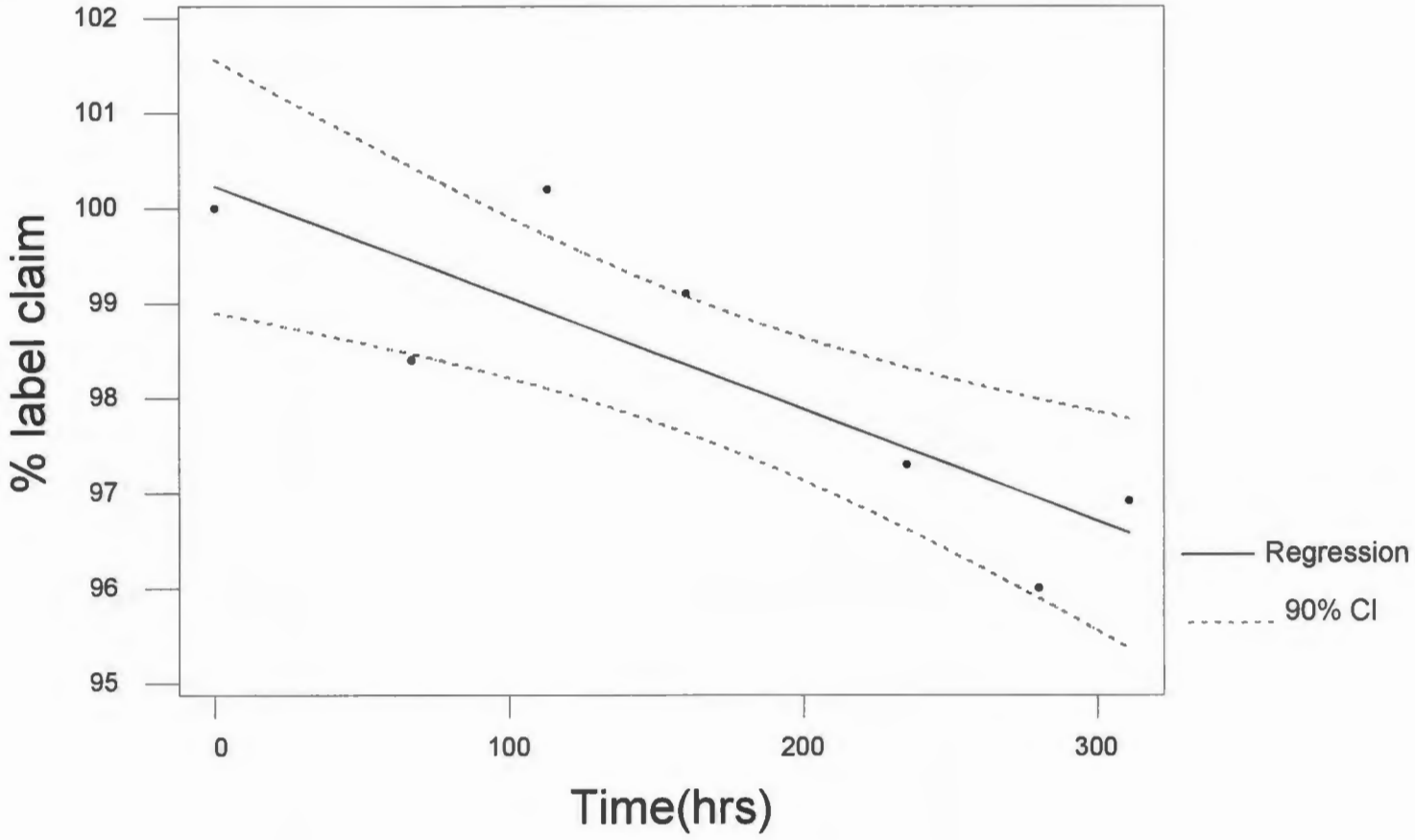
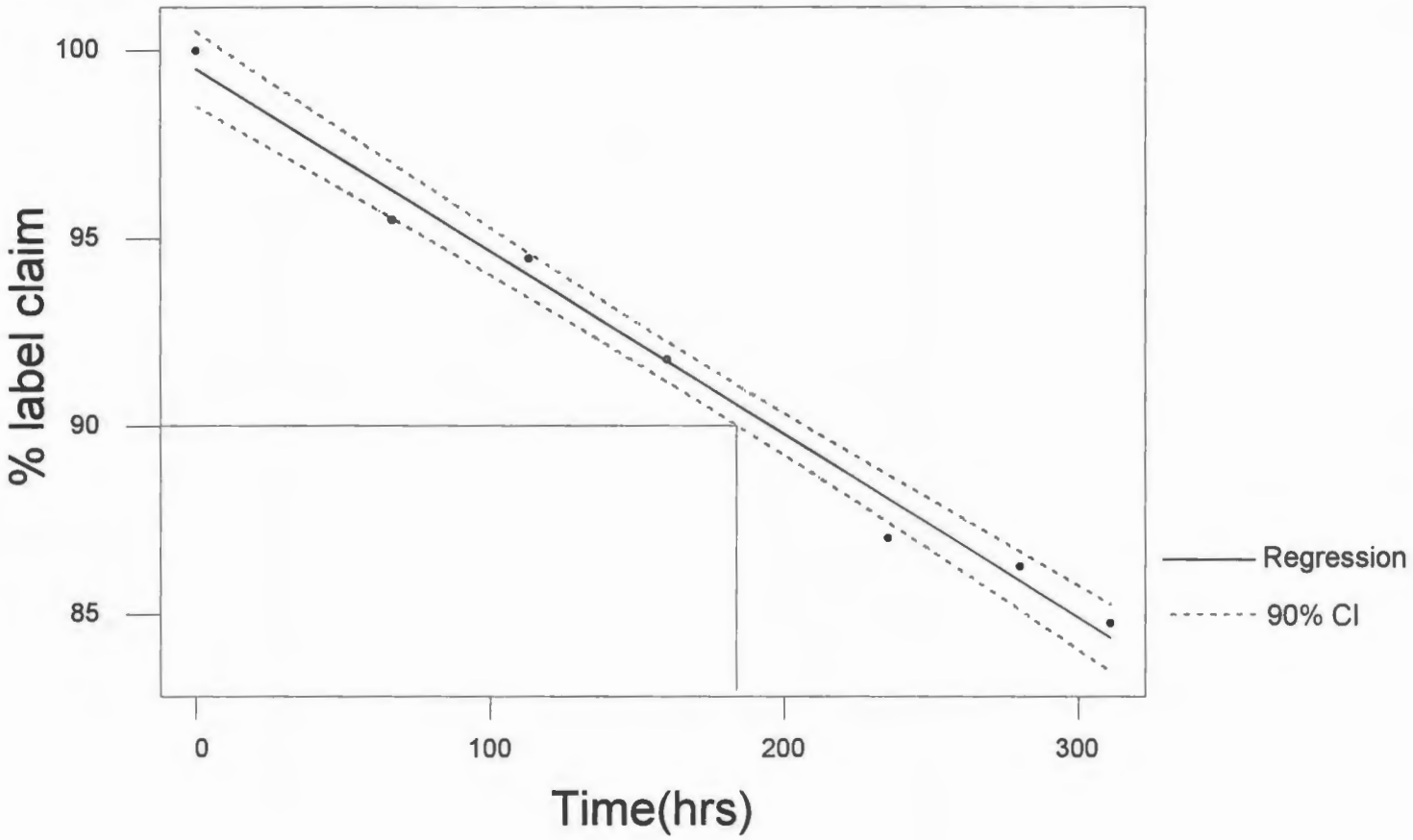


