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"Drug Stability": Review Article

[1]Mosarrat Jahan, [2]Dr. Hariom Sharma, [3]Dr. Gaurav K Sharma,[4]Dr. Kaushal K Chandrul

[1]Student of B. Pharma 4th year, [2]Guider, [3]HOD, [4]Principal, Department of Pharmaceutical Science, Mewar University Gangrar, Chittorgarh, Rajasthan

ABSTRACT

This includes drug stability studies Important parameters for new drugs and new drug development pharmaceutical formulation. Durability prediction plays a big role All dosage forms and their drug development Helps determine and suggest storage conditions for each Label description. Ensuring drug stability research Maintain product quality, safety and effectiveness throughout Durability is a prerequisite for acceptance Drug approval. These studies are necessary It will be implemented according to the guidelines issued by ICH. WHO or other institutions

. Keywords: Stability Studies, Pharmaceutical Products And Stability Testing.

Introduction

Stability studies of pharmaceutical products may be expressed as the time during which the pharmaceutical products retain its physical, chemical, microbiological, pharmacokinetic properties and characteristics throughout the shelf life from the time of manufacture.

Shelf life of the product can be defined as the substance reduces to 90% of its original concentration. Shelf life is a technical term used to denote the stability of the product and it is expressed as expiry date. Expiration varies for each pharmaceutical preparations.

The expiry of the pharmaceutical dosage form depends on various environmental factors such as temperature, humidity, light, radiations etc. and many physical and chemical active substances in the formulation, the nature of container-closures used and the storage conditions. Literature data on the decomposition process and degradability of active substances are generally available together with adequate analytical methods. Thus, stability studies may be restricted to the dosage form. The most important steps during the developmental stages include pharmaceutical analysis and stability studies that are required to determine and assure the identity, potency and purity of ingredients, as well as those of the formulated products. [1] Stability of a pharmaceutical product can also be affected because of microbiological changes like growth of microorganisms in non sterile products and changes in preservative efficacy. [2] Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation.

The Shelf life of the pharmaceutical drug products is established by the stability studies. Stability testing of pharmaceuticals is known to be a complex set of procedures which involves significant cost, time and scientific proficiency to generate safety, in quality and efficacy in a drug formulation.

The understanding of the drug development process and the infinite tasks and milestones that is essential to abroad development plan result in scientific as well as commercial success of any pharmaceutical product [1].

Stability defines as "The capability of a particular formulation in a specific container/closed system, to remain within its physical, chemical, microbiological, therapeutic, and toxicological specifications throughout its shelf life". Stability is officially defined as "the time lapse during which the drug product retains the same properties & characters that are processed at the time of manufacture" [2].

The various factors affecting the stability of a pharmaceutical product; because of their involvement, stability testing is known as a complex process. These factors mostly concern the stability of the active ingredient(s); interaction of active ingredients and excipients, type of dosage form and their manufacturing process followed, container/closure system used for packaging, heat, moisture and light come across during shipment, storage and handling etc. [3].

Importance of Stability Studies

- Instability of active drug and products may lead to under medication of the drug due to lowering concentration in the dosage form.
- The toxic product may be formed during the decomposition of active drug.
- Changing in physical appearance through the principles of kinetics due to instability, are used to forecast the stability of the drug.
- To save the reputation of the manufacturer by confirming the product will retain strength for use concerning all functionally related aspects for as long as they are in the market

- Stability testing is an important step in the drug approval process and how the quality of a drug or drug (including packaging) changes over time under the influence of environmental factors such as temperature, humidity and light
- In addition, stability testing establishes the shelf life and recommended storage conditions of the finished drug, as well as the drug substance retest period.
- Stability testing, which consists of two phases (stability preservation and downstream analytical testing), ensures compliance with international regulations that are part of the new active ingredient or drug registration process. For stability testing purposes, the International Council for Harmonization (ICH) divides the world into five climatic zones based on a combination of temperature and relative humidity (RH).
- •Stability storage and testing studies are performed to simulate climatic effects. The studies are based on where the products are going to be sold. Knowing all the ways a finished product or active pharmaceutical ingredients (APIs) could be affected by degradation is crucial in the storage of these products.

