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STABILITY TESTING IN PHARMACY: A REVIEW

Peerzada Mohd. Younis*[1], Khaleeq ur Rehman[1], Basharat Rashid[2]

1. Department of Ilmus Saidla (Unani Pharmacy), National Institute of Unani Medicine, Bangalore-91.
2. Department of Tahaffuzi wa Samaji Tib (Preventive and Social Medicine), National Institute of Unani Medicine, Bangalore-91.

For Correspondence:

Dr. Peerzada Mohd. Younis

Department of Ilmus Saidla (Unani Pharmacy), National Institute of Unani Medicine, Bangalore-91

E-mail:

dryounispeer@gmail.com

ABSTRACT

All objects are influenced by their environment and degrade with time. Medicinal products also degrade with time thus significance and indispensability of stability testing in development of dosage forms/formulation is well recognized. Stability testing is necessary to ensure that the product is of acceptable quality throughout its entire storage period. The purpose of stability testing is to provide evidence on how the quality of a drug substance varies with time under the influence of various environmental factors. Recent efforts by the International Conference on Harmonization with regards to stability have brought an increased regulatory scrutiny at very low level. Hence display of expiry date on container or package has been made mandatory, further Photostability testing should be conducted on at least one primary batch of the drug product if appropriate.

INTRODUCTION

Stability is interpreted as length of time and are specific conditions of storage that the product will remain within predefined limits of all its characteristics and also to retain its physical, microbiological and biopharmaceutical within specified limits throughout its shelf life.[1, 2] The stability of a product relates to its resistance to various chemical, physical and microbiological reactions that may change the original properties of a preparation during transport, storage and use.[3] Stability testing aims to document how environmental factors, such as humidity temperature and UV visible radiation may alter the quality of a drug substances or product.[4] Stability study can be that of long term study, conducted for 12 months with storage conditions of $25^{o}C\pm2^{o}C/60\%$ RH$\pm$5% or $30^{o}C\pm2^{o}C/65$ RH$\pm$5%RH. In case of intermediate stability study, the storage conditions are set as $30^{o}C\pm2^{o}C/65\%RH\pm5\%RH$, and this study is carried out for 6 months. Stability study can be that of accelerated type wherein storage conditions are: $40^{o}C\pm2^{o}C/75\%RH\pm5\%RH$, this type of stability is carried out for six months. At the accelerated storage condition, minimum of three points, including the initial and final time points [e.g, 0, 3, and 6 months], is recommended for analysis. In case of expectation exists that the results from accelerated studies are likely to approach significant change criteria, increased testing should be done either by adding samples at the final time point or by including a fourth time point in the study design. [5, 6] Photostability testing should be conducted on at least one primary batch of the drug product if appropriate.[6] According to ICH guidelines covering the stability testing of new drug substances and products notes that light testing should be an integral part of stress testing. The intrinsic photostability characteristics of new drug substances and products should be evaluated to demonstrate, that as appropriate light exposure does not result in unacceptable changes. Normally, photostability testing is carried out on a single batch of material selected [7]

CONCEPT OF STABILITY

All objects are influenced by their environment and degrade with time. Medicinal products also degrade with time thus significance and indispensability of stability testing for determination of shelf life of pharmaceuticals is well recognized. Stability testing is necessary to ensure that product is of acceptable quality throughout its entire storage period.[8]

Need of Stability Testing

Chemical degradation and physical degradation of drug substance may change their pharmacological effects, resulting in altered therapeutic efficacy as well as toxicological

consequences. Because the pharmaceuticals are used therapeutically based on their efficacy and safety, they should be stable and maintain their quality until the time of usage or until their expiration date. The quality should be maintained under the various conditions that pharmaceuticals encounter during production, storage in warehouses, transportation and storage in hospitals and community pharmacies, as well as in the home. Therefore, understanding the factors that alter the stability of pharmaceuticals and identifying ways to guarantee their stability are critical stability testing is carried to see how long the active ingredients retain there potency under the influence of environmental factors, besides stability testing is part of good manufacturing practices which is to be followed before the launch of drug in the market. Stability testing importance can be understood from the fact that the results generated out of stability study determine the expiry period beyond which use of the drug would be hazardous to health. Apart from this stability study is carried to confirm the type of packaging best suitable to the drug concerned and to ensure that the product meets the quantitative requirements for all the claimed active ingredients and physicochemical properties throughout the proposed shelf life.[9]

