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Review Article

Current Trend in Performance of Forced Degradation Studies for Drug Substance and Drug Product's

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ABSTRACT

The stability of a new drug substances and new drug products is a vital parameter which may affect purity, safety & potency. Changes in drug stability can threat patient safety by formation of toxic degradation products or deliver to lower dose than expected. Therefore it is to know the purity profile & behaviour of a drug substances under the various environmental condition. Forced Degradation studies show the chemical behavior of the molecule which in turn helps in the development of new formulation & package. Degradation study is required to the design of a regulatory compliant stability program for the both drug substances & products, and formalized as a regulatory requirement in ICH Guideline Q1A in 1993. Forced degradation studies (chemical and physical stress testing) of new chemical entities and drug product which is required to develop and demonstrate the specificity i.e stability indicating method. Forced degradation studies used to determination of the degradation pathways and degradation product of drug substances i.e during storage, development, manufacturing and packaging. Thus, this review discusses the current trends in performance of forced degradation studies by provide the information about strategy for conducting the studies of forced degradation

Keywords: - Regulatory Guidelines (ICH, FDA, EMA), Degradation condition, Forced degradation, Degradation product.

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Introduction

Forced degradation is a technique which means different stress condition applied to the drug substance and product. These studies also known as stress degradation and stress testing. These studies used for demonstrate stability of molecules under accelerated condition. Stability of molecules to help in selecting proper formulation, packaging and storage condition and also shelf life which is required for regulatory documentation. Forced degradation process, general condition like light, humidity, oxidation and heat. As per International Committee for harmonization (ICH) and FDA guidelines. Two type of studies i.e long term which is duration of study is about 12 Months, while accelerated stability studies about 6 Months. Intermediate stability studies about 6 months at milder condition than accelerated because the one can identify and separate the degraded product but its take a more time. Forced degradation detect the under different analytical equipment used i.e. HPLC, UV and HPLC photodiode array detector (PDA) used.^[1]

Needs for forced degradation studies

Forced degradation studies are more important belongs to following aspect. ^[1-2]

- 1) To studies the chemical behaviours.
- 2) To detect the degradation pathways.
- 3) To solve the problem related to stability.
- 4) To detect the structure of decomposition product.
- 5) To develop the method and detect stability.
- 6) Forced degradation is determination of intrinsic stability of drug in drug substances and drug product.
- 7) For required the production of stable formulation.
- 8) To establish a degradation profile under ICH condition.

Regulatory Guidelines

Many guidelines are mentioned about the forced degradation like ICH (International Committee for

harmonization), FDA (Food and drug administration), EMA (European Medicines Agency), USP (United States Pharmacopeia), JP (Japanese Pharmacopoeia), and ANVISA (Agencia Nacional de Vigilancia Sanitaria). These guidelines also explained about forced degradation studies. [7-20]

ICH Guidelines

In ICH guidelines discuss about Forced degradation studies which is ICH Q1A, Q1B, & Q2B, Q3A, Q3B, M4Q(R1).

ICH Q1A - Testing of Stability for New drug molecules & Products.

Determine the Intrinsic Stability of drug using these guidelines. Section 2.1.2 of Q1A guidelines. (Under Section ICH Q1A - Testing of Stability for new drug molecules & Products). These guidelines are essential in designing method for determining the stability of drug. According to Q1A, degradation depends on drug molecules and drug products. To conduct the forced decomposition analyses on drug substances & products at several accelerated conditions were mentioned. Those conditions were effect of humidity ($\geq 75\%$ Relative humidity), temperature, oxidation, and photolysis & range of pH (solution / suspension). [7]

ICH Q1B - Photostability Testing of New drug substances and drug products

This is used for estimation of photostability nature of drug molecules in the development stage. These guidelines provide information of how to assess the photo stability of molecules under the study for stability studies. [11]

