ACCELERATED STABILITY TESTING OF DOSAGE FORMS AS PER INTERNATIONAL CONFERENCE OF HORMONIZATION (ICH) GUIDELINES

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ABSTRACT

Objectives of accelerated stability studies are linked to the establishment assurance of safety, quality and efficiency of drug product from early phase development through the drug product. The stability data for the drug substance are used to determine optimal storage and packaging conditions for bulk lots of material. In order to assess stability, the appropriate physical, chemical, biological and microbiological testing must be performed. Pharmaceutical companies estimate the shelf life (Expiration date) of a drug in order to determine the amount of time the drug is at acceptable potency, color, etc., levels. The pharmaceutical company or the food and drug administration set the acceptable levels. The process in which the shelf-life is determined is called a stability analysis. During the shelf-life, a drug can stay on the shelf without degrading to unacceptable levels.

KEYWORDS: Accelerated stability, Shelf-life, Potency, Safety, Quality, Efficiency.

INTRODUCTION

The method of accelerated stability testing of pharmaceutical products is based on the principles of chemical kinetics, more specifically on the Arrhenius plot. According to this technique, the k values for the decomposition of the drug in solution at various elevated temperatures are obtained, and the logarithms of these k values are plotted against the reciprocals of the absolute temperatures (in Kelvin’s). The resulting line is then extrapolated to room temperature (25°C = 298K). The k25°C is used to obtain a measure of the drug under ordinary shelf conditions.¹⁻³

Prediction of shelf life from accelerated stability data

Based on the principle of chemical kinetics demonstrated by

1) Garret and Carper method
2) Free and Blythe method

Shelf Life Determination Based on Arrhenius Plot (Garret and Carper method)

The mathematical prediction of shelf life is based on the application of the Arrhenius equation, which indicates the effect of temperature on the rate constant, k, of a chemical reaction of thermodynamic temperature, 1/T, is a straight line.

If the slope of this line is determined from the results of temperature by extrapolation, the k value obtained. And this k value is substituted in appropriate order of reaction allows the amount of decomposition after a given time. Preliminary experiments are there for necessary to determine this order.

K=Ae⁻Ea/RT

Log K=Log A - Ea/2.303*RT

Where, K= rate constant
R= gas constant =1.987 cal/mole
T = absolute temperature
A = frequency factor
Ea = energy of activation

T10% = (2.303/K)*(log100/90)
T90% = (2.303/K)*(log100/10)

GARRET AND CARPER METHOD

1. Keep several samples of the drug product at least three temperatures, such as 40°C, 50°C and 60°C.
2. Determine the drug content at all three storage points by taking a number of samples and take the mean drug content. We do this for a few weeks.
3. At each temperature we plot a graph between time and log percent drug remaining. If the decomposition is first order this gives a straight line. If it is zero order, percent drug remaining versus time will give a straight line.⁴⁻⁶
4. Next we take the log K or log of reaction constant on Y axis and 1/T x 10^3 on X axis and draw a best fit line. This line is the Arrhenius Plot, extrapolate this line to get k at 25°C and from this we calculate the shelf-life.

**Arrhenius plot for predicting drug stability at room temp.**

If the reaction is following zero-order Expiration date at 25°C = Initial potency – minimum potency / reaction rate at 25°C

\[ t_x = \frac{Y_0 - Y_x}{K_o} \]

If the reaction is following first order Expiration date at 25°C (tx) = Log initial potency – log minimum potency/reaction rate at 25°C

\[ tx = \log Y_0 - \log Y_x / K_1 \]

Where  \( Y_0 \) = initial potency

\( Y_x \) = final potency

\( K_o \) = zero order constant

\( K_1 \) = first order constant

Pharmaceutical products can deteriorate with time, through both chemical decomposition of the active principles and excipients and sometimes also through microbiologically induced degradation. Therefore, all pharmaceutical products are required by law to display an expiry date on the packaging. Stability testing is the primary tool used to assess the expiration dating and storage conditions for pharmaceutical products. Many protocols have been used for stability testing, but most in the industry are standardizing on the recommendations of the international conference on Harmonization (ICH).[12-13]

**Product changes in accelerated stability studies.**

- **Physical changes** – appearance, Melting point, Clarity and color of solution, Moisture, Crystal Modification (Polymorphism), particle size.

- **Chemical changes** – Increase in degradation, decrease of assay.

- **Microbial changes**

ICH stands for international conference on Harmonization of technical requirements for registration of pharmaceuticals for human use.

