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Degradation and its forced effect: A trenchant tool for stability studies

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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. The purpose of forced degradation testing studies is to evaluate the overall photosensitivity of the material for method development purposes and/or degradation pathway elucidation. This testing may involve the drug substance alone and/or in simple solutions/suspensions to validate the analytical procedures. In these forced degradation studies, a variety of exposure conditions may be used, depending on the photosensitivity of the drug substance involved and the intensity of the light sources used.

Key-Words: Stability testing, Degradative pathways, Forced degradation studies, ICH guidelines

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.

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[1-3].

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FACTORS

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.[4]

TYPES OF DRUG DEGRADATION

Chemical degradative routes

Solvolysis: In this type of reaction the active drug undergoes decompositionfollowingreaction with the solvent present like water and co solvent like ethyl alcohol or polyethylene glycol. These solvent can act as nucleophiles, attacking the electropositive centers and drug molecules. The most common

solvolysisreactions encountered in pharmaceuticals are those involving 'labile' carbonyl compounds such as esters, lactones, and lactums.

Oxidation: These reactions are important pathways of drug decomposition. In pharmaceutical dosage forms oxidation is usually mediated through reaction with atmospheric oxygen under ambient conditions, a process commonly referred as auto oxidation.

Photolysis: Normal sunlight or room light may cause substantial degradation of drug molecules. The energy from light radiation must be absorbed by the molecules to cause photolytic reactions. Example of photolysis is the photo degradation of sodium nitroprusside in aqueous solution.Sodium nitroprusside is administered by IV infusion for management of acute hypertension .f the solution is protected from light it is stable for at least one year, if exposed to normal room light, it has a shelf light of only 4 hours.

Dehydration: The preferred route of degradation for prostaglandin E2 and tetracycline is the elimination of water molecule from their structure. The driving force for this type of covalent degradation is the formation of double bond that can then participate in electronic resonance withneibouring functional group. In physical processes, such as those occur in theophylline hydrate and ampicillin, trihydratewater removal does not create new bonds but often changes the crystalline structure of the drug.

Racemization: The racemization of pharmacologically active agents is of interest because enantiomers often have significantly different absorption, distribution, metabolism, and excretion. The best known racemization reactions of drugs are those that involve epinephrine, pilocarpine, ergotamine and tetracycline. In these cases, the reaction mechanism appears to involve an intermediatecarbonium ion and carbanium ion which is stabilized electronically by the neighboring substituent group.

Incompatibilities: chemical interaction between two or more drug components in the same dosage form, or between active ingredient and a pharmaceutical adjuvant, occur frequently. Incompatibilities have also been observed in solid dosage form. A typical tablet contain binder, disintegrates, lubricants and fillers .compatibility screening for a new drug should consider two or more excipients from such class.

Other chemical degradation reactions: other chemical reaction such as hydration,decarboxylation or pyrolysis ,are also potential roots for drug degradation .for example:cyanocobalmine may absorb about 12% of water when exposed to air, and par amino salicylic acid decomposes with evolution of carbon dioxide to form m-aminophenol when subjected to temperature above 40degee centigrade

Physical degraditive Routes

Polymorphs are different crystals forms of the same compound. They are usually prepared by crystallization of the drug from different solvent under diverse condition .However exposure to changes in temperature,pressure, relative humidity and comminutionwhich are encountered in process such as drying, granulation, milling andcompression may also lead polymorphic transformations.

Vaporization: Some drugs and pharmaceutical adjutants possess sufficiently high vapor pressure that their volatilization constitute a measure route of drug loss .flavors whose constituents are mainly ketones,aldehydeand esters and co solvents (low molecular weight alcohol)may be lost from the formulation in this manner .The most frequently cited example of pharmaceutical that "degrades " by this route is nitroglycerine, which has a vapor pressure of 0.00026mm at 20 degree Celsius and 0.31 mm at 93degree Celsius .significant drug loss to the environment can occur during patient storage and usein 1972,FDA issued special regulations governing the type of containers that may be used for used for dispensing sublingual nitroglycerine.