Figure 3(b): Prediction of Beyond-use date at 25 deg C for batch A



MANUSCRIPT IV

Potential of known individual single tablet assay by near-IR for the assignment of shelf-life

* *To be submitted for publication*

During the past decade or so the use of near-IR for pharmaceutical purposes has substantially increased (1). Since it is possible to use near-IR for non-destructive determination of the stability of known individual tablets, there is an exciting possibility of using the near-IR in stability studies which have a substantially improved precision compared to conventional methods.

The normal method of assigning a shelf life often consists in essence of the following exercise. Data on percentage label claim, obtained by use of a stability indicating assay, is plotted as a function of time and the regression line and its 90% confidence bounds determined by conventional statistical methods. The intersection of the lower 90% confidence bound and the 90% potency line is used to determine the conformance period (i.e. the time at which a 95% level of assurance the product is still of acceptable potency). Since conformance periods are often non-integral values we normally round down from a conformance period to obtain the shelf life which we assign to the product. Thus, if we obtain a conformance period of 28.7 months we would probably assign a two-year shelf life to the product.

The wider the 90% confidence envelope round the mean regression line is the shorter the conformance period will be. Thus anything which can be done to improve the precision of the data from which the regression line is obtained has the potential of significantly improving the shelf life of pharmaceutical products, without any change to formulation or processing variables.

When there are significant differences between the near IR spectrum of a parent drug and its degradation products there is the possibility of developing a near IR stability indicating assay for tablets containing the drug. Since the near IR method can be used as a non-destructive method it is possible to use the same tablet repeatedly. Further if the individual tablet used can be identified the stability data has the potential to significantly lengthen a products shelf life.

One possible way of implementing this new concept in stability testing would be as follows. Ten representative tablets are selected and individually packaged in the final market container and then stored in the retained stability sample chamber. At the appropriate time intervals the test tablets are removed from the stability chamber and non-destructively assayed for potency. They are then returned to the storage chamber. Thus, using this approach we will accumulate stability data on ten individual tablets.

For stability data on tablets obtained by conventional methods the scatter of experimental points seen in plots of percentage label claim as a function of time is due to a number of factors including both the imprecision of the assay and allowable content uniformity variation. For any USP tablet monograph there is a relevant content uniformity specification. In many instances, the allowable content uniformity limits are characterized by a standard deviation of six percent. Thus, any stability method, which can remove variability caused by allowable content uniformity limits, will have an improved precision.

Table I depict some virtual data for the stability of a tablet formulation derived by use of a near IR stability-indicating assay. It will be seen that the average potency value at time zero is very close to 100% and that the variability associated with the assay is

low. The raw experimental data as shown in Table I could all be used without regard for the identity of individual tablets and plotted in a conventional manner to obtain an estimate of the conformance period (Fig.1). However, since when using the near IR as a stability indicating assay, as described in this paper, we are able to follow the degradation of each of the ten individual tablets we can legitimately interpret our data in a way which allows us to circumvent content uniformity differences.

For potency values at all time intervals we normalize data by multiplying each value by (X0/P0) where P0 is the potency at time zero of the relevant potency at time t. the calculated values are shown in Table I in parenthesis. We then plot the values so obtained and determine the conformance period (Fig.2).

Obviously, the ability to follow the degradation in individual tablets and hence negate the variance due to content uniformity significantly tightens the 90% confidence envelope and thus improves our conformance period. The extent of the improvement that will be obtained by us eof this approach depends on the precision of the assay and the content uniformity limits for any given product. This approach could be adapted for any other non-destructive assay method, which can be shown to be stability indicating. For drugs, such as L-thyroxene, for which stability is a considerable problem, this type of approach would be most valuable.

Reference

1. Karen M. Morisseau and C.T.Rhodes, *Pharm. Tech.* (Tabletting Yearbook) 6-12 (1997).

Table I. Single tablet Assay Using Near IR Stability Data, % Label Claim

Tablet # / Test time (months)	1	2	3	4	5	6	7	8	9	10
0	96.5 (100.0)	97.4 (100.0)	98.4 (100.0)	99.1 (100.0)	99.4 (100.0)	100.6 (100.0)	101.0 (100.0)	101.5 (100.0)	102.5 (100.0)	103.5 (100.0)
3	95.6 (99.07)	96.5 (99.48)	97.5 (99.09)	98.1 (98.99)	98.5 (99.09)	99.5 (98.91)	99.9 (98.91)	99.6 (98.13)	101.4 (98.93)	102.4 (98.94)
6	94.6 (98.03)	95.4 (97.95)	96.6 (98.17)	96.9 (97.78)	97.6 (98.19)	98.5 (97.91)	99.1 (98.12)	99.5 (98.03)	100.6 (98.15)	101.4 (97.97)
9	93.5 (96.89)	94.6 (97.13)	95.4 (96.95)	96.0 (96.87)	96.5 (97.08)	97.4 (96.82)	98.0 (97.03)	98.6 (97.14)	99.4 (96.98)	100.5 (97.10)
12	92.6 (95.96)	93.6 (96.10)	94.5 (96.04)	95.6 (96.47)	95.4 (95.98)	96.5 (95.92)	97.1 (96.14)	97.4 (95.96)	98.5 (96.10)	99.6 (96.23)
18	90.4 (93.68)	91.5 (93.94)	92.4 (93.90)	93.5 (94.35)	93.6 (94.16)	94.4 (93.84)	94.9 (93.96)	95.5 (94.09)	96.5 (94.15)	98.6 (95.27)
24	88.4 (92.08)	89.5 (91.89)	90.6 (92.07)	90.9 (91.73)	91.5 (92.05)	92.5 (91.95)	93.0 (92.08)	91.6 (90.25)	92.5 (90.24)	94.5 (91.30)
ΣΔLC	8.1	7.9	7.8	8.2	7.9	8.1	8.0	7.9	8.0	8.0

Figure 1. Conformance period of tablets determined using NIR with the original data