ICH Q2B - Validation of analytical procedures: Methodology

These guidelines provide the knowledge about the protocols to be followed by validation of different analytical protocols. Sample usages for forced degradation studies mentioned in ICH Q2B, Part II, Section 1.2.2. Samples should be stressed under different accelerating condition like heat & humidity used for determination of specificity. In addition, essential for the quantitative determination of the degradation produced. [11-14]

ICH Q3 Impurities in New drug substances

These guidelines provide the knowledge about the determination of contaminants present in new drug molecules. In these Section insights about different aspects like identification, types & specification of impurities, analytical protocols & report. Most important, if the impurities are either completely absent or present in trace amounts in new batch of drug molecule is validation of chromatographic assays. In case of trace molecules, stability limit should be more than 90% and hence about 10% degradation is sufficient. [17]

ICH Q3B - Impurities in New Products

These guidelines provide knowledge about analytical procedures. It is essential for an analytical procedure to validate the specific or non-specific degradation products under various stress conditions. [18-19]

ICH M4Q (R1) - The common technical document for the registration of pharmaceuticals for human use: Module 3: Quality

This document guideline provides knowledge about types of studies performed, procedures used & outcomes of the studies. In conclusion, it provides the condition of storage, storage life & the date for reassessment. Outcomes of stability analysis covers in Section 3.2.S.7.3. Results give in

form of tabular, graphic, or narrative format & it also provides the analytical procedures along with the validation data.

FDA Guidelines (Food and drug administration)

This guideline provides information about the photo stability analysis of newer drug molecules & products (Q1B). According to the FDA, forced degradation studies should be conducted in normal development condition. It mentions the degradation pathway of samples when exposed to light. These guidelines also help to develop SIM & summarize the data of validation which are confirmatory studies. Section of these guidelines 211.166(a) (3), a SIM should be highly specific & it should be able to quantify the amount of active ingredient present, if these types of degradation products obtain and other components present in dosage form without any interference under stress condition. These stress conditions essential for forced degradation studies are pH, temperature & oxygen. [8-9]

EMA Guidelines (European Medicines Agency)

These guidelines essential for chemistry of active substances. It mentions the data for type of studies performed, procedures used, outcomes thus obtained from the analysis. This guideline explains about the stability testing for API & dosage form in section 2.1.2. It also includes the data of retest date & expiry date of substances. It also determined the development analytical method, validation of method, degradation pathways, & intrinsic stability. It also conducting stability studies for sensitive compound like photosensitive & hygroscopic drug. [15-19]

USP Pharmacopoeia: validation of compendia procedures

This guidelines provide the information about the if degradation standard or contaminants are not available, the specificity should be estimated in comparison of the data with the results obtained from analytes (degradation product or contaminants) by using an alternative procedure under the same accelerated condition. [13]

Japanese Pharmacopoeia

This guideline states that the proposed method should be specific, to be able to identify & in the sample detect the amount of analyte present. For the comparative studies, sample will be exposed in stress condition & for further studies degradation products may be used if reference standard are not available.

ANVISA (National Health Surveillance agency)

This guideline provides information about the requirements related to stability & forced degradation. These guidelines protect from production regarding to risk caused & uses of various drug products. It was developed to promote public health. It also promotes the states, districts & municipalities, according to the Brazilian unified health system principles, so to increase the quality of life of the people.

Time to perform degradation

It is known how to perform forced degradation studies & when to perform forced degradation studies for development for new drug substances & new drug products. According to FDA guidelines state that stress testing can be performed in phase III of regulatory submission process. Stress studies can be done in various pH solutions, i.e. presence of light, oxygen and at various increasing temperature & humidity to determine the stability of substances & drug product. [1-6]

Limits for Forced degradation studies

Most of regulatory guidelines mentioned about limits of degradation i.e 5% -20% accepted criteria for validation of chromatographic assays. Stability should be more than 90% & about 10% enough for degradation. In general, for the observing drug product stability, spiked sample mixture of known degradation drug substance & drug products are used, which determine the product that are monitored during the degradation. [8-20]