Aging: This is the process through which changes in the disintegration and / or dissolution characteristics of the doses form are caused by subtle, and sometimes unexplained, alterations in the physiochemical properties of the inert ingredients or the active drugs in the doses form. Since the disintegration and dissolution steps may be rate –determining step in the absorption of drug, changes in these processes as a function of the"age"of the dosage form may result in corresponding changes in the bioavailability of the drug product.

"Aging" of the solid dosage forms can cause adecrease in their in vitro rate of dissolution, but a corresponding decrease in invitro absorption cannot be assumed automatically.

Adsorption:Drug-plastic interaction is increasingly being recognized as a major potential problem when intravenous solutions are stored in bags or in fused via administration sets that are made from polyvinyl chloride (PVC) for example,upto 50%drug loss can occur after nitroglycerine is stored in PVC infusion bags for 7 days at room temperature .This loss can be attributed adsorption rather than chemical degradation because the drug can be recovered from the inner surface of the container by rinsing with the less polar solvent (methanol in this case). [2]

FORCED DEGRADATIONS

Forced degradation is a degradation of new drug substance and drug product at conditions more severe than accelerated conditions. It is required to demonstrate specificity of stability indicating methods and also provides an insight into degradation pathways and degradation products of the drug substance and helps in elucidation of the structure of the degradation products. Forced degradation studies show the chemical behavior of the molecule which in turn helps in the development of formulation and package. In addition, the regulatory guidance is very general and does not explain about the performance of forced degradation studies.

These studies are undertaken to elucidate intrinsic stability characteristics.Such testing is part of the development strategy and is normally carriedout under more severe conditions than those used for acceleratedtests. Stress testing is conducted to provide dataunforced decompositionproducts and decomposition mechanisms for the drug substance. Thesevere conditions that may be encountered during distribution can becovered by stress testing of definitive batches of drug substance.'

Objective of forced degradation studies

Forced degradation studies are carried out to achieve the following purposes:

1. To establish degradation pathways of drug substances and drug products.
2. To differentiate degradation products that are related to drug products from those that are generated from non-drug product in a formulation.
3. To elucidate the structure of degradation products.
4. To determine the intrinsic stability of a drug substance in formulation.
5. To reveal the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product.
6. To establish stability indicating nature of a developed method.
7. To understand the chemical properties of drug molecules.
8. To generate more stable formulations.
9. To produce a degradation profile similar to that of what would be observed in a formal stability study under ICH conditions.
10. To solve stability-related problems.

Strategy for selection of degradation conditions

Forced degradation is carried out to produce representative samples for developing stability-indicating methods for drug substances and drug products. The choice of stress conditions should be consistent with the product's decomposition under normal manufacturing, storage, and use conditions which are specific in each case. A general protocol of degradation conditions used for drug substance and drug product is presented in figure 1.

A minimal list of stress factors suggested for forced degradation studies must include acid and base hydrolysis, thermal degradation, photolysis, and oxidation and may include freeze–thaw cycles and shear. There is no specification in regulatory guidelines about the conditions of pH, temperature and specific oxidizing agents to be used. The design of photolysis studies is left to the applicant's discretion although Q1B specifies that the light source should produce combined visible and ultraviolet (UV, 320–400 nm) outputs, and that exposure levels should be justified. The initial trial should have the aim to come upon the conditions that degrade the drug by approximately 10%.

Some conditions mostly used for forced degradation studies are presentedin table 1.

Some scientists have found it practical to begin with extreme conditions such as 80 °C or even higher temperatures and testing at shorter (2, 5, 8, 24 h, etc.) multiple time points, so that the rate of degradation can be evaluated. The primary degradants and their secondary degradations products can be distinguished by testing at early time points and thus help in a better degradation pathway determination. In another approach degradation is started by considering the drug substance to be labile and doing degradation at the conditions mentioned above. Then stress would be increased or decreased to obtain sufficient degradation. As compared to harsher conditions and less time approach, this strategy is better due to the following reasons: (I) there may be a change in mechanism of reaction when a harsh condition is used, and (ii) there is a practical problem in neutralizing or diluting every sample, when it contains a high concentration of reactants, e.g., acid or base, before an injection can be made on the HPLC column. Both these reasons are strong enough to suggest that as normal as possible conditions should be used for causing the decomposition of the drugs. Studies should be repeated when formulations or methods change because the change may lead to the production of new degradation products.

