STABILITY TESTING OF NEW PHARMACEUTICAL DRUG PRODUCTS

[1]Archana Gahtori, [2]Taniya Mamgain*

[1,2]School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Patel Nagar, Dehradun-248001, Uttarakhand, India.

Abstract:

The ability of a specific pharmaceutical substance or product in a specific closed system (container), to remain stable or among its specifications of physical, therapeutic, chemical, microbiological parameters right through its shelf life, it is known as the stability. The stability studies is a vital parameter in every field including the pharmaceutical sciences for the manufacturing of new pharmaceutical drugs as well as new pharmaceutical formulations. The assumption of the shelf-life is vital for the manufacturing of a pharmaceutical product of all the dosage forms and also the stability testing is performed to determine the instructions and conditions for the label and storage of a specific pharmaceutical dosage form.

For the manufacturing and acceptance of the pharmaceutical product i.e. the drug product or the API (Active Pharmaceutical Ingredient) i.e. the drug substance, stability testing are needed. For the acceptance and approval of pharmaceutical finished products, stability testing are necessary for confirming the products safety, quality and efficacy right through its shelf life.

This review paper represents the stability parameter which is used for the analysis of new finished product. The stability testing are required to be performed in a planned manner as per the ICH (International Conference on Harmonisation), WHO (World Health Organization) or other regulatory bodies. The ICH guideline for performing the new pharmaceutical finished product's stability testing are shown in this review paper.

Keywords: *Stability studies, pharmaceutical product, stability zones, ICH guideline, stability testing*

Corresponding author:

Taniya Mamgain,

School of Pharmaceutical Sciences, Shri Guru Ram Rai University,

Patel Nagar, Dehradun, Uttarakhand, India. Ph.no. : 7895176835, E-mail:
tmamgain22@gmail.com

QR code

INTRODUCTION:

For the acceptance and approval of pharmaceutical finished products or API, stability testing are necessary for confirming the products safety, quality and efficacy right through its shelf life. The Active Pharmaceutical Ingredient (API), i.e. the "drug substance" is a raw material that can then be combined with excipients to make a dosage form. The mixing of the active pharmaceutical component and the excipients that results in the final marketable finished product is referred to as a "drug product."

Stability studies is an important part in every field such as life sciences, food and beverage including the pharmaceutical sciences. Stability studies can be defined as "the ability of a specific pharmaceutical substance or product in a specific closed system (container), to remain stable or among its specifications i.e. physical, therapeutic, chemical microbiological conditions throughout its shelf life". Shelf life of a drug product is related to the drugs quality over a specific period of time. Shelf life is defined as the time between when the drug is manufactured and the expiry date of the drug. In pharmaceutical sciences the stability studies of a new drug substances and a pharmaceutical product is performed as per the International Conference on Harmonization Q1A (R2) guideline. Drug Stability studies are performed to determine the effects of environmental factors on a pharmaceutical product. The finished product shelf life, and therefore the viability of product formulation can be affected by various factors of environment. For determining the product expiry date and the storehouse conditions, stability testing of the product give the aided information which the industries use. [50]

Stability testing established the "re-test period," for the drug substance or API i.e. the expected time period during which the API remain within its standards, so it can be used for the given dosage form's production. After the completion of the re-test period of the API, it can only be used if further testing is done for its specification and the API passed the inspection. Then after meeting the acceptance standard, the API can used again. Stability studies established the shelf-life for the finished product by determines the time period between which the drug product is is therapeutically effective and safe for consumption.[30]

For giving the confirmation that with respect to time and under variety of impacted parameters of environment such as light, moisture and temperature, in what manner the quality of pharmaceutical finished product and active pharmaceutical ingredient differ,

stability studies are performed. It also determines the time of re-test time for API, shelf lives and the storage conditions of the product.

During a stability testing, products are stored in stability chambers maintaining various conditions of temperature and humidity. The product samples are withdrawn and their testing is done at predetermined time intervals which includes various physical parameters, microbiological limits, preservative analysis, and chemical parameters using fully validated procedures. Before starting the stability testing the acceptance criteria are decided. The stability testing may be stopped and proceed again if a product fails or do not comply with its acceptance limits at any stage only after the modifications have done or after the remanufacturing of the product.

