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Review Article

Consideration of stability study in pharmaceutical product: A Review.

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ABSTRACT
As pharmaceutical industry, moving ahead with different innovative techniques is involved in it. Stability studies are a routine procedure for ensuring the maintenance of pharmaceutical product safety, quality and efficacy through the shelf life. These studies are required to be conducted in a planned way following the guidelines issued by ICH, WHO, or other drug approval agencies. Stability testing provides evidence that quality of a drug product under the influence of various environmental factors changes with time, temperature. Capacity of pharmaceutical product in given packaging. Performance through the retest or expiration period. This review article involves introduction about stability studies, types of stability studies, properties of stability studies, hazards of stability, region of world according temperature, drug stability.

KEYWORD
Stability, types of stability, stability guidelines, stability testing.

1. INTRODUCTION

Stability of a pharmaceutical product means how long it can maintain its original form without any visible changes under the influence various environmental factors like temperature, humidity, light. The physical, chemical and microbial properties of a pharmaceutical product may change under extreme storage conditions.

Drug stability refers to the extent to which a drug substance or product retains, within specified limits and throughout its period of storage and use, the same properties and characteristics that it possessed at the time of its manufacture.

Stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage and usage by the patient. It is measured by the rate of changes that take place in the pharmaceutical dosage forms.[1, 2]

The degradation of drugs and drug metabolites in samples can occur through either reversible or irreversible processes. Common factors that affect this stability include temperature, light, pH, oxidation and enzymatic degradation. CGMP Pharmaceutical Stability Studies and ICH Storage. They allow evaluation of active pharmaceutical ingredient (API) stability or drug product stability under the influence of a variety of environmental factors such as temperature, humidity and light.

The purpose of stability testing is to provide evidence on how the quality of an active pharmaceutical ingredient or medicinal product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the active pharmaceutical Clinical trials are understandably a critical and well-known part of the drug discovery, development and approval process, with results often featured in the media. Given the importance of drug safety, it is not surprising that there are a number of additional testing processes for the assessment of drug safety and efficacy. Although these tests are not as publicized as clinical trials, they are still very important. Stability testing is one such example.

An important step in the drug approval process, stability testing assesses how the quality of a drug substance or drug product (including its packaging) varies with time under the influence of environmental factors, including temperature, humidity and light. The process determines whether any physical, chemical or microbiological changes affect the efficiency and integrity of the final product, thereby ensuring that a pharmaceutical product is safe and effective, irrespective of where in the world it will be supplied. Moreover, stability testing establishes the shelf life and recommended storage conditions of a finished pharmaceutical product and the retest periods for a drug substance.

Comprised of two stages (stability storage and downstream analytical testing), stability testing ensures compliance with international regulations that form part of the registration process for a new drug substance or drug product.

For the purpose of stability testing, the International Conference on Harmonisation (ICH) divides the world into five climatic zones based on a combination of temperature and relative humidity (RH). This division ensures that the differences in climatic conditions in the varying regions of

the world are considered for stability studies. Zone I is defined as temperate, zone II as Mediterranean/subtropical, zone III as hot/dry, and zone IV as hot/humid. In addition, a zone IVb was introduced relatively recently, which is defined as hot/higher humidity and represents ASEAN (Association of Southeast Asian Nations) testing conditions. The climatic data that defines these regions is related to the Mean Kinetic Temperature (MKT), which is a widely used measure in the pharmaceutical industry to express the overall effect of temperature fluctuations during storage or transit.

The five climatic zones are replicated in long-term stability studies to simulate the conditions worldwide that a drug substance or drug product is subjected to. The ICH presents guidelines on the conditions that should be included in a stability study, which is often referred to as ICH conditions. The long-term testing conditions are shown in Table 2.