Selection of drug concentration

Which concentration of drug should be used for degradation study has not been specified in regulatory guidance. It is recommended that the studies should be initiated at a concentration of 1 mg/mL. By using drug concentration of 1 mg/mL, it is usually possible to get even minor decomposition products in the range of detection. It is suggested that some degradation studies should also be done at a concentration which the drug is expected to be present in the final formulations. The reason for proposing this is the examples of aminopenicillins and aminocephalosporins where a range of polymeric products have been found to be formed in commercial preparations containing drug in high concentrations.

Degradation conditions

Hydrolytic conditions

Hydrolysis is one of the most common degradation chemical reactions over a wide range of pH. Hydrolysis is a chemical process that includes decomposition of a chemical compound by reaction with water. Hydrolytic study under acidic and basic condition involves catalysis of ionizable functional groups present in the molecule. Acid or base stress testing involves forced degradation of a drug substance by exposure to acidic or basic conditions which generates primary degradants in desirable range. The selection of the type and concentrations of acid or base depends on the stability of the drug substance. Hydrochloric acid or sulfuric acids (0.1–1 M) for acid hydrolysis and sodium hydroxide or potassium hydroxide (0.1–1 M) for base hydrolysis are suggested as suitable reagents for hydrolysis and. If the compounds for stress testing are poorly soluble in water, then co-solvents can be used to dissolve them in HCl or NaOH. The selection of co-solvent is based on the drug substance structure. Stress testing trial is normally started at room temperature and if there is no degradation, elevated temperature (50–70 °C) is applied. Stress testing should not exceed more than 7 days. The degraded sample is then neutralized using suitable acid, base or buffer, to avoid further decomposition.

Oxidation conditions

Hydrogen peroxide is widely used for oxidation of drug substances in forced degradation studies but other oxidizing agents such as metal ions, oxygen, and radical initiators (e.g., azobisisobutyronitrile, AIBN) can also be used. Selection of an oxidizing agent, its concentration, and conditions depends on the drug substance. It is reported that subjecting the solutions to 0.1–3% hydrogen peroxide at neutral pH and room temperature for seven days or up to a maximum 20% degradation could potentially generate relevant degradation products. The oxidative degradation of drug substance involves an electron transfer mechanism to form reactive anions and cations. Amines, sulfides and phenols are susceptible to electron transfer oxidation to give N-oxides, hydroxylamine, sulfones and sulfoxide. The functional group with labile hydrogen like benzylic carbon, allylic carbon, and tertiary carbon or α-positions with respect to hetro atom is susceptible to oxidation to form hydro peroxides, hydroxide or ketone.

Photolytic conditions

The photo stability testing of drug substances must be evaluated to demonstrate that a light exposure does not result in unacceptable change. Photo stability studies are performed to generate primary degradants of drug substance by exposure to UV or fluorescent conditions. Some recommended conditions for photostability testing are described in ICH guidelines. Samples of drug substance and solid/liquid drug product should be exposed to a minimum of 1.2 million lx h and 200 W h/m^2 light. The most commonly accepted wavelength of light is in the range of 300–800 nm to cause the photolytic degradation. The maximum illumination recommended is 6 million lx h Light stress conditions can induce photo oxidation by free radical mechanism. Functional groups like carbonyls; nitro aromatic, N-oxide, alkenes, aryl chlorides, weak C—H and O—H bonds, sulfides and polyenes are likely to introduce drug photosensitivity.