Stability Studies and their Classification

Stability studies are the essential criteria for assuring the quality efficacy and integrity of the final product.

Although how a drug can deteriorate and lose its stability are numerous, they fall into three general categories: chemical, physical, and microbiological. Part of the formulation of drugs deals with the issue of stability loss as well as with ensuring that there is enough of the therapeutic agent in the drug to have the desired effect. For example, a drug may be formulated to be at a certain pH to ensure that it remains stable longer at room temperature.

A comprehensive pharmacopoeial protocol (USP) prescribes the criteria for acceptable levels of physical, chemical, microbiological, therapeutic and toxicological stability studies.

Physical stability

The original physical properties such as appearance, colour, dissolution, palatability, suspendability are retained. The physical stability may affect the uniformity and release rate, hence it is important for the efficacy and safety of the product.

Chemical stability

It is the tendency to resist its change or decomposition due to the reactions that occur due to air, atmosphere, temperature, etc.

Microbiological stability

The microbiological stability of the drugs is the tendency to resistance to the sterility and microbial growth. The antimicrobial agents used in the preparation retain the effectiveness within specified limits. This microbiological instability could be hazardous to the sterile drug product.

Therapeutic stability

The therapeutic effect (Drug Action) remains unchanged. Toxicological stability Toxicological stability has no significant increase in the toxicity occurs

Types of Stability Studies

Stability studies are used for testing the drug product for longer periods under varying conditions of temperature and Relative Humidity (RH). If the drug is to be distributed in different geographical regions and if shipping is required for transportation, in that case long term stability studies are of prime importance. Long term stability studies are performed by testing the sample at specific time intervals and conditions of external parameters are changed accordingly.

Main objective of this study is to determine shelf-life of the drug product. Stability studies are mainly four types, they are Long term stability, Intermediate stability, Accelerated stability and In-use stability Studies.

Types of Stability Studies	Storage Conditions	Minimum Time Period (Months)
Long Term	25±2°C and 60±5% RH or 30±2°C and 65±5% RH	12
Intermediate	30±2°C and 65±5% RH	6
Accelerated	40±2°C and 75±5% RH	6

Table 1: Types of Stability Studies.

Stability Testing Methods

Stability testing is a procedure performed for all the pharmaceutical products at various stages of the product development. In the early stages, the stability testing is performed by the accelerated stability studies which mainly are performed at high temperature\ humidity.

The accelerated stability studies is easy to predict the degradation of the drug within short period of time. In the accelerated stability studies mainly the drug is performed at long-term storage. During this elevated temperatures are used to determine the products shelf-life. The main aim for the stability testing is to provide the acceptance level of fitness/ quality throughout the period during which they are available for the patience and should be fit for the acceptance of the drug by the patient. This helps the patient to be cured easily and the acceptance of the drug would be easy and the known therapeutic uses of the pharmaceutical products manufactured.

[6] Depending upon the aim, steps followed, the stability testing procedures have been categorized into four types and they are

1. Real-time stability testing
2. Accelerated stability testing
3. Retained sample stability testing
4. Cyclic temperature stress testing

1. Real-Time Stability Testing

Real-time stability tests are usually performed over a long period of time to allow significant product deterioration under the recommended storage conditions. The duration of testing a product depends on the stability of the product. This clearly shows that the product does not deteriorate or deteriorate over time due to variability between assays. During the test, samples are collected on a regular basis, so data is collected at an appropriate frequency and analysts can identify daily degradation. Data can be increased by including a single batch of reference material with established stability. The reagents and equipment used should be consistent throughout the stability test. Control of drift and discontinuity results due to reagent and equipment changes should be monitored.