During stability testing, a drug substance or drug product is evaluated under the relevant ICH storage conditions, testing its thermal stability and its sensitivity to moisture. The storage conditions tested and the lengths of the studies chosen must cover the storage, shipment and use of the product. For example, if a drug is produced in the UK (Zone I) and shipped to Egypt (Zone IV) for distribution via Europe (Zones I and II), it would need to be tested under zones I, II and IV. Throughout the duration of the study, the stability of the drug is established through physical, chemical, biological and microbiological tests. An example of these tests is stress testing, of which photo stability testing is a specific case that assesses the effects of light exposure on the drug product or substance. A shelf life and label storage instructions are then determined from the results of the tests.[3, 4, 5]

1.1. Importance of stability studies

1. 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 re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.
2. Stability testing assesses how the quality of a drug substance or drug product (including its packaging) varies with time under the influence of environmental factors, including temperature, humidity and light.
3. The process determines whether any physical, chemical or microbiological changes affect the efficiency and integrity of the final product, thereby ensuring that a pharmaceutical product is safe and effective, irrespective of where in the world it will be supplied.
4. Stability testing establishes the shelf life and recommended storage conditions of a finished pharmaceutical product and the retest periods for a drug substance.[6]

1.2. Objective of stability studies

1) Our concerns for patients' welfare

♦ Obviously, our primary reason for stability testing should be our concern for the wellbeing of the patients who will use our products. Sometimes in the mad rush to comply with other requirements, this important fundamental may be discounted or forgotten. Indeed, sometimes one gains the impression that is some quarter's stability is regarded as having clinical relevance.

♦ Certainly, if a product that does not degrade to toxic decomposition products and that is characterized by a narrow therapeutic ratio is present on the market at only 85% of label claim; one would not expect patients to be dropping dead in the streets because of this deficiency instability.

♦ However, this is not to say that stability problems can never have serious clinical consequences. For example, in the early 1980s a packaging stability problem with nitro-glycerine tablets unfortunately resulted in some tablets have 10% of label claim. Since nitro-glycerine is used for the emergency treatment of a most serious cardiac conditions, angina, there is unfortunately strong cause for concern that some patients may have died as a result of this stability problem.

(2) To protect the reputation of the producer. We should be jealous for the reputation that the stability of our pharmaceutical products – compounded or manufactured – enjoys. Thus a most important reason for conducting a stability testing program is to assure ourselves the our products will indeed retain fitness for the use with respect to all functionally relevant attributes for as long as they are on the market.

(3) Requirements of regulatory agencies in many parts of the world, there are legal requirements that certain types of stability tests, as required by regulatory agencies, must be performed. Obviously, the law must be obeyed. However, it is wrong to abdicate from all scientific judgements and only conduct those stability tests that a regulatory agency is perceived as requiring. Indeed, there are occasions when any manufacturer with a true dedication to quality will perform stability tests that are over and above those required by regulation.

(4) To provide a database that may be of value in the formulation of other products. Data obtained in the stability evaluation of product X in 1999 may prove to be of value when, in 2003, we start developing product Y. There may be occasions, although they are probably rare, when it will worthwhile to continue stability testing on an R&D formulation that we know will never be marketed just because we are interested in the stability of a new excipient that we have included in the formulation.

(5) Shelf-life & storage condition and labeling specification: - By carrying out stability testing we can find out the shelf –life and expiry date can be calculated. We can have information about best storage condition at which drug will contain its characteristic for long time.

(6) Adequate formulation & container closer systems. We can have idea about the formulation which will be more stable. And if during stability testing we find any specification of container.

(7) How quality of drug substance or product varies with the time under the influence of various factors.

(8) Degradation product & possible degradation pathway

(9) Development & validation of stability indicating methodology

(10) Prevent great loss by recalling the batch due to stability. If any difficulty is found during storage and in marketed product, than industry has to recall all the drugs of that batch which is not economical. But if stability studies are carried out than we may overcome those problems.

(11) To verify that no changes have been introduced in the formulation or manufacturing process that can adversely affect the stability of the product
(12) Providing evidence on how quality of drug substance or product varies with the time under the influence of various factors like temp, humidity and light.
(13) Loss/increase in concentration of API
(14) Modification of any attribute of functional relevance, e.g., alteration of dissolution time/profile or bioavailability
(15) Loss of pharmaceutical elegance and patient acceptability.[7, 8]

1.3. Climatic Zones for Testing

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 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[9]

1.4. Regions of ICH stability zones

Table 1. Climatic zones.