Thermal conditions

Thermal degradation (e.g., dry heat and wet heat) should be carried out at more strenuous conditions than recommended ICH Q1A accelerated testing conditions. Samples of solid-state drug substances and drug products should be exposed to dry and wet heat, while liquid drug products should be exposed to dry heat. Studies may be conducted at higher temperatures for a shorter period. Effect of temperature on thermal degradation of a substance is studied through the Arrhenius equation:

$k = A e^{-Ea/RT}$.

where k is specific reaction rate, A is frequency factor, Ea is energy of activation, R is gas constant (1.987 cal/deg mole) and T is absolute temperature.Thermal degradation study is carried out at 40–80 °C[1].

ICH GUIDELINES FOR STABILITY STUDIES

- Q1A(R2)-stability testing of new drug substances and drugs.
- Q1B-stability testing: photo stability testing of new drug substances and products.
- Q1C-stability testing for new dosage forms.

- Q1D-braketing and matrixing designs for stability testing of new drug substances and products.
- Q1E-evaluation of stability data.
- Q1F-stability data package for registration applications in climate zones 3rd and 4th
- Q5C- stability testing of biotechnological/biological products.

STABILITY INDICATING METHOD (SIM)

A stability indicating method (SIM) is an analytical procedure used to quantitative the decrease in the amount of the active pharmaceutical ingredient (API) in drug product due to degradation. According to an FDA guidance document, a stability-indicating method is a validated quantitative analytical procedure that can be used to detect how the stability of the drug substances and drug products changes with time. A stability-indicating method accurately measures the changes in active ingredients concentration without interference from other degradation products, impurities and excipients.Stress testing is carried out to demonstrate specificity of the developed method to measure the changes in concentration of drug substance when little information is available about potential degradation product. The development of a suitable stability indicating method provides a background for the pre-formulation studies, stability studies and the development of proper storage requirements. Bakshi and Singh discussed some critical issues about developing stability indicating methods. Dolan made comments and suggestions on stability indicating assays. Smela discussed from a regulatory point of view about stability indicating analytical methods. The RP-HPLC is a most widely used analytical tool for separation and quantifying the impurities and it is most frequently coupled with a UV detector. The following are the steps involved for development of SIM on HPLC which meets the regulatory requirements.

Sample generation

For generating samples for SIM the API is force degraded at conditions more severe than accelerated degradation conditions. It involves degradation of drug at hydrolytic, oxidative, photolytic and thermal conditions as discussed earlier. The forced degradation of API in solid state and solution form is carried out with an aim to generate degradation products which are likely to be formed in realistic storage conditions.This sample is then used to develop an SIM.

Method development and optimization

Before starting the method development, various physiochemical properties like pKa value, log P, solubility and absorption maximum of the drug must be known, for it lays a foundation for HPLC method development. Log P and solubility helps select mobile phase and sample solvent while pKa value helps determine the pH of the mobile phase[2].

Reverse phase column is a preferred choice to start the separation of sample components as the degradation is carried out in aqueous solution. Methanol, water and acetonitrile can be used as mobile phase in various ratios for the initial stages of separation. Selection between methanol and acetonitrile for organic phase is based on the solubility of the analyte. Initially the water: organic phase ratio can be kept at 50:50 and suitable modifications can be made as trials proceed to obtain a good separation of peaks. Latter buffer can be added if it is required to obtain better peak separation and peak symmetry. If the method is to be extended to liquid chromatography–mass spectrometry (LC–MS), then mobile phase buffer should be MS compatible like triflouroacetic acid and ammonium format. Variation in column temperature affects the selectivity of the method as analytes respond differently to temperature changes. A temperature in the range of 30–40 °C is suitable to obtain good reproducibility. It is better to push the drug peak further in chromatogram as it results in separation of all degradation products. Also a sufficient run time after the drug peak is to be allowed to obtain the degradants peak eluting after the drug peak[3].