2. Accelerated Stability Testing

This type of stability test is performed at a higher temperature and the breakdown of this product is determined. The information is used to predict shelf life or used to compare the relative stability of alternative formulations. Accelerated stability studies allow the shelf life to be easily predicted, reducing the time required to find out the stability of the substance. In addition to temperature, stress conditions are applied such as humidity, light, pH, and gravity.

Due to the vibration measurement, the time is also reduced compared to the real time test. For stability acceleration studies, stability forecasting was performed at four different stress temperatures. However, projections are obtained when denaturing stress temperature is avoided. Accelerated stability studies can be easily predicted using the Arrhenius . equation

In this method the drugs are stored at different temperatures such as 40°C, 60°C, 70°C, 80°C, 100°C etc. These studies are to be done at room temperature and at refrigerator temperatures. During different intervals the samples are collected and examined for the stability. The sampling is done at 3 months in the first year and 6 months interval the next year and yearly thereafter. The products which degrade very fast for them regular sampling at short duration of time should be done. When the temperature increases the decomposition of the substance is also very rapid. The stress tests used in the current ICH guidelines (40% for products are to be stored at controlled room temperature) were developed from a model that assumes energy of activation of about 83 KJ/mole.

$$k = Ae^{-\frac{E_a}{RT}} \quad or \quad ln\ k = -\frac{E_a}{RT} + ln\ A$$

Where:

k =	Chemical Reaction Rate
A =	Pre-exponential Factor
E_a =	Activation Energy
R =	Gas Constant
T =	Temperature in Kelvin

As per ICH and WHO the storage condition for accelerated stability studies is 40°C ± 2°C 75% RH ± 5% RH. If the product is unstable on the prescribed temperature and humidity intermediate conditions are used i.e. 30°C ± 2°C 65% RH ± 5% RH. FDA prescribes the sampling testing for 0, 2, 4, and 6 months respectively. WHO prescribes for 0, 1, 2, 3, 4, and 6 months. ICH prescribes the test to be performed for every 3 months in a year, 6 months in 2 years and yearly thereafter. These accelerated tests are mainly done for photochemical stability and moisture absorption. This test is performed for all the pharmaceutical preparations but mainly this is a test used for dispersed systems like pharmaceutical emulsions and suspensions

3. Retained Sample Stability Testing

This is a usual practice for every marketed product for which stability is needed. In this type of testing, the stability is done by selecting one batch for a year. If the number of samples exceeds more than 50 then they are divided into two batches.

At the time of first introduction of the product into the market the samples of every batch are taken which may decrease from 2% to 5% of the marketed batches at the later stages. The samples stability studies help to predict the shelf life. The maximum shelf life of every product predicted could be 5 years which is conventional to the test samples at 3, 6. 9, 12, 18, 24, 36, 48 and 60 months. This method of testing is also known as constant interval method. [6,10]

This type of stability sampling 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

Real time stability study	Accelerated stability study
Verify shelf-life over a period longer than shelf-life	Verify shelf-life within a short period of time
Conditions as per user requirements	Stressfull conditions are used i.e. at a elevated temperature
Product subjected to stress simulating transport before study (sequential approach)	Provide information about degradation of product and the obtained data must be verified by performing real time stability testing
Results predicted through Levy-Jennings plot	Results predicted through Arrhenius equation

Accelerated stability data is not sufficient to support the claimed shelf-life; hence, the data should be verified and finalized through real-time testing (Evaluation of stability of In-vitro Diagnostic Reagents, 2009). qualified equipment to meet finalized approved ir process quality control specifications (Establishin stability of an in-vitro diagnostic for WHO Prequal fication, 2017).

4. Cyclic Temperature Stress Testing

This method is not widely used for product sampling. In this method, cyclic temperature resistance tests are designed with product knowledge in mind to mimic marketable storage conditions. In this test, sampling is considered to be performed on a 24-hour cycle known as the earth's 24-hour rhythm. For this sample test, minimum and maximum temperatures are noted for each product depending on the product's temperature, storage conditions, chemical and physical degradation. To predict shelf life, 20 cycles should be used.