Applicable guidelines on stability study

International conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human use (ICH) was formed in 1990, with primary focus on compilation of a common set of stability requirements for marketing authorization. An ICH Guideline on Stability testing (Q1A) was subsequently developed and published in 1993 after which it was adopted throughout the ICH region namely European Union, the USA, and Japan. Other countries like Australia, Canada, Switzerland and many followed the ICH guidelines in principle. Guidelines like European guidelines (EU), Japanese guidelines (MHW), Food and Drug Administration guidelines (FDA) and those prescribed by WHO are born out of ICH guidelines and have been named differently in different countries.[10]

Stability methods and storage conditions

Depending upon the aim and steps followed, stability testing procedures can be that of long term stability/real-time stability testing conducted for 12 months with storage conditions of $25^0C\pm2^0C/60\%$ RH$\pm5\%$ or $30^0C\pm2^0C/65\%$ RH$\pm5\%$.This type of stability study is of prime importance in case drug is to be distributed in different geographical regions and if shipping is required for transportation. Stability study can be that of intermediate type with storage conditions of $30^0C\pm2^0C/65\%RH\pm5\%RH$, conducted for six months, in case of accelerated type of stability study the storage conditions are set as $40^0C\pm2^0C/75\%RH\pm5\%RH$, and the

study is conducted for six months. [11] The proposal of dividing the world in different zones according to their climatic conditions was laid down by Grimm which facilitated the selection of storage conditions for different parts of the world, which otherwise would have resulted in large spread confusion. According to Grimm zone 1 indicates the areas with temperate climatic conditions, zone 11 indicates areas with subtropical and Mediterranean climate zone 111 indicates the areas with hot and dry climatic conditions and zone 1V is assigned to areas with hot and humid environmental conditions. [12] In 2005, the World Health Organization (WHO) proposed to split the climatic Zone 1V into two different Zones;1VA and 1VB in order to further facilitate the selection of storage conditions. Zone 1VA indicates the areas with hot and humid climate and Zone 1VB indicates the areas with hot and very humid climate. [13] Because of large geographical spread and diverse climatic conditions non of the storage conditions listed in new classification of WHO is suitable to India, the most justifiable test storage condition for India in case of long term stability study has been proposed as 30^0C/70%RH, although it was originally prescribed by the agency for Zone 1V.[14] Although for accelerated stability study storage conditions of 40^0C$\pm2^0$C/75%RH$\pm$5%RH as prescribed under ICH Q1A(R2) will be used.[15]

Accelerated stability studies

These studies include use of exaggerated storage conditions designed to increase rate of chemical and physical degradation and thereby monitoring degradation reactions and predicting the shelf life by real time stability studies. These type of studies are also employed to get comparative evidence of shelf life in cases where the drug is manufactured by different manufacturers, different processes are used, or manufacturing is done by different procedure or there is different packaging or in situations where volume and strength of the drug products is changed, in addition these type of studies can be used to assess long term chemical effects at non-accelerated conditions and to evaluate the effect of short-term excursions outside the label storage conditions such as that might occur during shipping. Accelerated study data is not always predictive of physical changes. The storage conditions in case of accelerated type of stability studies as recommended by ICH are 40^0C$\pm2^0$C/75%RH$\pm$5%RH and minimum time period covered at the submission of data is six months. [16]

Testing Frequency

Frequency of testing in case of long term study should normally be every 3 months over the first year, every 6 months over the second year and annually thereafter. In case of accelerated

study a minimum of three points including the initial and final time point is necessary e.g 0,3 and 6 months and in case of intermediate study four time points are proposed. In accelerated type of study if there is expectation that the results are likely to approach significant change criteria, increased testing should be conducted either by adding samples at the final time point or including a fourth time point in the study design. Significant change is defined as failure to meet specification like a 5% potency change from initial assay value, any specified degradient exceeding its acceptance criteria, failure to meet acceptance criteria for appearance and physical properties, the pH exceeding its acceptance criteria and dissolution exceeding the acceptance criteria for 12 dosage forms.[17]

Selection of batches

Stability information from accelerated and long term testing is to be provided on three batches of the same formulation and dosage form in the containers and closure proposed for marketing. [19]

Drug stability and effecting factors

Chemical, physical and microbiological stability together determines the drug stability, where physical stability implies that the formulation (Drug) is totally unchanged throughout its shelf life and has not suffered any changes in physical attributes, on the other side chemical stability implies that there is neither qualitative nor quantitative change in chemical setup of drug, while as microbiological stability of drug means that drug has not suffered from any microbial attack and is meeting the accepted criteria in terms of number/presence of microbes is concerned. [20]