During the method development it may happen that the drug peak may hide an impurity or degradant peak that co-elutes with the drug. This requires peak purity analysis which determines the specificity of the method. Direct analysis can be done on line by using photo diode array (PDA) detection. PDA provides information of the homogeneity of the spectral peak but it is not applicable for the degradants that have the similar UV spectrum to the drug. Indirect method involves change in the chromatographic conditions like mobile phase ratio, column, etc. which will affect the peak separation. The spectrum of altered chromatographic condition is then compared with the original spectra. If the degradant peaks and area percentage of the drug peak remain same, then it can be confirmed that the drug peak is homogeneous. Thedegradant that co-elutes with the drug would be acceptable if it is not found to be formed in accelerated and long term storage conditions. The method is then optimized for separating closely eluting peaks by changing flow rate, injection volume, column type and mobile phase ratio.

Method validation

The developed SIM is then validated according to USP/ICH guideline for linearity, accuracy, precision, specificity, quantitation limit, detection limit,

ruggedness and robustness of the method. It is required to isolate, identify and quantitative the degradants found to be above identification threshold (usually 0.1%).If the method does not fall within the acceptance criteria for validation, the method is modified and revalidated[4-5].

Other analytical methods for developing SIM

Stability-indicating methods will be characterized by potency, purity and biological activity. The selection of tests is product specific. Stability indicating methods may include various methods like electrophoresis (SDS-PAGE, immunoelectrophoresis, Western blot, and isoelectrofoccusing), high-resolution chromatography (e.g., reversed phase chromatography, SEC, gel filtration, ion exchange, and affinity chromatography) and peptide mapping. The analytical method of choice should be sensitive enough to detect impurities at low levels (i.e., 0.05% of the analyte of interest or lower) and the peak responses should fall within the range of detector's linearity. The analytical method should be capable of capturing all the impurities formed during a formal stability study at or below ICH threshold limits. Degradation product identification and characterization are to be performed based on formal stability results in accordance with ICH requirements. Conventional methods (e.g., column chromatography) or hyphenated techniques (e.g., LC–MS, LC–nuclear magnetic resonance (NMR)) can be used in the identification and characterization of the degradation products. Use of these techniques can provide a better insight into the structure of the impurities that could add to the knowledge space of potential structural alerts for genotoxicity and the control of such impurities with tighter limits. It should be noted that structural characterization of degradation products is necessary for those impurities formed during formal shelf-life stability studies and above the qualification threshold limit[6-7].

New analytical technologies that are continuously being developed can also be used when it is appropriate to develop stability indicating method. The unknown impurity, which is observed during the analysis, pharmaceutical development, stress studies and formal stability studies of the drug substances and drug product, can be separated and analyzed by using various chromatographic techniques like reversed phase high performance liquid chromatography (RP-HPLC), thin layer chromatography (TLC), gas chromatography (GC), capillary electrophoresis (CE), capillary electrophoresis chromatography (CEC) and super critical fluid chromatography (SFC). An excellent combination of hyphenated chromatographic and spectroscopic technique such as HPLC-photodiode array ultraviolet detector (DAD), LC–MS, LC–NMR and GC–MS are used when degradants cannot be isolated in pure form. HPLC-DAD and LC–MS are used to compare the relative retention time (RRT), UV spectra, mass spectra (MS/MS or MSN) Singh and Rehman discussed the role of hyphenated systems for the isolation of degradants and impurities.[8]

MAKING THE LINK BETWEEN FORCED DEGRADATION STUDIES AND STABILITY DATA

Forced degradation of drug substances has the potential to form many more degradation products than those observed to form during stability testing. However, this minimizes the potential for not detecting the actual degradation products formed during stability testing. Thus, if appropriate forced degradation studies have been performed, the method can be considered to be stability indicating. In such cases, the absence of observed degradation products demonstrates that the drug substance is stable to degradation under the conditions it was stored rather than the method being incapable of detecting degradation products.

The results from the forced degradation studies can also be used to investigate the mechanism of degradation for a drug substance on storage. In turn, this understanding can be used to define the appropriate packaging to minimize or eliminate the degradation of the drug substance[9].