Guidance of Stability Studies

The drug to be administered for wellbeing of the patient the pharmaceutical preparation should be optimally stable and products are manufactured according to the standard guidance which are proposed by WHO, FDA, ICH. ICH plays a key role in the preparation and marketing of the preparations. ICH stands for "International Conference of Harmonization" which is used for the register of the pharmaceuticals products for human use.
The ICH was established in 1991, was a consortium formed inputs from both regulatory and industry from European commission, Japan, USA and various guidelines for drug substance and drug product came into existence regarding their quality, safety, efficacy and multidisciplinary (also known as Q, S, E, M). The secretariat of ICH is situated at Geneva, Switzerland. These guidelines include basic issues related to stability, the stability data requirements for application dossier and the steps for execution. Later in the year 1996 WHO (World Health Organization) has modified the guidelines proposed by ICH and WHO, in 2004 released the guidelines for stability studies in global environment. [6]

As the ICH did not assess the extreme climatic conditions found in many countries and it only covered new drug substances and the products which were earlier established. In 1997, June the United States Food and Drug Administered (US FDA) situated at Silver Spring also issued the guidelines but they were not entitled. The CDSCO (Central Drug Standards Control Organization) is a drug regulating authority for India situated at New Delhi.

ICH Codes	Guideline Titles
Q1A	Stability testing of new drug substances and products (second revision)
Q1B	Photo stability testing of new drug substances and products
Q1C	Stability testing of new dosage form
Q1D	Bracketing and Matrixing Designs for the stability testing of drug substances and products
Q1E	Evaluation of stability data
Q1F	Stability data package for registration applications in climatic zones III and IV
Q5C	Stability testing for biotechnological/ biological products
Q6A	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances
Q6B	Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products

Table 2: Codes and Titles used in ICH Guidelines.

The regulatory requirements vary from country to country. Thus, organizing the data and scrutinizing the application became difficult. Hence, there was an urgent need to rationalize and harmonize the regulations. The ICH Steering committee was established at the meeting and A decision was to be Series of guidelines related to stability testing have also been issued by the Committee for Proprietary Medicinal Products (CPMP) under the European agency for the Evaluation of Medicinal Products (EMEA) to assist the seeking marketing products. The Codes and Titles used in ICH[1,3] and CPMP. [1,3,12] Guidelines were tabulated in Table 2 .

Climatic Zones for Stability Studies

Stability studies are conducted worldwide, these stability studies cannot be performed in one location because temperature and other factors vary from country to country and location. For this reason, the world has been divided into four regions based on their climatic conditions so that product degradation and shelf life can be accurately predicted. Based on this data, real-time stability tests and accelerated stability tests were launched.

The standard climatic zones for the use of pharmaceutical stability studies are listed and the distribution of environmental conditions derived from the WHO long-term storage conditions are also listed. presented in Table 4.

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Climatic Zones	Climate	Countries	MAT*	Long-Term Testing Conditions
I	Temperate	United Kingdom, Russia, USA	<15C/<11hPa	21°C/45%RH
II	Subtropical and Mediterranean	Japan, Southern Europe	>15-22°C />11-18hPa	25°C/60%RH
III	Hot and Dry	Iraq, India	>22°C/<15hPa	30°C/35%RH
IV a	Hot and Humid	Iran, Egypt	>22°C/>15-17hPa	30°C/65%RH
IV b	Hot and very humid	Brazil, Singapore	>22°C/>27hPa	30vC/75%RH

*MAT - Mean annual temperature measured in open air.[3, 13, 14, 15]

Table 4: Climatic Zones and Long term stability conditions.