Zones	Type of climate	Temperature	Humidity
Zone 1	Temperate zone	21ºC ± 2ºC	45% rH ± 5% rH
Zone 2	Mediterranean/subtropical zone	25ºC ± 2ºC	60% rH ± 5% rH
Zone 3	Hot dry zone	30ºC ± 2ºC	35% rH ± 5% rH
Zone 4 A	Hot humid/tropical zone	30ºC ± 2ºC	65% rH ± 5% rH
Zone 4 B	Hot higher humidity	30ºC ± 2ºC	75% rH ± 5% rH

Table 2. Long Term Testing Conditions.

Climatic Zone	Temperature	Humidity	Minimum Duration
Zone I	21ºC ± 2ºC	45% rH ± 5% rH	12 Months
Zone II	25ºC ± 2ºC	60% rH ± 5% rH	12 Months
Zone III	30ºC ± 2ºC	35% rH ± 5% rH	12 Months
Zone IV	30ºC ± 2ºC	65% rH ± 5% rH	12 Months
Zone IVb	30ºC ± 2ºC	75% rH ± 5% rH	12 Months
Refrigerated	5ºC ± 3ºC	No Humidity	12 Months
Frozen	-15ºC ± 5ºC	No Humidity	12 Months

Table 3. Accelerated and Intermediate Testing Conditions.

Climatic Zone	Temperature	Humidity	Minimum Duration
Accelerated Ambient	40ºC ± 2ºC	75% rH ± 5% rH	6 Months
Accelerated Refrigerated	25ºC ± 2ºC	60% rH ± 5% rH	6 Months
Accelerated Frozen	5ºC ± 3ºC	No Humidity	6 Months
Intermediate	30ºC ± 2ºC	65% rH ± 5% rH	6 Months

1.5. Factors affecting drug stability[10]

1. Temperature: high temperature accelerate oxidation, reduction and hydrolysis reaction which lead to drug degradation

2. PH: • Acidic and alkaline pH influence the rate of decomposition of most drugs.

• Many drugs are stable between pH 4 and 8.

• Weekly acidic and basic drugs show good solubility when they are ionized and they also decompose faster when they are ionized.

• So if the pH of a drug solution has to be adjusted to improve solubility and the resultant pH leads to instability then a way out of this tricky problem is to introduce a water miscible solvent into the product. It will increase stability by: - suppressing ionization - reducing the extreme pH required to achieve solubility - enhancing solubility and - reducing the water activity by reducing the polarity of the solvent. For example, 20% propylene glycol is placed in chlordiazepoxide injection for this purpose.

• Reactions catalysed by pH are monitored by measuring degradation rates against pH, keeping temperature, ionic strength and solvent concentration constant. Some buffers such as acetate, citrate, lactate, phosphate and ascorbate buffers are utilized to prevent drastic change in pH.

• Sometimes pH can have a very serious effect on decomposition. As little as 1 pH unit change in pH can cause a change of ten fold in rate constant. So when we are formulating a drug into a solution we should carefully prepare a pH – decomposition profile and then formulate the solution at a pH which is acceptable physiologically and stability-wise also.

3. Moisture:

a. Water catalyses chemical reactions as oxidation, hydrolysis and reduction reaction

b. Water promotes microbial growth

4. Light: affects drug stability through its energy or thermal effect which lead to oxidation

5. Pharmaceutical dosage forms: solid dosage forms are more stable than liquid dosage forms for presence of water.

6. Concentration: rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution. Stock solutions are concentrated solutions which diluted by using (i.e. syrup 85%) at high concentration the stability is high

7. Drug incompatibility: reactions between components of pharmaceutical dosage forms it self or between these components and cover of the container

8. Oxygen: exposure of drug formulations to oxygen affects their stability

1.5.1. Three stabilities of drug must be considered

A. Physical stability

B. Chemical stability

C. Microbiological stability

1.5.1.1. A. Physical stability

Physical instabilities possibilities are:

1. Crystal formation in pharmaceutical preparations:

Causes:

a. Polymorphism phenomena: i.e. Chloramphenicol (change of amorphous to crystalline form.

b. Saturated solution: by different temperature precipitation of solute may occur.

c. In suspension: when very fine powder is used a part of suspending agent will dissolve then precipitate as crystal.