OVERVIEW OF REGULATORY GUIDANCE

Forced degradation studies are described in various international guidelines. The International Committee for Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) [10] has published a set of guidelines which have been discussed, agreed upon and adopted by the American, European and Japanese regulatory authorities. In the majority of cases, the ICH guidelines only apply to the marketing applications for new products, i.e., they do not apply during clinical development. However, since the conditions used for forced degradation are only defined in general terms, it is possible to apply them for developing stability indicating methods during clinical development. The same forced degradation conditions can then be applied to the drug substance during development and commercialization. The ICH guidelines that are applicable to forced degradation studies are:

- ICH Q1A – Stability Testing of New Drug Substances and Products [2]
- ICH Q1B – Photostability Testing of New Drug Substances and Products [3]
- ICH Q2B – Validation of Analytical Procedures: Methodology [4]

In ICH Q1A, section 2.1.2 (Stress Testing), there are recommended conditions for performing forced degradation studies on drug substances and drug products. The recommendations are to examine the effects of temperature (above that for accelerated testing, i.e., >50°C), humidity (≥75% relative humidity), oxidation and photolysis. Testing in solution should also be performed across a wide pH range either as a solution or suspension. These samples are then used to develop a stability-indicating method[11].

ICH Q1B gives recommended approaches to assessing the photostability of drug substances and drug products. Forced degradation conditions are specified in Section II (drug substance) and Section III (drug product)[12]. Exposure levels for forced degradation studies are not defined, although they can be greater than that specified for confirmatory (stability) testing. The actual design of photostability studies is left to the applicant; however, scientific justification is required where light exposure studies are terminated after a short time, e.g., where excessive degradation is observed. Photostability testing can be performed on the solid or in solution/suspension. These samples are then used to develop a stability indicating method.

Both guidance's, Q1A and Q1B, note that some of the degradation products formed during forced degradation studies may not actually be observed to form during stability studies, in which case they need not be examined further.

ICH Q2B gives guidance on how to validate analytical methodology and in section B 1.2.2 (impurities not available) there is a recommendation to use samples from forced degradation studies to prove specificity. Specificity is a key factor in determining whether or not the analytical method is stability indicating. Co-elution of peaks or components being retained on the column will underestimate the amount of degradation products formed and could compromise quality and increase risk to the patient[13].

Conclusion

Forced Degradation Studies are an essential component in developing stability-indicating methodology. There are many aspects to cover and the use of good scientific judgement and knowledge is required to ensure that the forced degradation samples produced contain realistic primary degradation products. There is a strong likelihood that many more forced degradation products will be observed than what actually form in accelerated or real-time stability trials. If these criteria are followed, then the analytical methodology has the maximum potential to detect real degradation products formed on accelerated or real-time stability testing. Thus, the absence of observed degradation products can be attributed to the stability of the drug substance rather than deficiencies in the analytical methods[14].