Sources of degradation products

Degradation is one of the sources for impurities. Under various stress condition like Heat, humidity, isolation, pH, Storage & transportation processes, drug molecules under the degradation due to chemical instability. Forced degradation should be carried out through different pathways like oxidation, heat, photolysis, and hydrolysis. [1-2]

Plan for selection of forced degradation condition

Intrinsic stability of drug substance & drug product should be determined by using normal various conditions like pH & High temperature. Later than, drug molecule were targeted to additional stress to study the stability. To study the forced degradation, the solution including the sample was refluxed for a particular time. During that time, if degradation substance & product were monitored, the process would be stopped, further identification, isolation & monitored degradation product will be carried out. If no degradation monitored, the reaction time would be enhanced to monitor any signs of degradation because the increasing of time. [1-2]

Forced degradation studies used by following condition presented in Table 1 & Figure 1.

Table 1: Condition used for Forced degradation studies

Types for Degradation	Experimental condition	Storage condition	Sampling time (days)
Hydrolysis	Control API (no acid/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
	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% H2O2	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
Photolysis	Light 1x ICH	NA	1,3,5
	Light 1x ICH	NA	1,3,5
	Light control	NA	1,3,5
Thermolysis	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 chamber	Room temp	1,3,5

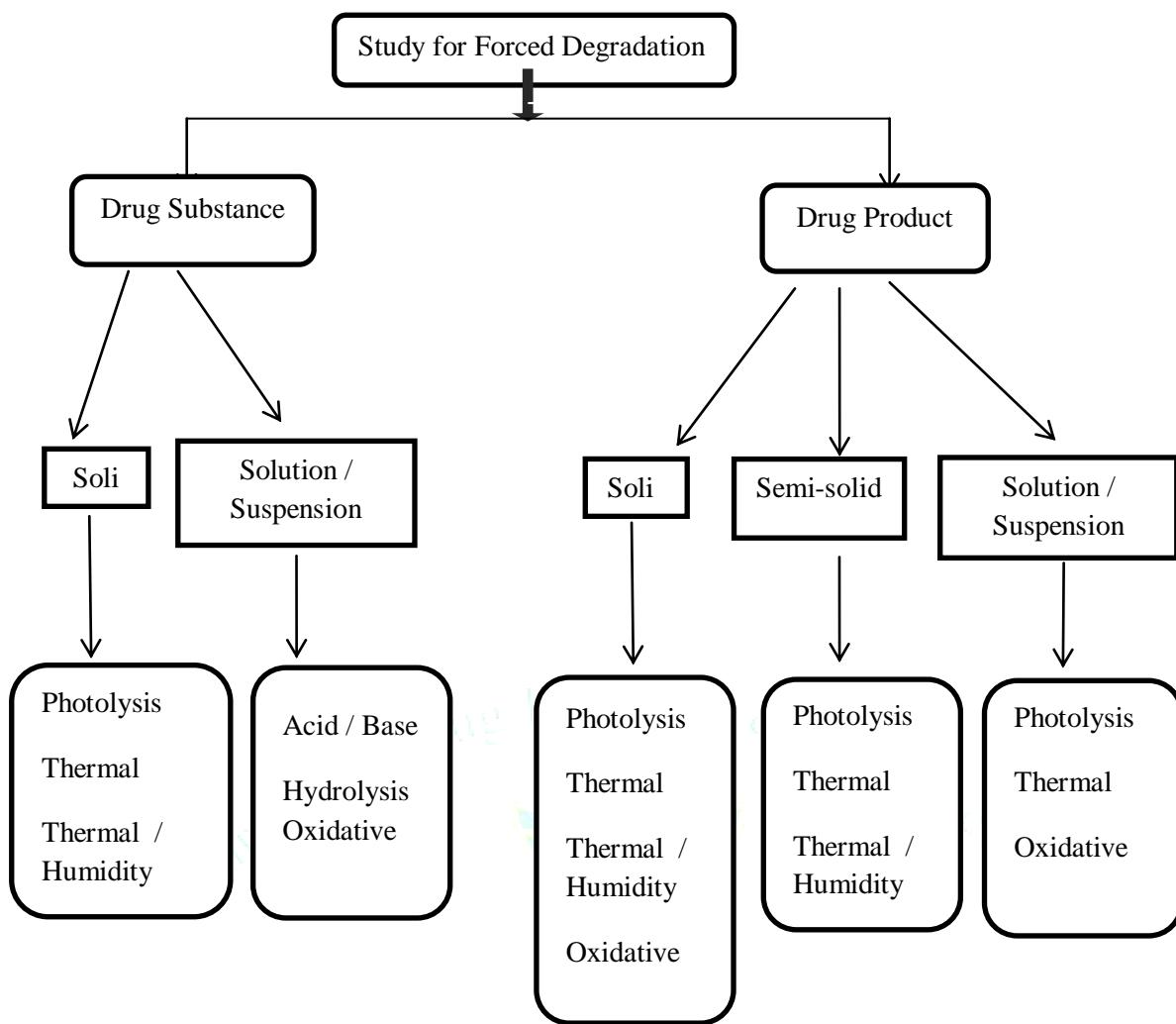


Figure 1: Diagrammatic representation of degradation studies of drug substance & product under various stress condition

Forced Degradation Condition

Hydrolysis Condition

This forced degradation condition is one of the most common chemical reaction over the wide range of pH. This chemical reaction decomposition by water. These forced degradation condition study under the acidic and basic condition. It involves catalysis of ionization functional group present in the molecule. In hydrolysis drug substance is exposure by acidic or basic condition. In acidic condition conc hydrochloric acid or sulfuric acid (0.1-1M) and sodium hydroxide or potassium hydroxide (0.1 - 1M) for basic condition. If the compound is poorly soluble in water so then used the co solvent dissolve in HCl or NaOH. The selection of co solvent depends on drug substances structure. Forced degradation trial is normally started at room temperature (50°C-70°C) is applied. It should not exceed more than 7 days. After that degraded sample neutralized by using suitable acid, Base or buffer, to avoid other decomposition. [1-6]