2. Loss of volatile substances from pharmaceutical dosage forms:

Examples:

a. Aromatic waters

b. Elixirs

c. Spirits

d. Some types of tablets which contain aromatic water (Nitro-glycerine tablets)

3. Loss of water: This can be seen in the following dosage forms:

a. Saturated solution: by loss of water they become supersaturated and precipitate as crystal is formed

b. Emulsions: Loss of water leads to separation of the two phases and change to other type

c. Creams: especially oil/water, they become dry by loss of water

d. Pastes

e. Ointments: especially aqueous base ointments Humectants is added to the previous dosage forms which defined as hydrophilic substances added to aqueous phase to absorb water from atmosphere and prevent its loss from the dosage forms. Examples: Glycerine

4. Absorption of water: These phenomena can be seen in the following pharmaceutical forms:

a. Powders: Liquification and degradation may occur as a result of absorption of water

b. Suppositories which base made from hydrophilic substances as Glycerine, Gelatine, and poly ethylene glycol. The consistency of these forms becomes jelly-like appearance

5. Change in crystalline form: • Example: Cocoa butter which is capable of existing in four polymorphic forms.

1.5.1.2. B. Chemical stability

• It is discussed in chemical incompatibility unit

1.5.1.3. C. Microbiological stability

1. Contamination from microorganisms is a big problem for all formulations containing moisture but it can be a bother in solid dosage forms also if some natural polymers are used because many natural polymers are fertile sources of microorganisms.

2. In the type of hygienic manufacture carried out today where "Quality Assurance" is a prerequisite as per the GMP procedures, there are definite procedures to prevent microbial contamination in all formulations.

• ***Sources of Microbial Contamination***

1. Water
2. Air
3. Raw materials, containers and closures
4. Personnel
5. Instruments and apparatus

1.5.2. Packaging and Stability

Packaging of the drug product is very important when its stability is being considered.

• The immediate container and closure are particularly important in affecting product stability.

• Glass, plastic, rubber (natural and synthetic) and metal are the four types of containers commonly utilized for packing drug products.

1. Glass • Glass is resistant to chemical and physical change and is the most commonly used material, but it has the limitations of:

1. Its alkaline surface may raise the pH of the product.
2. Ionic radicals present in the drug may precipitate insoluble crystals from the glass 3. The clarity of the glass permits the transmission of high energy wavelength of light which may accelerate decomposition.

• ***All these limitations are overcome by the technologists in the following way***

1. The first problem is overcome by the use of Borosilicate glass which contains fewer reactive alkali ions
2. Treatment of glass with chemicals or the use of buffers helps in overcoming the second problem
3. Amber coloured glass which transmits light only at wavelengths above 470 nm is used for photolytic drug products.

2. Plastics • Plastics include a wide range of polymers of varying density and molecular weight, each possessing different physicochemical characteristics. The problems with plastic are:

1. Migration of the drug through the plastic into the environment.
2. Transfer of environmental moisture, oxygen, and other elements into the pharmaceutical product.
3. Leaching of container ingredients into the drug.
4. Adsorption or absorption of the active drug or excipients by the plastic. • For all these problems the solution is to suitably pretreat the plastic chemically. The drug product packed in the final container must be tested for stability.

3. Metals

•Various alloys and aluminium tubes may be utilized as containers for emulsions, ointments, creams and pastes.

• They may cause corrosion and precipitation in the drug product.
• Coating the tubes with polymers or epoxy may reduce these tendencies.