Factors affecting any of the stability (Physical, chemical and microbiological) will result in drug instability. The factors affecting chemical stability include intrinsic factors as molecular structure of drug itself and environmental factors such as, temperature, pH, buffer species, ionic strength, light, oxygen, moisture, additives, and excipients, while the physical stability of pharmaceuticals is affected by many of the same variables that affect chemical stability but the amount of moisture plays a crucial role in physical stability. [21] Microbial contamination can result from various means present in environment such as air, soil, water, sewage, decomposing matter etc, which could render the drug hazardous and thereby result in microbiological instability of drug. The accepted level/presence of microbes for herbal drugs intended for internal use is,(1)Total bacterial count, maximum 10^5 per gram(2)Total fungal count: maximum 10^3 per gram(3) E.coli: maximum 10 per gram(4) clostridia, salmonella, and shigella should be absent per gram.[22]

PHOTOSTABILITY

The capacity of ultraviolet light to interact with chemicals was known and reported by Scheele in 1777, Ritter in 1801, Davy in 1812, and Becquerel in 1868 reported similar results. In 1851 the first edition of Dutch pharmacopoeia prescribed that iodine and silver nitrate is to be stored in closed black bottles, in order to restrict the changes caused by the light as much as possible, latter this approach was extended to all pharmaceutical preparations in latter editions. This clearly indicates that affect of light on drug substances and consequent photodegradation was scientifically proven before three millennium. [4]

Need of photostability testing

The photostability studies are conducted to determine that the appropriate light exposure which is expected to be faced by the drug does not result in unacceptable variation in dosage form. Photostability is concerned with the affect of light on stability of pharmaceutical substances. Active principle of drug can be affected by the light thereby result in loss of therapeutic profile.[24] According to ICH guidelines covering the stability testing of new drug substances and products, light testing should be an integral part of stress testing. Normally, photostability testing is carried out on a single batch of material (Drug) selected. [24]

Photostability Testing

Drug stability information is an important aspect towards systematic approach of the stability evaluation and for ensuring good quality. Photostability testing is an integral part of stability studies as recommended by ICH under Q1B guideline which deals with photostability testing of new drug substances and products. In case of drugs photostability testing consists of two parts; forced degradation and confirmatory testing. Forced degradation studies are conducted to determine overall photosensitivity of the drug substance, which will in turn facilitate the stability-indicating method development, degradation pathway, and types of degradation products formed. The aim of the confirmatory study is to estimate the response of the drug material to the light under standardized conditions. [25]

Radiation source

Photodegsradation of pharmaceuticals depends largely on the spectral distribution of light source, thus differences might generate with testing using different light sources in the evaluation of photostability. Therefore selection of light source is of utmost importance. In European countries evaluation of photostability of pharmaceuticals has been done using light sources that simulate sunlight, such as a xenon lamp, whereas the affect of room lighting has been evaluated in Japan using white fluorescent lamp. ICH guidelines regarding

photostability does not specify the selection of light source, but gives two options for light sources: (1) Option 1: Lamps having output similar to standard daylight e.g. Xenon or metal halide lamp. (2) Option 2: White fluorescent lamp and near-UV fluorescent lamps. To reduce the differences in evaluation between the two options, the minimum requirement for exposure level for both visible and near UV light was designated at 1.2 million lux hours and 200 watt hours per square meter, respectively. [21]

Presentation of samples

The solid drugs substances should be placed in glass or plastic dishes and covered with a suitable transparent cover, spreading them across the dish to give a thickness of typically not more than 3 millimeters is advocated. Drug substances which are liquid should be exposed in chemically inert and transparent containers. The samples should be positioned to provide maximum area of exposure to the light source. If the testing is to be done in marketed containers, the samples should be placed horizontally or transversally with respect to light source, which provides most uniform exposure to the samples. [23]

Analysis of samples

At the end of the exposure period, the samples should be examined for any changes in physical attributes like appearance, clarity, color etc. For the assay of degardients suitable method validated for the type of drug substances and likely nature of the degradardients should be taken in to consideration. The analysis of the exposed sample should be performed along with that of any protected sample used as dark control if used in the study. [23]

Interpretation of data

Photostability testing according to the ICH guideline will provide an indication as to whether photochemical degradation of the drug substance or drug product is likely to occur during transportation and shelf life. The results obtained are used to make packaging and labeling decisions as well as patient use decisions i.e. labeling directions for use.[4]

CONCLUSION

Stability is a critical quality attribute of pharmaceutical products, therefore stability testing plays a crucial role in the drug development process. The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity and light and to establish a retest period for a drug substance or a shelf life for the drug product and recommended storage conditions. Therefore it encompasses all the phases of the drug development process.

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