Real-time Stability Modelling Using Accelerated Environmental Profiles

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Abstract: Stability studies ensuring the maintenance of product quality, safety and efficacy throughout the shelf life are considered as pre-requisite for the acceptance and approval of any pharmaceutical product. These studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO and or other agencies. Importance of various methods followed for stability testing of pharmaceutical products, guidelines issued for stability testing and other aspects related to stability of pharmaceutical products have been presented in a concise manner in the present review

[Srinivas, R. **Real-time Stability Modelling Using Accelerated Environmental Profiles**. *The International Journal of Interpretation, Observation and Analysis*, 2024; Volume 3, Issue 1:18-21 (July-September). ISSN 2349-0713, Peer-reviewed (online/offline), Refereed, Indexed and International Journal (Since 2013), Global Impact Factor: 5.776

Keywords: Stability, Stability studies, Stability testing

Introduction

Stability testing of pharmaceutical products is a complex set of procedures involving considerable cost, time consumption and scientific expertise in order to build in quality, efficacy and safety in a drug formulation. Scientific and commercial success of a pharmaceutical product can only be ensured with the understanding of the drug development process and the myriad tasks and milestones that are vital to a comprehensive development plan. 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 (Singh et al., 2000). 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, toxicological, protective and informational specifications (Kommanaboyina et al., 1999). In other words, it is the extent to which a product retains, within the specified limits, throughout its period of storage and use, the same properties and characteristics possessed at the time of its packaging. Stability testing thus evaluates the effect of environmental factors on the quality of the a drug substance or a formulated product which is utilized for prediction of its shelf life, determine proper storage conditions and suggest labeling instructions. Moreover, the data generated during the stability testing is an important requirement for regulatory approval of any drug or formulation (Singh et al., 2000). Stability testing is termed as a complex process because of involvement of a variety of factors influencing the stability of a pharmaceutical product. These factors include stability of the active ingredient(s); interaction between active ingredients and excipients, manufacturing process followed, type of dosage form, container/closure system used for packaging and light, heat and moisture conditions encountered during shipment, storage and handling. In addition, degradation reactions like oxidation, reduction, hydrolysis or racemization, which can play vital role in stability of a pharmaceutical product, also depend on such conditions like concentration of reactants, pH, radiation, catalysts etc., as well as the raw materials used and the length of time between manufacture and usage of the product. A pharmaceutical product may undergo change in appearance, consistency, content uniformity, clarity (solution), moisture contents, particle size and shape, pH, package integrity thereby affecting its stability. Such physical changes may be because of impact, vibration, abrasion, and temperature fluctuations such as freezing, thawing or shearing etc. The chemical reactions like solvolysis, oxidation, reduction, racemization etc. that occur in the pharmaceutical products may lead to the formation of degradation product, loss of potency of active pharmaceutical ingredient (API), loss of excipient activity like antimicrobial preservative action and antioxidants etc. (Carstensen et al., 2000). 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 (Matthews et al., 1999).

IMPORTANCE OF STABILITY TESTING

The primary reason for stability testing is the concern for the well-being of the patient suffering from the disease for which the products is designed. Apart from degradation of the unstable product into toxic decomposition products, loss of

activity up to a level of 85% of that claimed on the label may lead to failure of the therapy resulting in death e.g. nitroglycerine tablets for angina and cardiac arrest. Because of this concern, it has become a legal requirement to provide data for certain types of stability tests for the regulatory agencies before approval of a new product. Second important concern is to protect the reputation of the manufacturer by assuring that the product will retain fitness for use with respect to all functionally relevant attributes for as long as they are on the market. Other benefits of stability studies at the developmental stage or of the marketed products are to provide a database that may be of value in selection of adequate formulations, excipients and container closure systems for development of a new product, to determine shelf life and storage conditions for development of a new product, preparation of registration dossier, to substantiate the claimed shelf life for the registration dossier and to verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product (Singh et al., 2000; Carstensen et al., 2000).

STABILITY TESTING METHODS

Stability testing is a routine procedure performed on drug substances and products and is employed at various stages of the product development. In early stages, accelerated stability testing (at relatively high temperatures and/or humidity) is used in order to determine the type of degradation products which may be found after long-term storage. Testing under less rigorous conditions i.e. those recommended for long-term shelf storage, at slightly elevated temperatures is used to determine a product's shelf life and expiration dates. The major aim of pharmaceutical stability testing is to provide reasonable assurance that the products will remain at an acceptable level of fitness/quality throughout the period during which they are in market place available for supply to the patients and will be fit for their consumption until the patient uses the last unit of the product (Kommanaboyina et al., 1999). Depending upon the aim and steps followed, stability testing procedures have been categorized into the following four types.

Real-Time stability testing

Real-time stability testing is normally performed for longer duration of the test period in order to allow significant product degradation under recommended storage conditions. The period of the test depends upon the stability of the product which should be long enough to indicate clearly that no measurable degradation occurs and must permit one to distinguish degradation from inter-assay variation. During the testing, data is collected at an appropriate frequency such that a trend analysis is able to distinguish instability from day-to-day ambiguity. The reliability of data interpretation can be increased by including a single batch of reference material for which stability characteristics have already been established. Stability of the reference material also includes the stability of reagents as well as consistency of the performance of the instrument to be used throughout the period of stability testing. However, system performance and control for drift and discontinuity resulting from changes in both reagents and instrumentation must be monitored (Anderson et al., 1991).