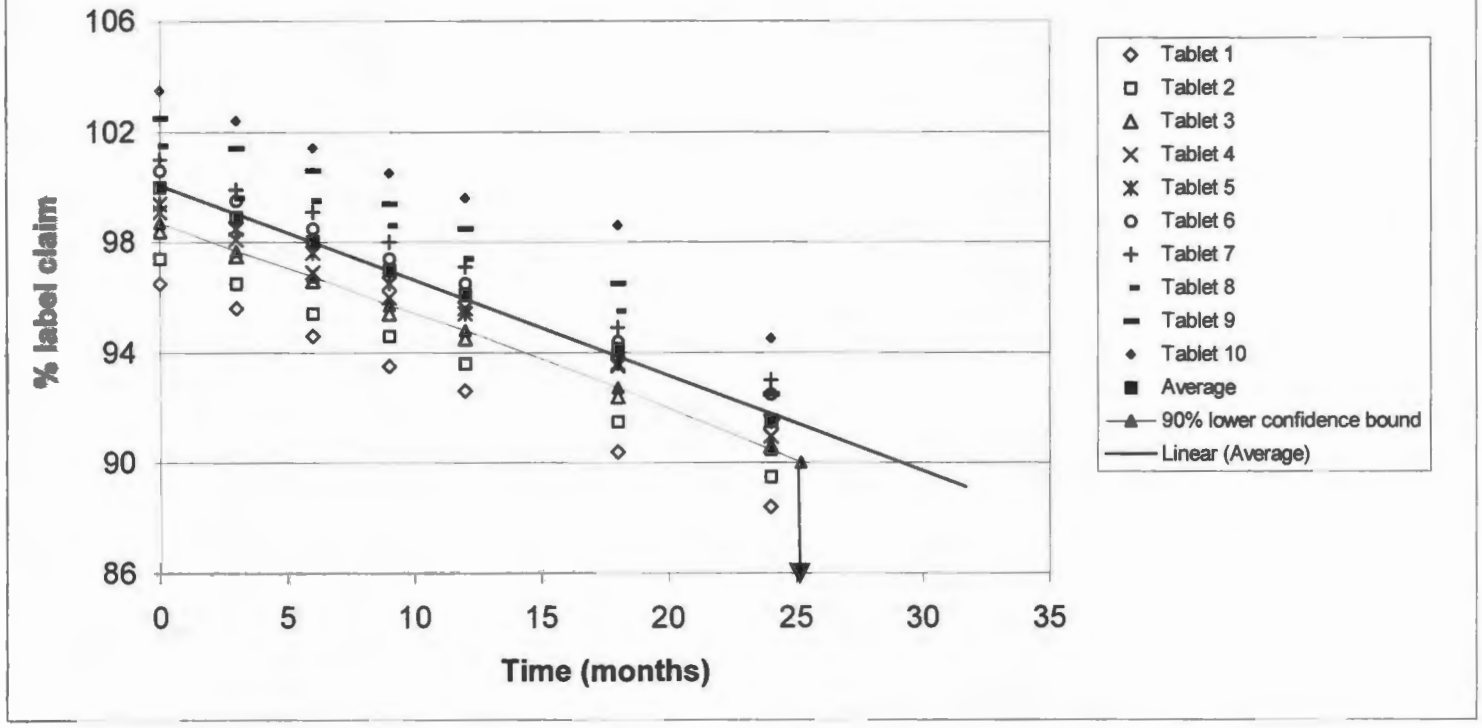
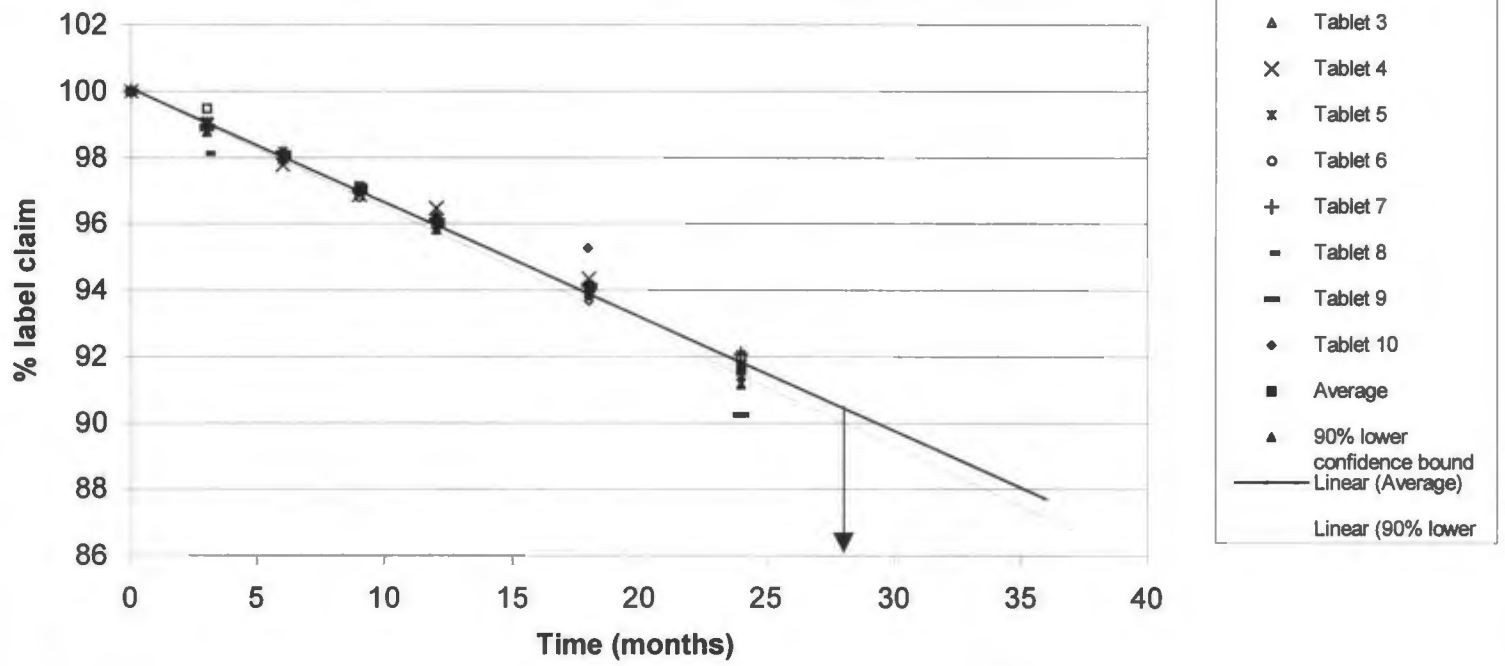


Figure 2. Conformance period of tablets detrmined using NIR with the normalized data



SECTION III

APPENDIX A

LIST OF PUBLICATIONS

The following is a list of the journals the manuscripts were prepared for and their publication status.