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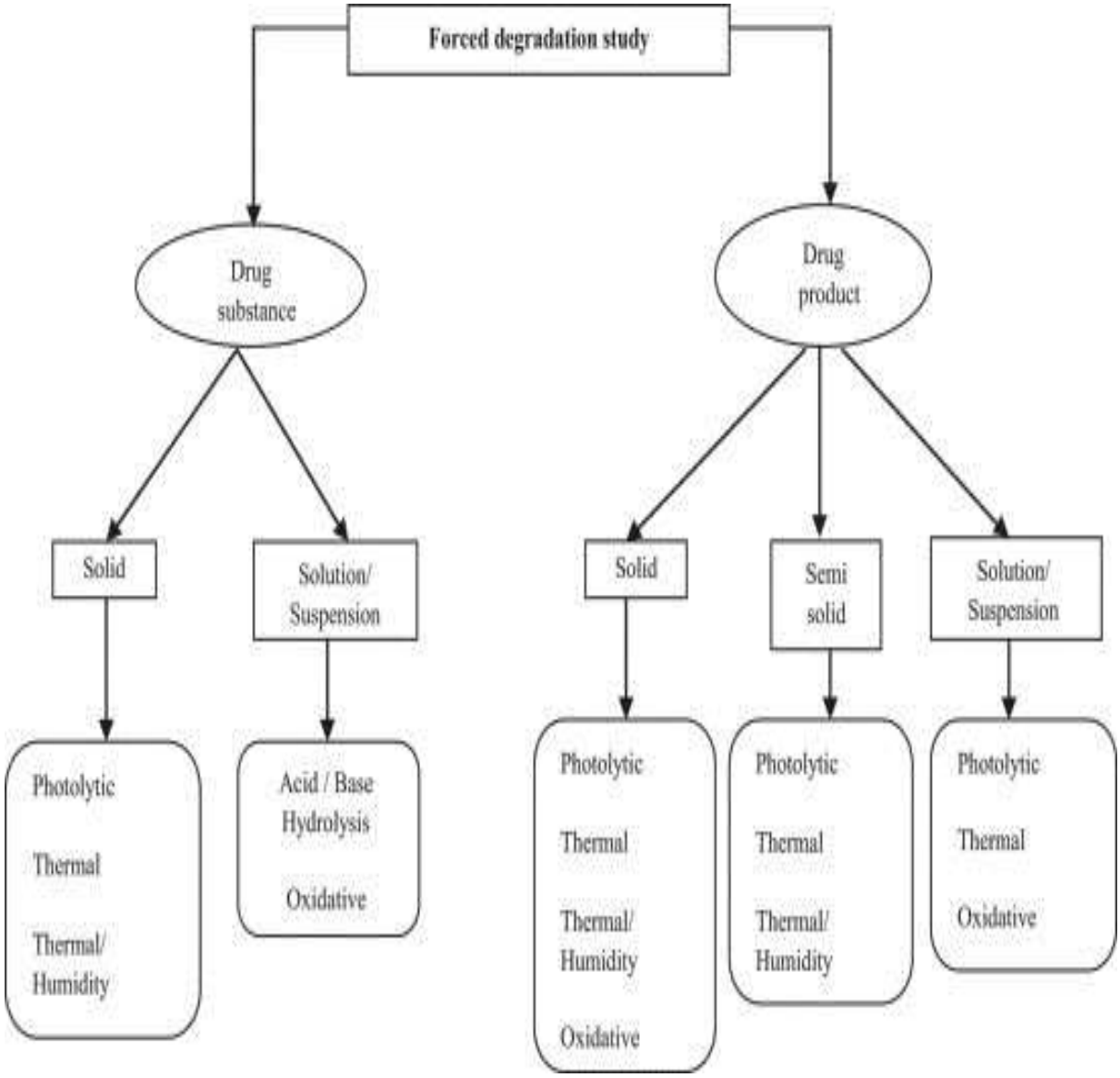

Figure 1: An illustrative flowchart describing various stress conditions used for degradation of drug substance and drug product

Table 1: Conditions mostly used for forced degradation studies

Degradation type	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid or base)	40 °C, 60 °C	1,3,5
	0.1 M HCl	40 °C, 60 °C	1,3,5
	0.1 M NaOH	40 °C, 60 °C	1,3,5
	Acid control (no API)	40 °C, 60 °C	1,3,5
	Base control (no API)	40 °C, 60 °C	1,3,5
	pH: 2,4,6,8	40 °C, 60 °C	1,3,5
Oxidation	3% H_2O_2	25 °C, 60 °C	1,3,5
	Peroxide control	25 °C, 60 °C	1,3,5
	Azobisisobutyronitrile (AIBN)	40 °C, 60 °C	1,3,5
	AIBN control	40 °C, 60 °C	1,3,5
Photolytic	Light 1× ICH	NA	1,3,5
	Light 3× ICH	NA	1,3,5
	Light control	NA	1,3,5
Thermal	Heat chamber	60 °C	1,3,5
	Heat chamber	60 °C/75% RH	1,3,5
	Heat chamber	80 °C	1,3,5
	Heat chamber	80 °C/75% RH	1,3,5
	Heat control	Room temp.	1,3,5

NA: Not applicable.

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