Factors Affecting Dose Stability

3.1 pH

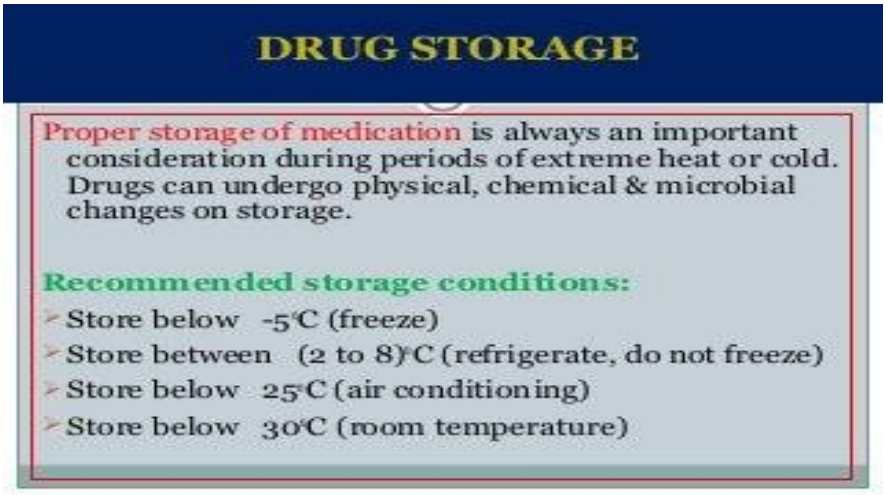
Value The pH value plays an important role in the solubility of the active ingredient and thus its bioavailability. Under extreme conditions, the rate of degradation is much higher. The optimal pH determines the pH at which a particular molecule is most soluble.

Buffer is also included in the pharmaceutical formulation, providing excellent stability. However, the pH and stability of formulations using these drugs can vary

3.2 Temperature

This is one of the most important factors for drug stability. It will rise to about 10°C during storage. Depending on the temperature, the decomposition reaction rate can be increased 2-5 times.

For some molecules the physicochemical stability is only ideal over a narrow temperature range. An increase in decline is observed outside this range. For the kinetics of the decomposition reaction of most active substances, we obey Arrhenius' law. Therefore, the stability of the formulation at room temperature can be determined by performing stability studies at elevated temperatures (e.g. 40 °C).