**Objectives of ICH**

Harmonization of registration applications within the three regions of the EU, Japan, and the United States. ICH is a joint initiative program involving both regulatory and industry as equal partners in the scientific and technical discussions of the testing procedures which required ensuring and assessing the safety, quality and efficacy of medicines.[12-13]

Tripartite guideline in the stability testing of new drug substance and product (Q1A) IN 1993 has become standard for stability evaluation in Japan, US, Europe.

**ICH Guidelines**

- Quality guidelines “Q” (Chemical and Pharmaceutical QA)
- Safety guidelines “S” (In vitro and in vivo pre-clinical studies)-
  - Covering carcinogenicity testing, Genetic toxicity testing, toxic kinetics and pharmacokinetics.
  - Efficiency guidelines “E” (Clinical studies in human subject)-
  - Covering clinical safety, Dose response studies, good clinical practices, Clinical evaluation.

**Multidisciplinary guidelines “M”**

- Covering Medical Technology, electronic standards for transmission of regulatory information.

Guideline M4-The common technical document.(CTD)

**Accelerated stability studies**

1. Storage condition 0°C to 4°C and relative humidity of 75% has been recommended for all the four zones for drug substances and drug products.
2. Studies carried out for 6 months
3. Accelerated storage conditions must be at least 15°C above the expected actual storage temperature and appropriate relative humidity.

**Protection against hydrolysis:**

Good packaging practices like moisture resistant packing. Eg- Strip pack stored in controlled humidity and temperature conditions, even using desiccant such as silica gel.

Buffering agent for pH control.

Alteration of Dielectric constant.

Use of surfactants, Good refrigeration.

Addition of complexing agent like caffeine.

**Protection against oxidation:**

Incorporation of Antioxidants such as BHA, BHT, Propyl gallate, tocopherol.

Chelating agents using EDTA, Citric acid, Tartaric acid.

Use of inert gases like nitrogen

Protection from light by use of amber colored container.

Storage at low temperature.

Type, size, No.of batches (ICH/WHO Guidelines)

At least 3 primary batches of drug product should be of the same formulation, packed in same container as proposed for marketing.

2 out of 3 batches should be pilot scale batches.

Stability to be performed on each strength, container size.

**Long term stability studies**

1. Stability is performed at 25°C/60% or 30°C/65%
2. Ideally 12 months date is to be generated, but 6 months date is also acceptable in circumstances for submission of registration dossier, continued till end of shelf-life.
3. For parenteral stability has to be carried out at 2-8°C. For drugs to be stored in freezer testing should be done at -20°C.
Chemical properties
Assay
Degradation

Microbial properties
Container closer system properties – Functionality test.
Testing seep Liquid dosage forms for injections and pernent-
Physical-chemical properties - PH
Loss of weight
Color & clarity of solution

Chemical properties
Assay
Degradation products
Degradation preservatives
Microbial properties -
Pyrogen testing
Container closer system -
Functionality test
Leakage test

Testing seep for oral liquid form
Physical-chemical properties - PH
Viscosity
Color & clarity of solution
Particle size distribution (For oral suspension only)
Chemical properties -
Assay
Degradation products
Degradation preservatives
Antioxidants
Microbial properties

Testing seep for solid dosage forms
Physical-chemical properties – Appearance, Elasticity,
Moisture, Hardness, Disintegration, Dissolution
Container closer system
Functionality test.

Limitations of Accelerated stability study
1. Stability predictions are based on Arrhenius’
equation, which has limitation for energy of
activation for validation of thermal decomposition,
which lies in the range of 10-30 Kcal/mole.
2. Functionality test
Testing seep for semisolid dosage form

Physical-chemical properties -
Appearance
Color
Homogeneity
Consistency
Loss of weight
Content uniformity
Viscosity
Chemical properties -
Assay
Degradation products
Degradation preservatives

Antioxidants.
Microbial properties –
Container closer system -

3. At accelerated conditions some new reactions may
take place, which usually do not take place at normal
storage conditions. Therefore, obtaining correct
information is difficult.
4. Order of reaction may also differ in some cases with
accelerated conditions.
5. Accelerated testing cannot be used for
microbiological decomposition and also for handling
during transport.
6. Thermolabile materials and products are not suitable
candidates for accelerated stability study.
7. Some products appear stable at higher temperature
than at normal storage conditions.