IMPORTANCE OF STABILITY STUDIES:

* Stability studies is vital in estimation of shelf life of a product under controlled environmental conditions.
* Instability of an active pharmaceutical ingredient in a product results in under medication because of the decreased amount of the active ingredient in a dosage form.
* Stability studies are vital during the decomposition of the pharmaceutical drug or pharmaceutical product it may lead to toxic products.
* It is necessary because during the transportation of the pharmaceutical product from one place to another it has the ability to change its physical parameters.
* It helps to improve the drug quality and efficacy by estimating the impurities from the bulk pharmaceutical formulation.
* It supports the prediction of the expiry date of the pharmaceutical product and recommends the product storage conditions.

TYPES OF STABILITY STUDIES:

Testing primarily covers physical, chemical and microbiological attributes:

* Physical stability: Physical stability is the testing of the physical characteristics of the pharmaceutical drug product which includes description, appearance, water content, pH, dissolution rate, disintegration characteristics, melting point, clarity, viscosity etc.
* Chemical stability: Chemical stability is the testing of the chemical characteristics of the pharmaceutical drug product which includes related substances, degradation products, & assay.

- Microbial stability: Microbial stability is the testing of the microbial growth in the pharmaceutical drug product which includes preservatives content like antimicrobial & antioxidant preservatives and analyze the microorganisms growth.

Stability testing are performed at all the levels of the life cycle of the pharmaceutical drug product, starting from the initial stage of the production of the pharmaceutical product to the later stage of the stability (follow-up stability). The life cycle of the drug product is divided into 6 different stages as shown below [10]:

- Stage 1- Early stage stress- and accelerated testing with drug substances

- Stage 2- Stability on pre-formulation batches

- Stage 3- Stress testing on scale-up batches

- Stage 4- Accelerated and long term testing for registration purposes

- Stage 5- On-going Stability Testing

- Stage 6- Follow-up Stabilities.

METHODS OF STABILITY TESTING [5]:
According to ICH guideline the three major types of stability testing methods are:

Table 1: Stability testing methods

STABILITY TESTING METHODS	MINIMUM TIME PERIOD (MONTHS)
Long Term stability	12
Intermediate stability	6
Accelerated stability	6

Long term stability or real time stability:
Long term stability testing is needed for determining the shelf life of the drug product or for the approval of the finished product along with the accelerated stability study. It is performed for longer duration to allow deterioration of the product under the effect of humidity and temperature. Long term stability studies are performed for at least 12 months at $30 \pm 2°C$ temperature and $75 \pm 5\%$ of Relative humidity. For the study of the pharmaceutical product the time duration depends upon the product's stability that should enough extended that understandably tells that the product is not degraded and no quantitative deteriorate takes place for longer duration. The instruments and the chemicals used should be constant till the end of the testing in this type of studies of stability. There should be control on interruption in the results and also monitoring is done on the changes of both the instruments and the chemicals.

Intermediate stability:
Intermediate stability studies are not necessarily needed and they are only performed when the pharmaceutical product cannot bear the higher temperature and a significant change appears. The pharmaceutical drug product subjected in the accelerated stability condition, cannot bear the elevated temperature and fails the testing of the accelerated stability. Hence Intermediate stability testing is done at the condition below the accelerated stability studies i.e. below $40 \pm 2°C$ temperature and $75 \pm 5\%$ of Relative Humidity. Intermediate stability studies are performed for at least 6 months at $30 \pm 2°C$ temperature and $65 \pm 5\%$ Relative humidity. Intermediate stability testing are planned to relatively rise the time of the physical or chemical changes for the API or finished product.

ACCELERATED STABILITY:
In the testing of accelerated stability, a product is stored at conditions more than ambient relative humidity and temperature to determine the amount of humidity and heat needed to cause product degradation. Accelerated stability studies are performed for at least 6 months at $40 \pm 2°C$ temperature and $75 \pm 5\%$ of Relative humidity. As comparing the long term stability testing, the instability in this type of stability is decreased because for the duration studying the accelerated stability is short. Within the same assay, comparison of the unstressed sample with stressed sample is further done and it is indicated as percent of unstressed product recovery for the stressed product recovery. Accelerated stability testing is needed for the release and acceptance of the finished product simultaneously with the long term testing to confirm the shelf-life of a

product.

ICH STABILITY ZONES:

For performing stability studies, the storage conditions plays a vital role. From the actual climates of the different countries, the different storage conditions are obtained. Within the world, there are variety of climates with respect to countries. With respect to the

climatic conditions the stability testing of the pharmaceutical drug product should performed in that country. [1,11]

The world's climate is splitted into five zones as per the stability testing standards of ICH as shown in table 2.