Oxidation Condition

Hydrogen peroxide mostly used for oxidation of drug substance in stress testing studies but other oxidizing agent like, metal ion, oxygen and radicals initiators (eg. Azobisisbutyronitrile, AIBN) can be used. Selection of oxidizing agents its depends on concentration, & drug substance. Hydrogen peroxide is reported the solution 0.1-

3% at neutral pH and room temperature for 7 days. These conditions involve the electron transfer mechanisms to form reactive anion and cations. Amine, sulfide and phenols are able to electron transfer oxidation to give N - oxide, hydroxylamine, sulfonic and sulfoxide. [1-6]

Photolytic Condition

The photo stability testing drug substances mostly evaluated to illuminate that light exposure does not result in unacceptable change. These condition most of exposure to UV or fluorescent condition. This condition recommended for photo stability testing is describing ICH guideline. Sample of drug substances and solid / liquid drug product should be exposed to a minimum of 1.2 million 1X h and 200 W h/m²light. The most of accepted wavelength of light is in the range of 300- 800nm to cause the photolytic degradation. The maximum demonstrate recommended are 6 million 1 x h. photolytic conditions can include photo oxidation by free radical mechanism. Fictional group such as chlorides, weak C-H and O-H, sulfides and polyenes are likely introduce drug photosensitivity. [11]

Thermal condition

Thermal degradation (eg. dry heat and wet heat) should be carried out at various strenuous conditions than recommended ICH Q1A short testing condition. Sample of solid state drug substances and drug product should be dry heat & wet heat, as well as liquid drug product should be

exposed dry heat. Studies may be conducted at higher temperature for shorter period. Effect of temperature on thermal degradation of substances studies through the Arrhenius equation:

$$K = A e^{-E_a/RT}$$

Where K is Specific reaction rate, A is Frequency factor, E_a is energy of activation, R is gas constant (1.987 cal/ deg mole) and T is absolute temperature. Thermal degradation study is carried out 40-80 °C. [7]

Factors affecting Degradation

Below to the various factors which cause degradation of drug substances. [1]

Moisture

Water soluble substances may get dissolved, if the presence of moisture .this leads to physical and chemical changes within the molecule.