Accelerated stability testing

In accelerated stability testing, a product is stressed at several high (warmer than ambient) temperatures and the amount of heat input required to cause product failure is determined. This is done to subject the product to a condition that accelerates degradation. This information is then projected to predict shelf life or used to compare the relative stability of alternative formulations. This usually provides an early indication of the product shelf life and thus shortening the development schedule. In addition to temperature, stress conditions applied during accelerated stability testing are moisture, light, agitation, gravity, pH and package (Kommanaboyina et al., 1999). In accelerated stability testing the samples are subjected to stress, refrigerated after stressing, and then assayed simultaneously. Because the duration of the analysis is short, the likelihood of instability in the measurement system is reduced in comparison to the real-time stability testing. Further, in accelerated stability testing, comparison of the unstressed product with stressed material is made within the same assay and the stressed sample recovery is expressed as percent of unstressed sample recovery. For statistical reasons, the treatment in accelerated stability projections is recommended to be conducted at four different stress temperatures. However, for thermolabile and proteinaceous components, relatively accurate stability projections are obtained when denaturing stress temperatures are avoided (Anderson et al., 1991)

Retained sample stability testing

This is a usual practice for every marketed product for which stability data are required. In this study, stability samples, for retained storage for at least one batch a year are selected. If the number of batches marketed exceeds 50, stability samples from two batches are recommended to be taken. At the time of first introduction of the product in the

market, the stability samples of every batch may be taken, which may be decreased to only 2% to 5% of marketed batches at a later stage. In this study, the stability samples are tested at predetermined intervals i.e. if a product has shelf life of 5 years, it is conventional to test samples at 3, 6, 9, 12, 18, 24, 36, 48, and 60 months. This conventional method of obtaining stability data on retained storage samples is known as constant interval method (Kommanaboyina et al., 1999; Carstensen et al., 1993). Stability testing by evaluation of market samples is a modified method which involves taking samples already in the market place and evaluating stability attributes. 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 marketplace (Kommanaboyina et al., 1999).

PROTOCOL FOR STABILITY TESTING

The protocol for stability testing is a pre-requisite for starting stability testing and is necessarily a written document that describes the key components of a regulated and well-controlled stability study. Because the testing condition is based on inherent stability of the compound, the type of dosage form and the proposed container-closure system, the protocol depends on the type of drug substance or the product. In addition, the protocol can depend on whether the drug is new or is already in the market (Ali et al., 2008; Cha et al., 2001). The protocol should also reflect the regions where the product is proposed to be marketed e.g. if the product is planned to be used in climatic zones I-III, IVa and IVb, the stability program must include all these zones (Cha et al., 2001). A well designed stability protocol should contain the following information.

CLIMATIC ZONES FOR STABILITY TESTING

For the purpose of stability testing, the whole world has been divided into four zones (I - IV) depending upon the environmental conditions the pharmaceutical products are likely to be subjected to during their storage. These conditions have been derived on the basis of the mean annual temperature and relative humidity data in these regions. Based upon this data, long-term or real-time stability testing conditions and accelerated stability testing conditions have been derived. The standard climatic zones for use in pharmaceutical product stability studies have been presented in the Table 4. The break-up of the environmental conditions in each zone and also the derived long-term stability test storage conditions, as given by WHO have also been presented. The stability conditions have also been harmonized and adjusted to make them more practical for industry application and rugged for generalized application (Singh et al., 2000; ICH Q1A(R2), 2003)

PRESENTATION AND RECORDING OF STABILITY DATA

Stability data is recorded in an organized, comprehensive and cumulative format. The stability data table is the means for reporting the results of the stability study in a concise format for ease of review and interpretation. The data is recorded in a proper tabular format and all-encompassing information on a batch is recorded at one place. Similar sheets are prepared for each batch. When, it is not possible to collect a sample exactly at the designed time (i.e., 3, 6, 9, 12 month, etc.), the sample may be withdrawn conveniently, and the actual time of collection should be indicated in the format sheet. The data can be grouped by storage condition and time interval to present the stability as a function of time for each environmental condition studied. Data can be presented in multiple tables taking care that it is easily interpretable. In addition, a graphical presentation of stability data versus time for the test data can be used to illustrate trends in data and may be helpful for data evaluation. A graphical presentation of the data, however, cannot replace the tabular presentation for a regulatory filing. The results of the statistical analysis, wherever appropriate and analysis of impurities should also be discussed. Details on the above are available in ICH Q3A and Q3B (Cha et al., 2001).

QUALITY BY DESIGN (QbD)

Quality by design is a systematic approach to pharmaceutical product development that begins with pre-defined objectives and emphasizes product and process understanding and process control, based on sound science and quality risk management. It means designing and developing formulations and manufacturing processes to ensure a predefined quality. Thus, QbD requires an understanding of how formulation and process variables influence product quality. Relevant documents from the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH), ICH Q8, Pharmaceutical Development, along with ICH Q9, Quality Risk Management, and ICH Q10, Pharmaceutical Quality Systems, indicate on an abstract level how quality by design acts to ensure drug product quality (Lionberger et al., 2008). QbD is a scientific, risk based, holistic, and proactive approach to pharmaceutical development. It is a deliberate design effort from product conception through commercialization. The goal of QbD is to fully understand how certain

product attributes and process relate to the overall product performance. The potential advantage of the QbD approach to stability studies is to avoid conducting additional stability studies and filings when the scale, site, process, and route are altered from the initial registration stability batches. The barriers of this approach are related to cost, regulations, and guidelines.

CONCLUSION

Stability testing is now the key procedural component in the pharmaceutical development program for a new drug as well as new formulation. Stability tests are carried out so that recommended storage conditions and shelf life can be included on the label to ensure that the medicine is safe and effective throughout its shelf life. Over a period of time and with increasing experience and attention, the regulatory requirements have been made increasingly stringent to achieve the above goal in all possible conditions to which the product might be subjected during its shelf life. Therefore, the stability tests should be carried out following proper scientific principles and after understanding of the current regulatory requirements and as per the climatic zone.

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