% of Relative humidity (RH) = Water-vapour
pressure in atmosphere/Saturated water-vapour
pressure x 100

ICH Summary of Stability Parameters

<table>
<thead>
<tr>
<th>Study</th>
<th>Storage conditions</th>
<th>Minimum time period</th>
</tr>
</thead>
<tbody>
<tr>
<td>General case</td>
<td>25°C (±2°C) at 60 % RH (± 5 %RH)</td>
<td>12 Months</td>
</tr>
<tr>
<td>Long term</td>
<td>30°C (±2°C) at 65 % RH (± 5 %RH)</td>
<td>12 Months</td>
</tr>
<tr>
<td>Intermediate</td>
<td>30°C (±2°C) at 65 % RH (± 5 %RH)</td>
<td>6 Months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>35°C (±2°C) at 70 % RH (± 5 %RH)</td>
<td>6 Months</td>
</tr>
<tr>
<td>Refrigeration</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term</td>
<td>5°C (±3°C)</td>
<td>12 Months</td>
</tr>
<tr>
<td>Accelerated</td>
<td>25°C (±2°C) at 60 % RH (± 5 %RH)</td>
<td>6 Months</td>
</tr>
<tr>
<td>Freeze</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Long term</td>
<td>-20°C (± 5°C)</td>
<td>12 Months</td>
</tr>
</tbody>
</table>

Product Characteristics Affecting Shelf-Life
Spoilage – Microbial spoilage occurs in products that
provide an environment that supports microbial growth,
or are subjected to contamination during storage. The
leaching of chemicals, or similar reactions, promoted by
long- term contact with packaging materials leads to
chemical spoilage.

Flavors – Off-flavors’ developed during storage are
often due to chemical reactions or microbial growth.
Rancidity occurs as a result of oxidative reactions and produces off-flavors. Texture – Products containing similar ingredients do not necessarily exhibit similar textures. Water contributes greatly to a product’s texture. Stalling, breakdown of gel structures, phase separation, water activity, moisture migration and crystallization, all contribute to textural changes during storage.

Appearance - An unacceptable appearance in colour resulting in browning or fading is caused by fat and/or moisture migration and chemical reactions. Other processes affecting appearance making the product undesirable during storage include surface crystal formation, phase separation, syneresis and caking.

Overview of storage conditions and storage period for solid, semisolid and liquid dosage forms.

<table>
<thead>
<tr>
<th>Stability investigation</th>
<th>Dosage form</th>
<th>Storage condition</th>
<th>Storage period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Organoleptic and photochemical stability</td>
<td>Solid</td>
<td>Storage in open container until equilibrium at 25°C/60%, 30°C/70%, 40°C/75%.</td>
<td>1-2 weeks</td>
</tr>
<tr>
<td></td>
<td>Semisolid</td>
<td>5°C; &gt;-10°C; 5°C; -40°C Temperature cycle within 24 hrs.</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>5°C; &gt;-10°C</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Photo stability</td>
<td>All</td>
<td>Xenon lamp</td>
<td>48 hrs</td>
</tr>
<tr>
<td>Chemical stability</td>
<td>Solid</td>
<td>40°C, 50°C, 60°C, 70°C.</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Semisolid</td>
<td>30°C, 40°C, 50°C.</td>
<td>3 months</td>
</tr>
<tr>
<td></td>
<td>Liquid</td>
<td>40°C, 50°C, 60°C, 70°C.</td>
<td>3 months</td>
</tr>
</tbody>
</table>

Addition of overages
1. Excess amount of the drug can be added to the preparation to maintain 100% of the labeled amount during the shelf-life of the product.
2. Overages are calculated from the accelerated stability studies and added to the preparation at the time of manufacture.
3. They should be within the limits compatible with the therapeutic requirement.
4. Addition of overages doubles the shelf-life of the product.
5. Overages are added in multi-vitamin preparations.

Freeze thaw stability testing
Freeze-thaw cycle testing is a part of stability testing that allows you to determine if your formula will remain stable under various conditions. This type of test puts your sample through a series of extreme, rapid temperature changes that it may encounter during normal shipping and handling processes. Freeze-thaw stability testing is highly recommended, especially for liquid-based cosmetics. These products may experience phase separation that can negatively affect the intended function. Freeze-thaw testing is conducted by exposing the product to freezing temperatures (approximately -10°C) for 24 hours, then allowing thawing at room temperature for 24 hours. The sample is then placed in a higher temperature (approximately 45°C) for 24 hours, and then placed at room temperature again for 24 hours. The sample is analyzed for significant changes. This completes one cycle. If, after three cycles of freeze-thaw testing, no significant changes are observed, you can be confident that the stability of your product is sufficient for transport.

CONCLUSION
Knowledge of stability of a formulation is very important for three primary reasons.
1) A pharmaceutical product must appear fresh, elegant and professional for as long as it remain on the shelf.
2) Since some products are dispensed in multiple dose container uniformity dose of the active ingredient over time must be ensured.
3) The active ingredient must be available to the patient throughout the expected shelf-life of the preparation. A break down in the physical system can lead to non availability or of the medication to the patient.

REFERENCES