Manuscript I

TRENDS IN STABILITY TESTING WITH EMPHASIS ON STABILITY DURING DISTRIBUTION AND STORAGE

Published in *Drug Development and Industrial Pharmacy,* 25(7): 857-868 (1999)

Manuscript II

EFFECTS OF TEMPERATURE SPIKES ON MEAN KINETIC TEMPERATURE AND SHELF LIFE

Submitted to *Pharmacopeial Forum*

Manuscript III

SOME STUDIES OF THE STABILITY OF COMPOUNDED CEFAZOLIN OPHTHALMIC SOLUTION

Accepted for publication in *International Journal of Pharmaceutical Compound*ing

Manuscript IV

POTENTIAL OF KNOWN INDIVIDUAL SINGLE TABLET ASSAY BY NEAR-IR FOR THE ASSIGNMENT OF SHELF LIFE

To be submitted for publication

APPENDIX B

ROLE OF CO-AUTHORS IN PAPERS

Dr. Christopher T.Rhodes, my major Professor, is instrumental in getting the thesis done in manuscript form. His enthusiasm, guidance and positive directions played a major role in all the four manuscripts, without which it would have not been possible to present the thesis in this format.

Manuscript III is co-authored by Dr. C.T.Rhodes, Dr. Richard F. Lindaeur and Dr. Lee T.Grady.

Dr. Lee T.Grady is the Executive Vice-President, Drug Standards Development, USP. He was instrumental in getting the summer fellowship. His involvement in the project in his capacity made the work progress in a faster pace than expected. Also, his suggestions and recommendations were valuable.

Dr. Richard F.Lindaeur is the Director of DRTL-USP. He acted as an acting major Professor during my stay in USP. His in-depth involvement in the research part, guidance and monitoring of the work, in his capacity, created a wonderful atmosphere in the laboratory, which was critical in the completion of this project. His involvement in editing the manuscript was also of immense value.

Manuscript IV is co-authored by Dr. C.T.Rhodes and Dr. Karen M.Morrisseau.

Dr. Karen M.Morrisseau worked on the stability of tablets using NIR data for her Ph.D., which was submitted in 1996. This manuscript has the theme taken from her Dissertation and also some of her ideas were used.

APPENDIX C

(Supplement to Manuscript III)

The raw data was obtained from the analysis of drug content using USP stability-indicating HPLC assay. The percentage of drug remaining as a function of time for batches A, B & C at 7^0, 17^0, 25^0 & 40 ^{0}C were incorporated in Tables I, II, III & IV respectively. The log percentage of drug remaining as a function of time at 7, 17, 25 & 40 deg C for batch A was depicted in Fig 1 of Manuscript III. The log percentage of drug remaining as a function of time at 7, 17, 25 & 40 deg C for batches B & C are depicted in Figs 1 & 2. The slopes of the regression lines were used to calculate the values of k at different temperatures for all the three batches. Using the k values and their respective temperatures, the Arrhenius plots were constructed. The correlation coefficients are not close to unity at 3 degrees of freedom (four temperature data), which is depicted in Fig 7. Also, the calculated Ea values are deviating from Grimm average. This may be due a different mechanism occurring at 7 deg C. Therefore, Arrhenius parameters were calculated using 17, 25 and 40 deg C data in which the correlation coefficients are close to unity at 2 degrees of freedom (see manuscript III).

The 90% confidence intervals for the percentage label claim were obtained using the software package MINITAB®. The Beyond-use dates at 7^0 and 25 ^{0}C for batches A, B & C were obtained using the 90% confidence bounds. The conformance periods (in days) were obtained when 90% label claim intersects the 90% lower confidence bound. The beyond-use date plots were depicted in Figs. 3, 4, 5 & 6 for batches B & C at 7 ^{0} & 25 ^{0}C (see Figs. 3(a) & 3(b) in Manuscript III for batch A).

Table I. Percentage of drug remaining after predetermined intervals at 7 ^{0}C for batches A, B & C

Time (hrs)	A	B	C
0	100.0	100.0	100.0
67	98.40	98.56	101.3
113	100.2	100.6	102.1
161	99.10	98.61	100.1
237	97.30	98.10	99.94
281	96.00	96.70	99.08
311	96.92	94.72	97.83

Table II. Percentage of drug remaining after predetermined intervals at 17 ^{0}C for batches A, B & C

Time (hrs)	A	B	C
0	100.0	100.0	100.0
67	97.58	98.97	98.00
113	98.86	99.34	100.9
161	96.05	96.29	99.26
237	93.61	95.82	97.20
281	94.40	94.84	96.50
311	93.65	93.72	95.50

Table III. Percentage of drug remaining after predetermined intervals at 25 ^{0}C for batches A, B & C

Time (hrs)	A	B	C
0	100.0	100.0	100.0
67	95.51	95.34	102.5
113	94.47	94.66	95.69
161	91.79	92.96	94.00
237	87.03	86.89	88.96
281	86.27	85.17	85.87
311	84.77	83.81	85.61

Table IV. Percentage of drug remaining after predetermined intervals at 40 ^{0}C for batches A, B & C

Time (hrs)	A	B	C
0	100.0	100.0	100.0
67	81.40	81.80	85.67
113	72.18	71.15	73.80
161	61.10	61.52	63.34
237	46.35	46.16	47.01
281	40.10	39.71	39.87
311	37.80	36.01	35.84

Figure 1: Plot of the log % drug remaining as a function of time at 7, 17, 25 & 40 deg C for batch B