4. Rubber • Rubber also has the problems of extraction of drug ingredients and leaching of container ingredients described for plastics.
• The use of neoprene, butyl or natural rubber, in combination with certain epoxy, Teflon or varnish coatings reduces drug-container interactions.
• The pre-treatment of rubber vial stoppers and closures with water and steam removes surface blooms and also reduces potential leaching

1.5.1.2. Preservatives

• Extremely hygienic manufacture ensures a product that is free of contamination in the case of all non-sterile preparations and a sterile preparation in the case of all parenterals.
• There are two strategies followed in the manufacture of microbiologically stable, acceptable pharmaceutical preparations:
1. The first step is to prevent contamination of the product.
2. The second is to formulate the final product so that it is hostile to microorganisms and it is usually done by the addition of preservatives.
• For sterile preparations there is either a terminal sterilization process or a closely controlled aseptic manufacturing procedure. In every case the final product is so made to protect the product during storage and minimize contamination while the product is in use.
• When discussing microbiological stability we have to discuss parenterals as one class and the rest of the formulations as one class.
• Parenterals are either terminally sterilized or manufactured by an aseptic manufacturing procedure. To prevent contamination to the formulation during storage and use many steps are taken such as:
1. Suitably containers,
2. Usually using single dose containers,
3. Stickingto proper storage conditions
4. Adding an antimicrobial substance as preservative.

1.6. Mechanism of degradation

Safety, quality and purity of a drug and drug product are the essential attributes and form a fundamental basis for designing the stability studies. Pharmacopoeias are traditionally considered to be the safeguards and guarantee for the quality of drugs. The FDA emphasizes on the drug safety issue in terms of, efficacy of drug therapy determined by the side effect profile of the drug. Quality and purity of the drug product is determined by the various pathways of degradation such as, physical, chemical, microbiological and environmental degradation.
Drug substances used as pharmaceuticals have diverse molecular structures and are, therefore, susceptible to variable degradation pathways.

1.6.1. Physical degradation

Physical degradation emphasizes on the physical state of the drug substance or the excipient affecting the stability of the drug product. Components of pharmaceuticals (drug substances and

excipients) exist in various microscopic physical states with differing degrees of order ranging from, amorphous to crystalline and hydrated to solvated states. With time, the drug or the excipient may change from metastable to a more thermodynamically stable state. Changes in the physical state of the drug substance are assessed by DSC, DTA and X-ray diffraction analysis. Physical degradation is generally considered in terms of, physicochemical degradation to design stability studies.

1.6.2. Chemical degradation

Chemical degradation includes susceptibility of functional groups in the drug molecules to various reaction pathways that include hydrolysis, dehydration, isomerization, racemization, elimination, oxidation, photo degradation, and complex interactions with excipients and other drugs. If one could predict the chemical instability of a drug based on its molecular structure, it would help in designing the stability studies and identifying routes for formulating problematic drugs, at the earliest stages of drug development. Most parenteral drug products come in contact with water, and even in solid dosage forms; moisture is present that can lead to hydrolytic degradation.

1.6.2.1. Hydrolysis

Hydrolysis is a very common reaction pathway followed mainly in drug molecules that generally possess ester, ether or amide linkages. Lactones, lactams, spirans, carbozyclic acids, and other analogs are known to extensively undergo hydrolytic mechanism and processes.

1.6.2.2. Oxidative degradation

Oxidative degradation is one of the most frequently occurring mechanisms of pharmaceutical degradation and stability and methods for stability evaluation have been widely researched. Oxygen is abundant in the environment to which pharmaceuticals are exposed, either during processing or long-term storage conditions. Oxidative mechanism is known to follow any one of the three major pathways,

(i) autoxidation or radical-mediated involving 7 the reversal loss of electrons catalysed by peculiar initiators like, azobisisobutyronitrile (AIBN) or with transition metals such as Fe(II) or Cu(II)

(ii) peroxide-mediated, involving the exposure of drug products to dilute solutions of peroxide;

(iii) photochemically induced, in which the there is a direct reaction of ground state oxygen with electronically excited state of drug molecule or from photosensitization of triplet oxygen to singlet oxygen and direct reaction with the drug molecule.