Table 2: Stability Zones [11]

STABILITY ZONES	CLIMATIC CONDITION FOR THE ZONE	COUNTRIES	TEMPERATURE & HUMIDITY FOR LONG TERM STABILITY
I	Temperate	Canada, Russia, Romania, Germany	$21\pm2°C$ temperature and $45\pm5\%$ Relative Humidity
II	Subtropical	United States, Iran, South Africa, Australia, Spain	$25\pm2°C$ temperature and $60\pm5\%$ Relative Humidity
III	Hot & Dry	Iraq, Jordan, Botswana	$30\pm2°C$ temperature and $35\pm5\%$ Relative Humidity
IV a	Hot Humid & Tropical	Bangladesh, Saudi Arabia, Fiji, Pakistan, Sri Lanka	$30\pm2°C$ temperature and $65\pm5\%$ Relative Humidity
IV b	Hot & Very Humid	India, Ghana, Malaysia, Singapore	$30\pm2°C$ temperature and $75\pm5\%$ Relative Humidity

STABILITY TESTING OF A DRUG PRODUCT [5]:

General:

The framework for conducting the stability testing for the finished product should depends upon the knowledge of the stability testing of the active pharmaceutical ingredient and on the characteristics & behavior of the active pharmaceutical ingredient. It also depends upon the data from the production studies of the pharmaceutical product.

Photostability Testing [6]:

Photostability testing is an important form of stress studies. Photostability testing should performed on one batch of the pharmaceutical finished product at least which is the primary batch of that product.

❖ One batch of the product is selected only as mentioned in selection of batches for the

photostability studies.
❖ For photostability studies a planned approach is suggested which includes the following recommended studies:
a. Photostability testing on active pharmaceutical ingredient.
b. Photostability testing on the finished product which is exposed to the light & is outside of the immediate packing.
c. Photostability testing on the finished product which is inside the immediate packing.
d. Photostability testing on the finished product which is inside the marketing packing.

❖ Light sources:
a. Xenon lamps, UV-VIS (Ultraviolet-Visible) outputs fluorescent lamp, or metal lamp of halide.

b. UV lamp & fluorescent lamp which is white in coloured and is cooled.

Selection of Batches:
Three batches of the finished product is required at least for the stability testing. The batches should be of the same quality, having the same content & manufacturing and it should be packed in the same primary and secondary packaging which is meant for its marketing. The procedure and method for the production of the batches should be same as followed for the manufacturing batches and should produce product which follows same conditions meant for marketing of the product and produce products of the exact quality.

From the three batches for the stability studies, one batch can be of small-scale and the other two batches should be of pilot-scale batches at least. The stability testing should be conducted on each separate size of container and on each finished product strength except when bracketing is put in.

Container Closure System:
Stability studies of the pharmaceutical finished product should be performed on the same container or the same primary packaging in which the drug is packed. The product's marketed container and closure is exactly used for the study, which includes any label of the container or any secondary packaging material. Information regarding stability studies on the pharmaceutical drug product conducted outside of the immediate packaging of the product or conducted on packaging other than the actual material, supports the data of stability studies and is a helpful part of the pharmaceutical drug products stress studies.

Specification:
Stability testing of the pharmaceutical finished products should follows studies of those parameters of the finished product that have capability to change its characteristics during the transportation or storage and can affect the safety, quality and/or efficacy of the drug product. The stability studies of the drug product includes chemical, biological, microbiological and physical parameters, functionality studies like for a delivery system of the drug dose and the antimicrobial, antioxidant preservative level. There should be validated procedures for analytical testing which should indicates the stability. According to the validation testing results the replication should carried out.

From the information of all the stability testing of the drug product the acceptance criteria of the shelf life should obtained. Any changes between the antimicrobial preservative level's acceptance criteria of shelf life and release should justify with the validated correlation of effectiveness of preservative and chemical level showed during product (without preservative level) meant for marketing. For effectiveness of antimicrobial preservative (additional to preservative level) one batch of the finished product should be tested for verification at the shelf life mentioned, in a case where there is difference between the acceptance criteria of the shelf life and the release for preservative level.

Frequency of test:
Testing should be done frequently enough to assess the stability profile of the medicinal product in long-term studies. Testing at the long-term storage condition should be done every 3 months for the first time, every 6 months for the alternate time, and once a year for the remaining period for items with a predicted shelf life of at least 12 months. A least of three time points from a 6-month trial are recommended for the accelerated storehouse condition, including the original and final time points (e.g., 0, 3, and 6 months). When there is a fair assumption (based on development history) that accelerated testing findings would meet significant change standards, more tests must be conducted, either by enlisting the help of more testers or by providing more time.