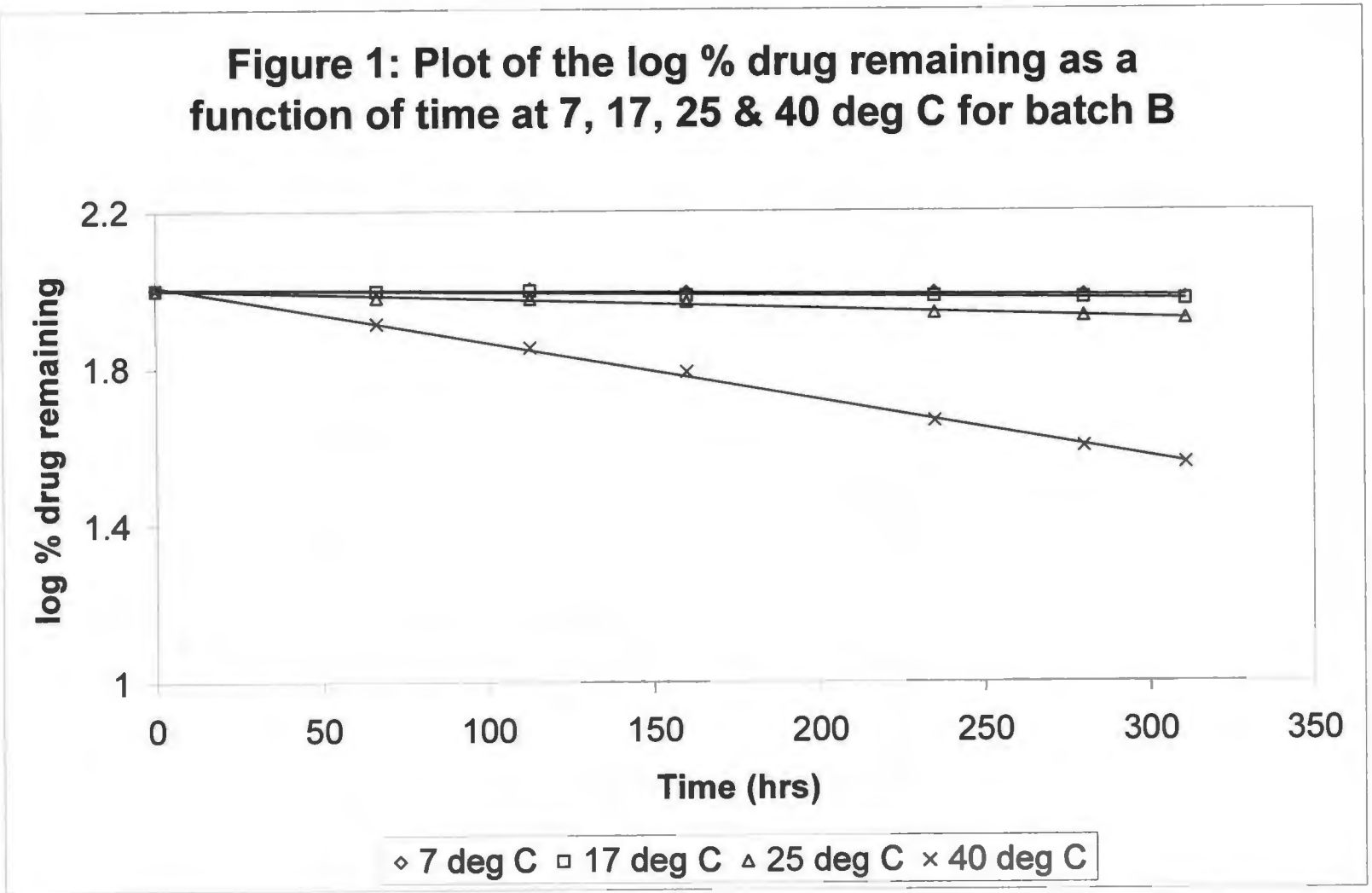


Figure 2: Plot of the log % drug remaining as a function of time at 7, 17, 25 & 40 deg C for batch C