(i) Autooxidation

(ii) Peroxide-mediated oxidation

1.6.2.3. Photo degradation

Photo chemically induced oxidation Photo degradation has been reported for a large number of drug substances. The mechanisms for these reactions are inherently complex and known to lead to loss in potency due to the formation of toxic photodegradation products. Light, generally sunlight may cause degradation of the drug or excipient molecule. In order to initiate a photolytic reaction, the energy from the light radiation must be absorbed by the molecules. If the energy

absorbed is sufficient to achieve the activation energy, then degradation of the molecule is possible. In certain cases, the molecules absorbing the light pass on their increased energy to other molecules which then degrade (photosensitization). Since the light energy may be converted to heat, photolysis is generally accompanied by a thermal reaction. [10]

***1.7. Guidelines for stability testing*[9, 11]**

ICH is the committee provides the stability guidelines for pharmaceutical products .ICH stand for international conference of harmonization. The guidelines give proper direction to check the stability of the pharmaceutical product and also the test for check the stability of the products.

Following is the stability guidelines of the pharmaceutical products.

1. Q1A (R2): Stability testing of new product and substances
2. Q1B: "Photo stability Testing of New Drug Substances and Products"
3. Q1C: "Stability Testing of New Dosage Forms"
4. Q3A: "Impurities in New Drug Substances"
5. Q3B: "Impurities in New Drug Products"
6. Q5C: "Stability Testing of Biotechnological/Biological Products"
7. Q6A: "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances"
8. Q6B: "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Biotechnological/Biological Products"

1.8. Stability testing methods

Stability of a pharmaceutical product means how long it can maintain its original form without any visible changes under the influence various environmental factors like temperature, humidity, light. The physical, chemical and microbial properties of a pharmaceutical product may change under extreme storage conditions. That's why; the shelf-life of a product has been studied during the stability testing. The pharmaceutical industry conducts this testing to develop a new product and establish the shelf-life of a product. Let's discuss the importance of stability study in the pharmaceutical industry.[12, 13]

1. Shelf-life determination

The quality of a pharmaceutical product varies with time under temperature, humidity and light intensity. Stability testing studies; how long a pharmaceutical product can be stored at normal and accelerated conditions without any degradation. This study helps to determine the shelf-life of that product. As per the report of the study, the expiry date of the product is fixed.

2. Storage condition recommendation

Different products require different storage conditions. Instability lab, storage conditions and changes in the substances are recorded. As per the stability study, storage condition is recommended for a particular product.

3. Elimination of impurities

Instability testing, each ingredient has been analysed under various environmental factors. So, it becomes easy to eliminate impurities.

4. Product Development

Stability testing is a reliable way to study the effectiveness of a new product. This testing helps to assess physical, chemical, therapeutic stability of a product. As per the study, R&D professionals redesign the existing product and develop a new product.

1. Ensures Quality

Quality assurance is an integral part of the pharmaceutical industry. The product is kept under the influence of high stresses and rate of decomposition is observed. Stability testing assures the purity of ingredients and the quality of the final product. The stability report ensures that the pharmaceutical product is fit for human consumption. This gives the companies confidence to launch new product in the market. The chances of product recall may decrease.

2. Packaging material selection

During stability testing, the pharmaceutical product is exposed to humidity and temperature. As per the effect of water activity and temperature on the product, packaging materials are chosen for the product. The ideal container must tolerate the stresses. The packaging should maintain the quality of the product during transportation and storage.

3. Legal approval

Stability testing of the pharmaceutical product is required for legal approval. If a product failed to meet the quality standards prescribed by ICH and WHO, the product will not get approval for commercialization.

1.8.1. Real-Time stability testing[14]

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.