When testing at the intermediate storehouse condition needed as a result of the significant change at the storehouse conditions of accelerated studies , a minimum of four time points from a 12 month testing, along with the original and final time period (e.g., 0, 6, 9, 12 months) is recommended.

Storage Conditions:
Usually, the stability of the pharmaceutical finished product should be tested under its given conditions for storage. The condition for storage of the drug product studies its ability to tolerate heat and moisture and studies its tolerance for solvent loss. For the drug product the extent and time till when the studies will performed and the condition for storage of the drug product should enough to cover its use, storage and transportation.

Table 3: Storage condition for different cases

STABILITY TESTING METHODS	TYPES OF CONTAINERS & STORING	CONDITIONS FOR STORAGE	MINIMUM TIME PERIOD (MONTHS)
Long term	General case	30 ± 2°C temperature and 75 ± 5% Relative Humidity	12
	Semi-permeable container	25 ± 2°C temperature and 40 ± 5% Relative Humidity or 30 ± 2°C temperature and 35 ± 5%	
	Storing in Refrigerator	Relative Humidity 5° ± 3°C temperature	
	Storing in Freezer	-20 ± 5°C temperature	
Intermediate	General case	30 ± 2°C temperature and 65 ± 5% Relative Humidity	6
Accelerated	General case	40 ± 2°C temperature and 75 ± 5% Relative Humidity	6
	Semi-permeable container	40 ± 2°C temperature and NMT 25% Relative Humidity	
	Storing in Refrigerator	25 ± 2°C temperature and 60 ± 5% Relative Humidity	

Storage condition for impermeable containers:
Pharmaceutical products stored in impermeable containers is not sensitive for loss of solvent and moisture. This type of container have the ability to stops permanently the solvent loss from the container or moisture to pass through it. So the drug product which are hygroscopic or having the ability for the loss of solvent, is safe when packed in an impermeable containers. Thus for the pharmaceutical finished products packed in an impermeable container the stability testing can be performed under any controlled condition or in any room temperature.

Evaluation of stability information:
An organized plan should be followed for the presentation of the stability data and its evaluation. Applicable results from the biological, chemical, microbiological, and physical parameters should cover by the plan, and also covers the specific properties of the dosage form like solid oral dosage forms dissolution tests. Based on the data collected from the testing of at least 3 batches of the finished products, the stability testing determined the storage conditions and the shelf life of the pharmaceutical products.

These storage conditions and shelf lives is for all the batches of the pharmaceutical product produced and packed under same environment and under same conditions that will manufactured in future. It is usually nit important to undergo the qualitative study when the analysis exhibit small variations and small degradations that is clear from the analysis that the asked shelf life will be allowed. Covey a reason for this is enough.

Labelling and statement on the containers:
A statement for the storage of the finished product should be set for the container label of the product with respect to the applicable regional or national necessities. Depending upon the analysis of the stability of the finished product, the statement should be established. Particular instructions should be allowed where relevant, especially for the finished products that cannot bear cold or chilling. "Room temperature" or "ambient condition" these words should not use.
The indicated stability of the finished products and the mentioned statement on the products storage label should have the direct connection. On the label of the container, expiry date should be indicated.

Significant change:
- ❖ According to ICH guideline:
  - For active pharmaceutical ingredients, when they do not follow their specifications, it is called the significant change.
  - Significant change for a finished drug product is:
1. From its actual value a 5% variation in the potency of the drug.
2. Any degradation substance not complying its acceptance criteria.
3. The physical parameter, appearance, etc., such as colour, hardness, caking, dose delivery, fails to comply its acceptance criteria.
4. Fails to meet the specification for pH.
   5. Fails to follow the specification for the 12 dosage of the dissolution test.

LIST OF ABBREVIATIONS:

ICH	International Conference on Harmonisation
WHO	World Health Organization
API	Active Pharmaceutical Ingredient
UV-VIS	Ultraviolet-Visible
NMT	Not More Than

CONCLUSION:
Stability testing of pharmaceutical finished products is a critical step in the manufacturing of novel pharmaceutical medications and formulations, and these studies have made it easier to forecast the shelf life, including the impact of environment conditions on product degradation. Any variation from the stated stability profile may have an impact on the product's quality, safety, and effectiveness. In order to add on the label of the containers the appropriate storehouse conditions and shelf life, stability tests are carried out. Confirming that the drug is safe and efficient for the duration of its shelf life. As a result, stability tests should be conducted using sound scientific principles, after a thorough understanding of current regulatory standards, and in accordance with climatic zones.

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