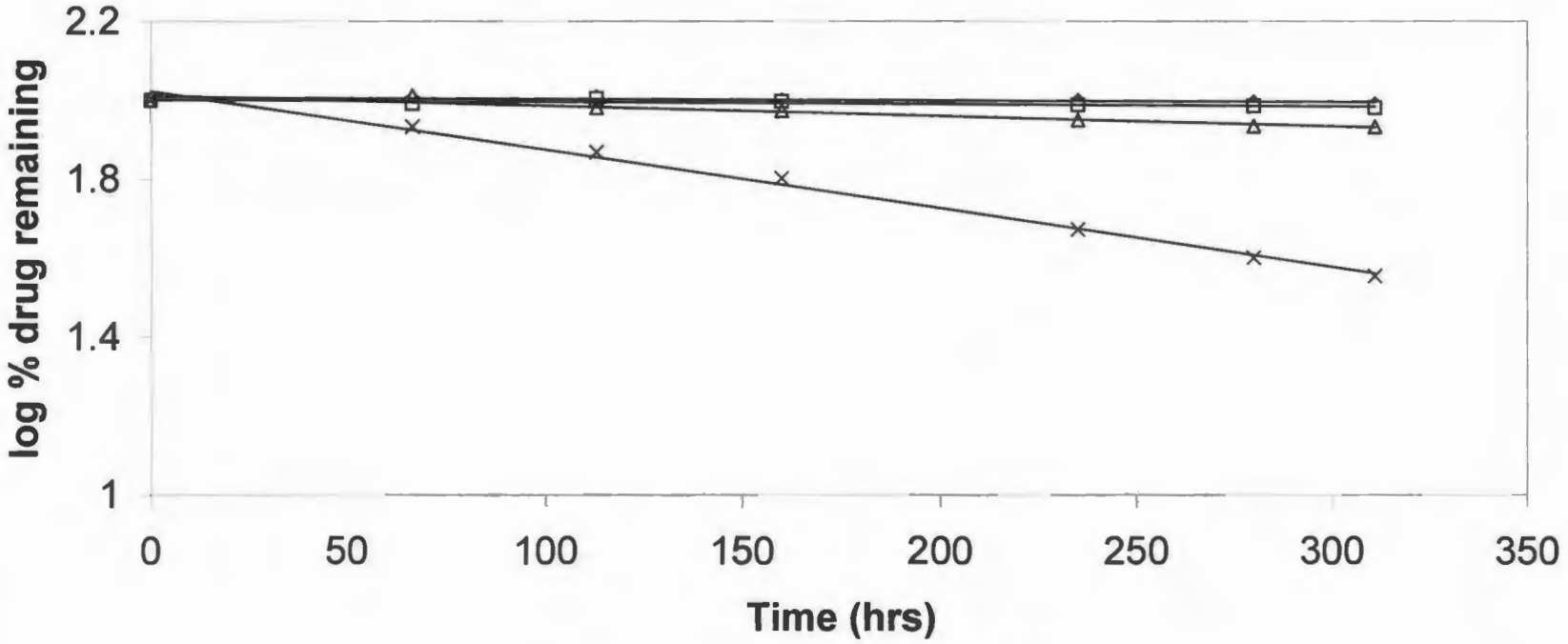


Figure 3: Prediction of Beyond-use date at 7 deg C for batch B

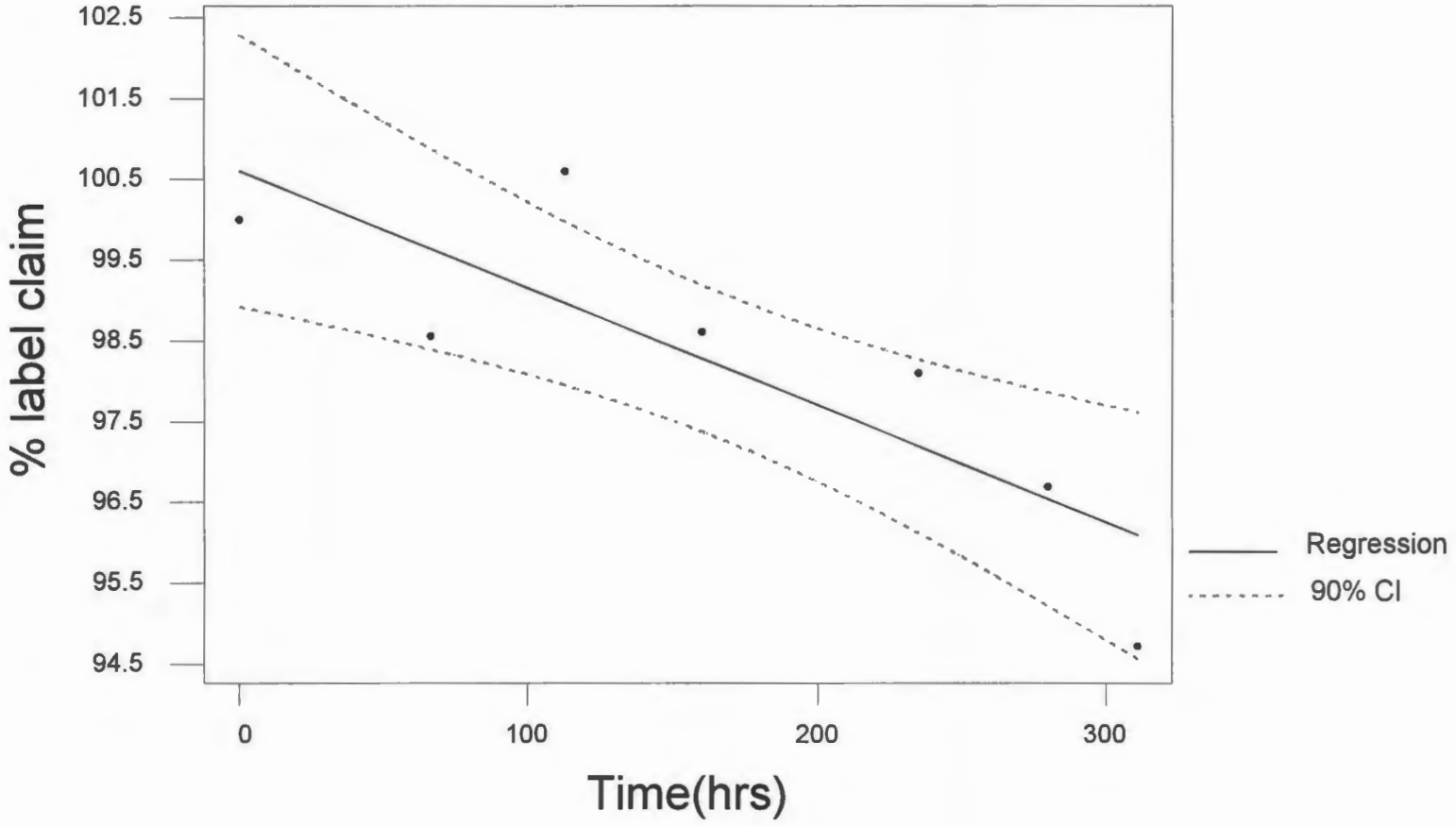


Figure 4: Prediction of Beyond-use date at 7 deg C for batch C