1.8.2. Accelerated stability[14, 15, 16]

In accelerated stability tests, a product is stored at elevated stress conditions (such as temperature, humidity, and pH). Degradation at the recommended storage conditions can be predicted using known relationships between the acceleration factor and the degradation rate

The capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specification. In accelerated stability tests, a product is stored at elevated stress conditions (such as temperature, humidity, and pH). Degradation at the recommended storage conditions can be

predicted using known relationships between the acceleration factor and the degradation rate the capability of a particular formulation in a specific container/closure system to remain within its physical, chemical, microbiological, therapeutic and toxicological specification

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. 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 present 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 thermo labile and proteinaceous components, relatively accurate stability projections are obtained when denaturing stress temperatures are avoided. The concept of accelerated stability testing is based upon the Arrhenius equation (1) and modified Arrhenius equation:

$k=Ae^{-Ea/RT}$ ---Formula 1

Where, k=specific rate constant
A=frequency factor
Ea. = activation energy
R=ideal gas constant
T=absolute temperature.

These equations describe the relationship between storage temperatures and degradation rate. Using Arrhenius equation, projection of stability from the degradation rates observed at high temperatures for some degradation processes can be determined. When the activation energy is known, the degradation rate at low temperatures may be projected from those observed at "stress" temperatures. The stress tests used in the current International Conference on Harmonization (ICH) guideline (e.g., 40% for products to be stored at controlled room temperature) were developed from a model that assumes energy of activation of about 83 kJ per mole. A common practice of manufacturers in pharmaceutical industries was to utilize various shortcuts such as Q rule and bracket tables for prediction of shelf life of the products but these methods are not official either in ICH or FDA. The Q rule states that a product degradation rate decreases by a constant factor Q10 when the storage temperature is decreased by 10°C. The value of Q10 is typically set at 2, 3 or 4 because these correspond to reasonable activation

energies. This model falsely assumes that the value of Q does not vary with temperature. The bracket table technique assumes that, for a given analyte, the activation energy is between two limits (e.g., between 10 and 20 kcal). As a result, a table may be constructed showing days of stress at various stress temperatures. The use of a 10 to 20 kcal bracket table is reasonable because broad experience indicates that most analytes and reagents of interest in pharmaceutical and clinical laboratories have activation energies in this range.

1.8.3. Retained sample stability testing **[17]**

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 method2, 10. 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.

1.8.4. Cyclic temperature stress testing **[18]**

This is not a routine testing method for marketed products. In this method, cyclic temperature stress tests are designed on knowledge of the product so as to mimic likely conditions in market place storage. The period of cycle mostly considered is 24 hours since the diurnal rhythm on earth is 24 hour, which the marketed pharmaceuticals are most likely to experience during storage. The minimum and maximum temperatures for the cyclic stress testing is recommended to be selected on a product-by-product basis and considering factors like recommended storage temperatures for the product and specific chemical and physical degradation properties of the products. It is also recommended that the test should normally have 20 cycles.

1.8.5. Isothermal stress testing **[19, 20]**

Isothermal stress testing (IST) involves storage of drug–excipient blends with or without moisture at high temperature for a specific period of time (normally 3–4 weeks) to accelerate drug ageing and interaction with excipients. Samples can then be visually observed and the drug content determined quantitatively. Although more applicable, the disadvantage with this method is that it is time consuming and requires quantitative analysis using HPLC. Ideally, the techniques of DSC and IST should be used in combination for the selection of excipients. Chemical interaction between isosorbide mononitrate and cellulose acetate was confirmed by IST. A screening model to determine a potential stability problem due to interactions of drug substances with excipients in solid dosage forms has been developed. The model involved storing drug-excipient blends with 20% added water in closed glass vials at 500 C and analyzing them after 1 and 3 weeks for chemical and physical stability. Effect of factors like chemical

nature of the excipient, drug-to-excipient ratio, moisture, micro environmental pH of the drug-excipient mixture, temperature, and light, on dosage form stability could be identified by using the model. The compatibility of nateglinide with selected excipients was done by thermal and isothermal stress testing techniques

2. CONCLUSION

Stability testing of pharmaceutical product is the key procedure for contribution in the devlopment programe for new drug as well as new formulation. It is usefull to build the quality of the product. Over a period of time and with increasing experiences and attention in the regulatory requirments have been made incresingly stringent to achive the goal. Therefore the stability tests should be carried out following proper scientific principles and considering regulation guidelines.

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