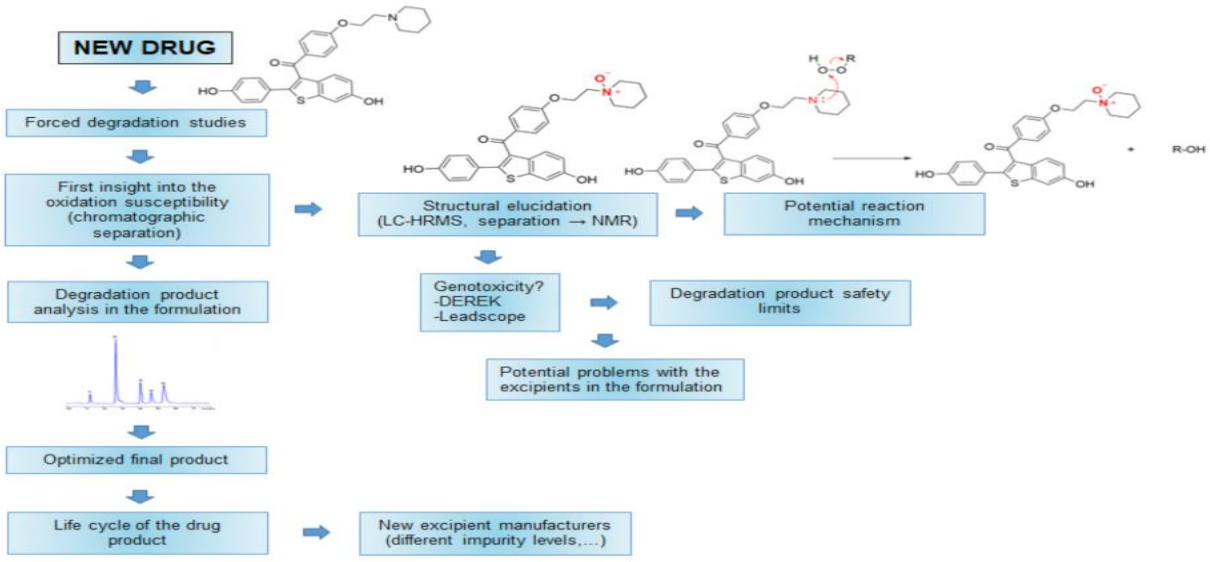
3.3 Surfactants

However, micelles in solution are formed by different types of surfactants (anionic, cationic, or nonionic). This trap of drug molecules alters their bioavailability in solution. Surfactants can be used to protect and limit the decomposition of active ingredients of hydrolyzing groups such as hydroxyl groups.

3.4 Oxidation

Oxidation of one of the drug components caused by the presence of oxygen in the oxygen formulation can lead to instability. The use of antioxidants and proper manufacturing techniques, such as under nitrogen, are essential.

A proper container with guaranteed integrity is an important factor in preventing the ingress of oxygen over time.



3.5 Light

Light is an important factor as it can cause chemical instability in photosensitive molecules. If precautions are applied during manufacturing, it is important to ensure that, for example, the selection of suitable packaging materials can be prevented and that they are maintained for a long period of time [10].

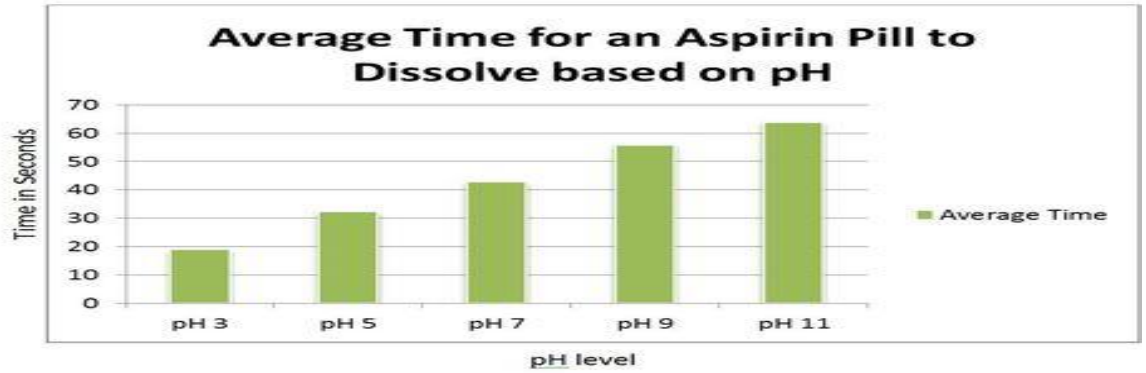
3.6 pH Rate Profile

The pH rate profile is the pH dependence of a particular rate constant for the decomposition of a compound. Sometimes referred to as the pH stability profile or rate-pH profile, it is easily represented by a log (k) vs. pH plot.

The pH profile helps develop more stable solution formulations, and the lyophilized product also provides insight into the catalytic properties of the reaction. Many drug degradation reactions are usually plotted in a pH rate profile that is subject to certain common acid-base catalysis, following an apparent primary reaction rate. General acid-base catalysis needs to be corrected by buffer components by extrapolation to zero buffer concentration if

the catalysis effect is significant. Analysis of a pH-rate profile can be started by assuming all possible pathways and writing down the corresponding rate equations The presence or absence of a certain mechanism can then be verified by analyzing the kinetic data..

Like as pH rate profile of aspirin



Conclusion

The review concluded that stability studies were used on the product to be formulated to predict shelf life, shelf life, determine appropriate storage conditions, and recommend labeling guidelines label.

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