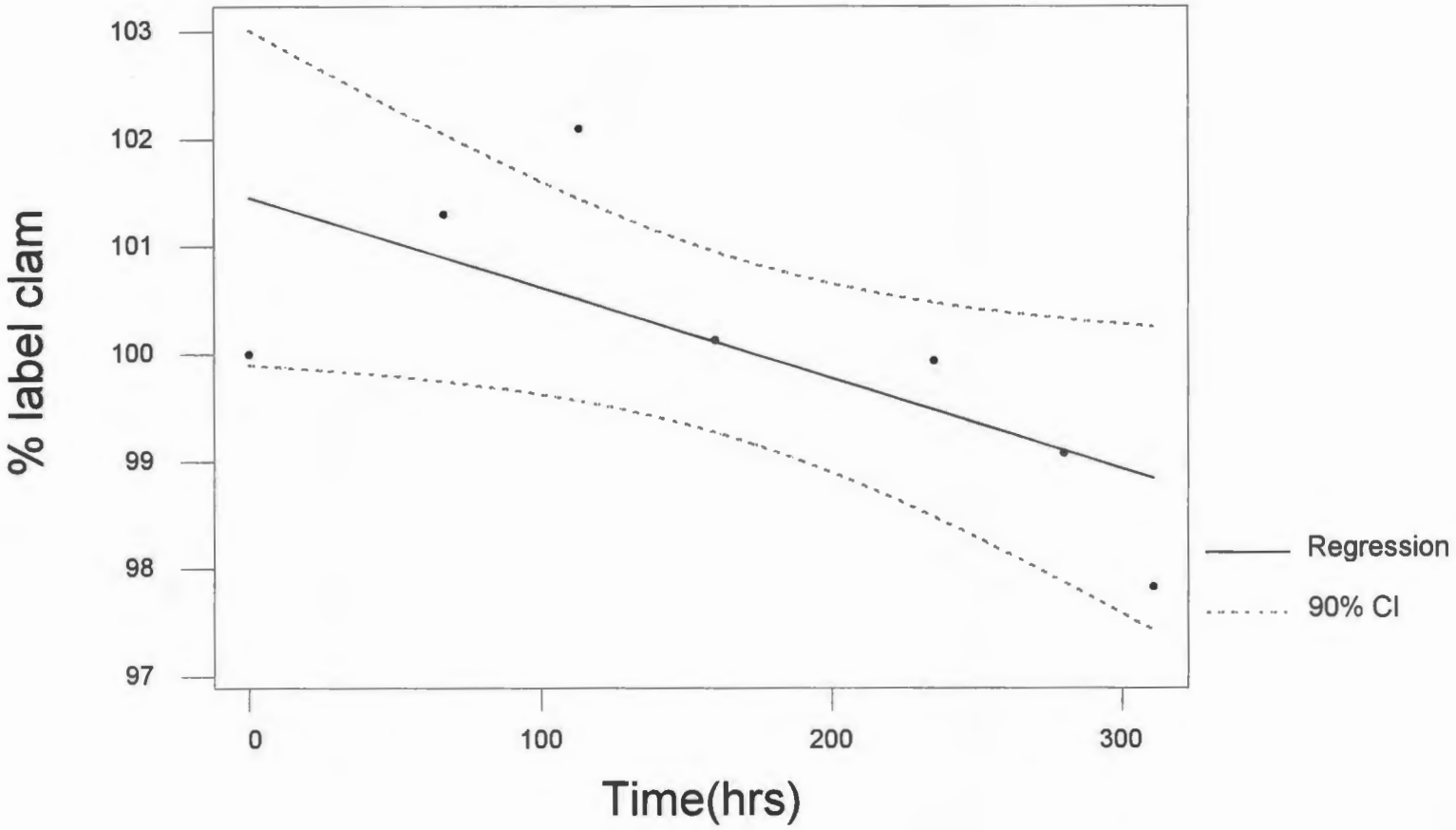


Figure 5. Prediction of Beyond-use date at 25 deg C for batch B

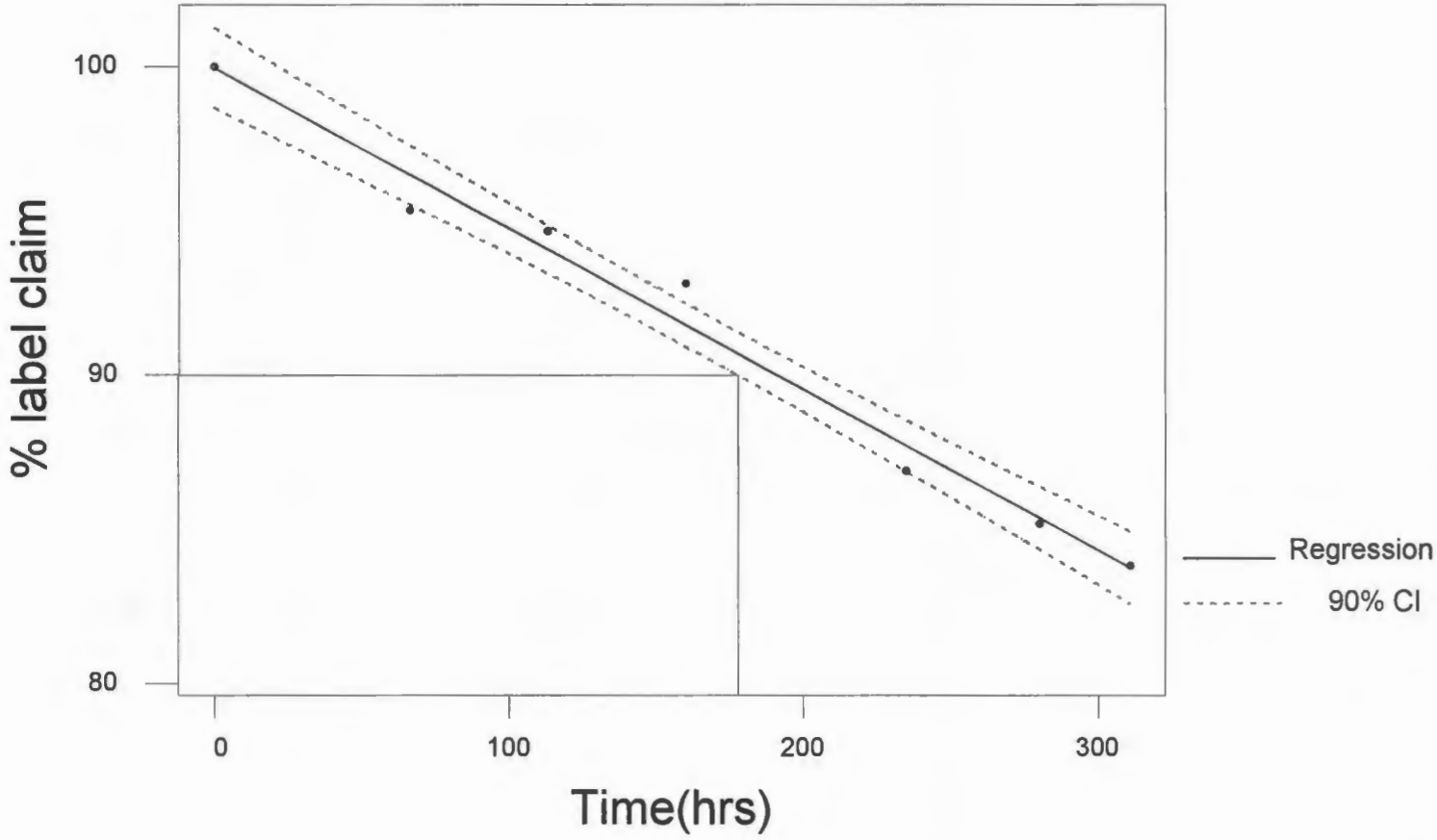
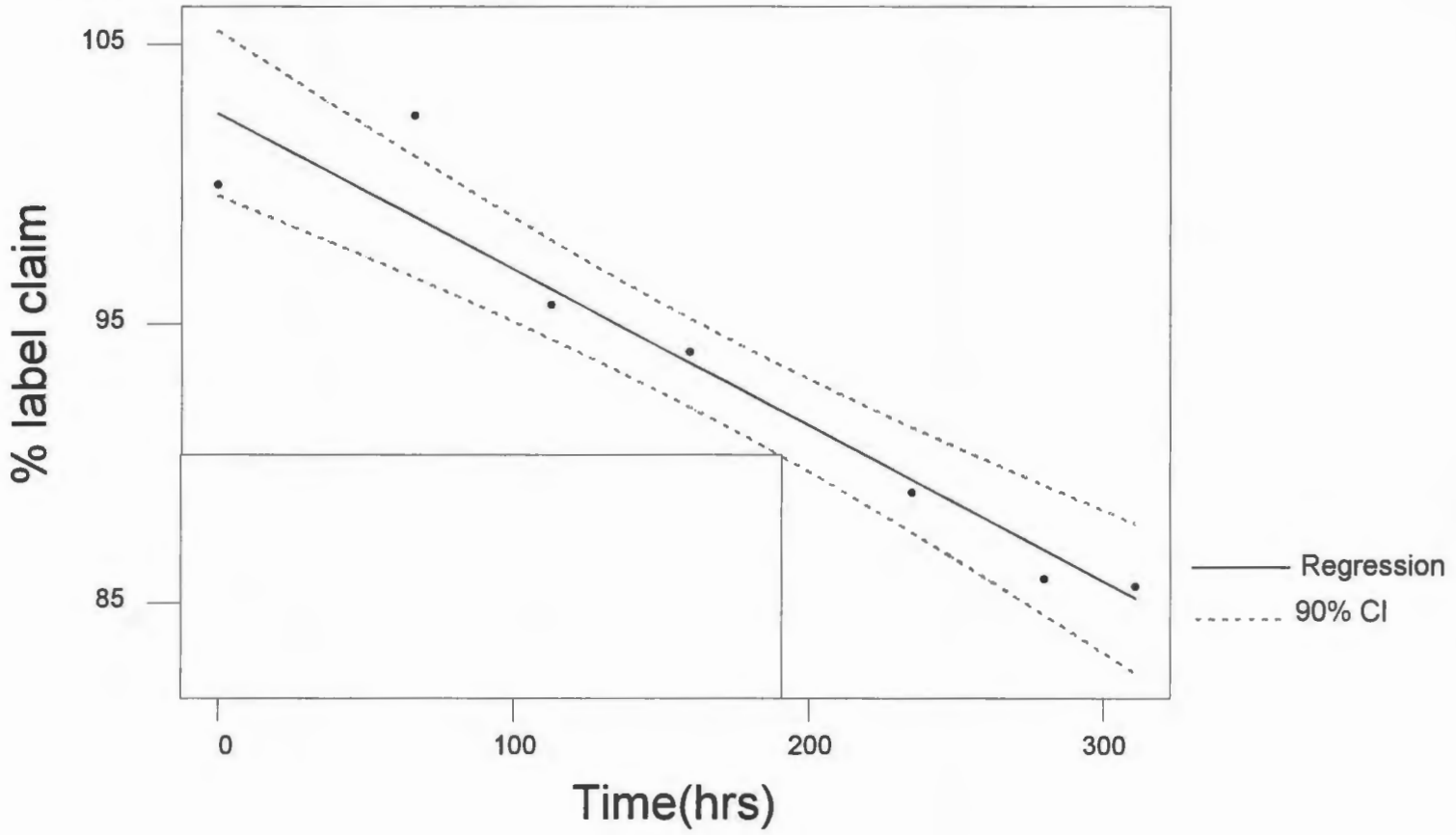


Figure 6. Prediction of Beyond-use date at 25 deg C for batch C



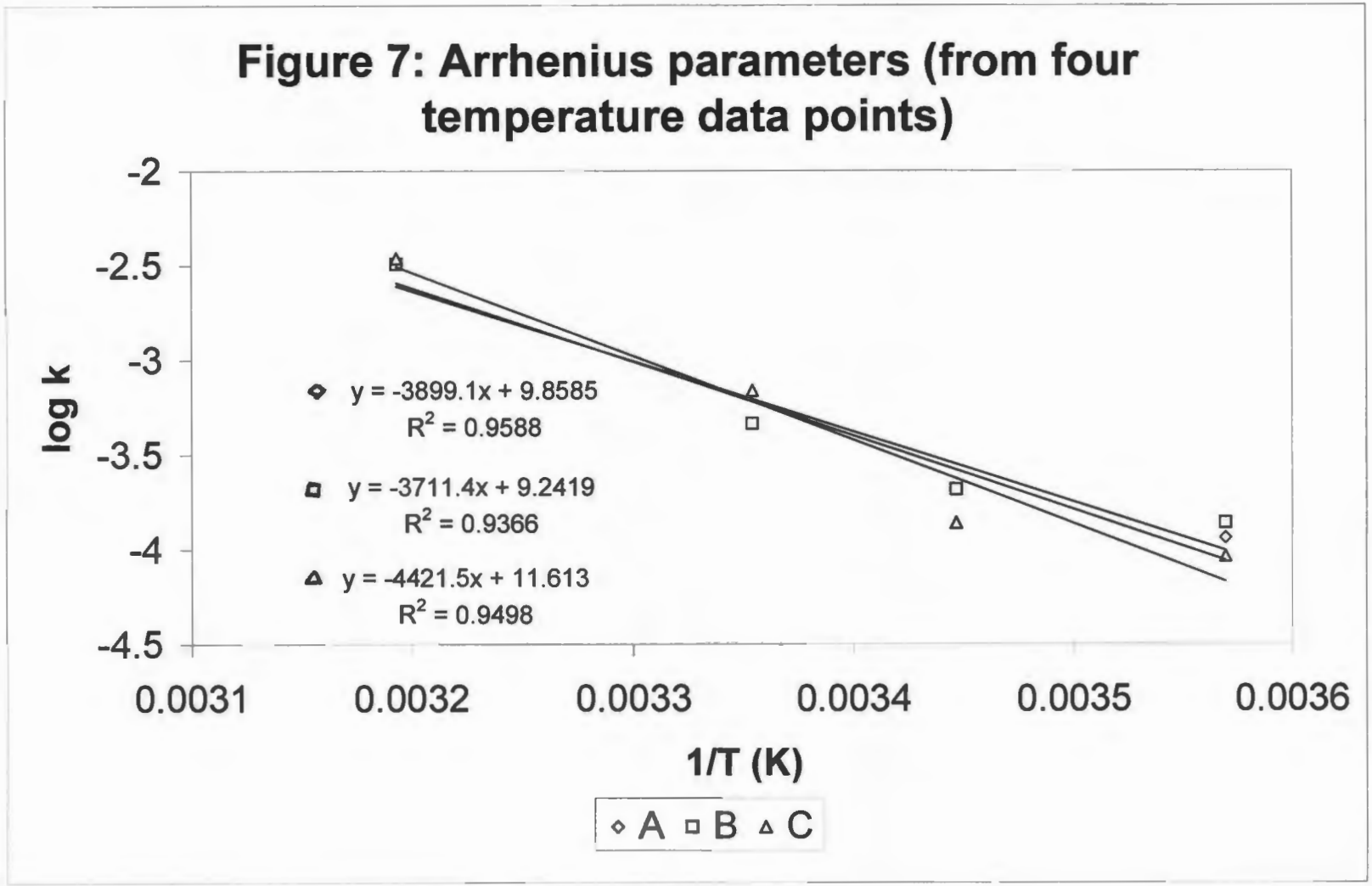


Figure 7: Arrhenius parameters (from four temperature data points)
log k
-2
-2.5
-3
-3.5
-4
-4.5
y = -3899.1x + 9.8585
R2 = 0.9588
y = -3711.4x + 9.2419
R2 = 0.9366
y = -4421.5x + 11.613
R2 = 0.9498
0.0031
0.0032
0.0033
0.0034
0.0035
0.0036
1/T (K)
A
B
C

SUMMARY OF CONCLUSIONS

1. The increasing attention is now being given to the possible effects of storage and transport on the stability of pharmaceutical products. This lead to an improved level of confidence about the stability of drug products among the patients.
2. The effect of temperature spikes on mean kinetic temperature has been evaluated.
3. For a system with a baseline storage temperature of 22.5 ^{0}C total spikes equivalent to 2 months at 30 ^{0}C may be tolerated if the shelf life is 12 months or more.
4. If the baseline storage temperature is more than 22.5 ^{0}C or the shelf life is less than 12 months then adverse effects on the validity on the assigned shelf life are more likely.
5. A single 30 ^{0}C spike of 7 hours or less would probably not adversely affect the shelf life of any normal product.
6. Compounded cefazolin ophthalmic solution, when stored at refrigerator and CRT conditions, a beyond-use date of 2 weeks and six days respectively can be assigned.
7. The activation energy of the product (Compounded cefazolin ophthalmic solution) was found to be almost in accordance with the Grimm's average value.
8. The conformance period of tablets determined using NIR stability-indicating assay was found to be more in the normalized data than the original data.

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