Excipient

It was observed that some excipient may contain high content of water. This moisture may leads to increase water level in formulation which later affects the stability of the drug. In some cases, chemical photolytic decomposition can be tested by comparing its stability in the presence of light and stability when stored under dark. Photo labile compound should be stored in amber glass containers and

should be stored in dark .interaction that occurs between the excipient and the drug material often results in decreased stability.

Temperature

Changes in temperature at time its show deleterious effect on the stability of the drug. Increase in temperature usually causes increase the rate of drug hydrolysis.

pH

pH shows a significant effect on the degradation rate of drugs by hydrolysis. To reduce this effect, formulation of the drug is carried out using buffer solution of pH with maximum stability.

Oxygen

In the presence of oxygen to increase the oxidation. In the presence of oxygen cause increased rate of decomposition .stabilized by using purging nitrogen or carbon dioxide in the storage in container.

Light

Some drug is photo labile and tends to decompose when they are exposed to light. Hydrolysis drug molecules are dissolved in 0.1-1 M of potassium hydroxide or sodium hydroxide. Sample treated 2 – 7 days at room temperature. Treated sample were neutralized with relevant acid or base to prevent additional degradation.

Table 2:- Below the some drugs studies results reported

S.N.	Drugs Name	Study results
1	Aceclofenac Na	This drug Stable at dry it or below 80°C and in the absence of light
2	Diacerein	This drug Unstable at base hydrolysis, photolytic, and thermal conditions it remains stable under acid hydrolytic and oxidative stress condition
3	Proteins	This drug Unstable at photolytic conditions. Secondary packing is required to protect from light
4	Idarubicin	Drug degradation observed in hydrolysis and oxidative stress condition. In oxidative stress condition and base hydrolysis, two degrading were produced, & in acid hydrolysis, one degrading was produced.
5	Valsartan	This drug is unstable at acid stress condition and it produced three degradation products.2 methyl-N-{{2'-(1H -tetrazol-5-yl)biphenyl 3yl]methyl}propan-1-amine and N-methyl-N-{{[2'-91H-tetrazol-5-yl)biphenyl-3-yl]methyl} butanamide were produced due to oxidative stress.
6	Meloxicam & piroxicam	This drug stable at thermal stress & unstable at hydrolytic, oxidative and photolytic stress condition.
7	Tetrabenazine	In base condition, poor degradation was occurs, but in acidic condition, more degradation had observed.
8	Wheat straw	In higher temperature, aromatic aldehydes were produced as degrades.
9	Anastrozole	In alkaline hydrolysis & oxidative stress, drug molecule degraded and two degrades were produced. Drug impurities were characterized as 2, 2'-(5-((1H-1, 2, 4-triazol-1-yl) methyl)-1, 3-phenylene-2-yl) phenyl)-2methylpropanoicacid (monoacid).
10	Ivabradine	Ivabradine drug was unstable at acid -alkaline hydrolysis condition & five degradation products were produced at hydrolytic condition
11	Amlodipine	It was stable at thermal stress condition; in acidic stress two degrades & basic stress four degradative products & in oxidative stress condition one degradation product was produced.
12	Lisinopril	This drug was unstable at acid hydrolytic condition and four degradation products were produced.
13	Midazolam maleate	Unstable at acid hydrolytic & thermal stress condition.

14	Saikosaponin	This drug under the acid hydrolysis, two degradant were produced; these impurities characterized as SS-B2 & hydroxysaikosaponin A.
15	Moxidectin	Its shows good stability under the thermal stress condition; at base hydrolysis two degradans produced which were characterized as 2-epi and 2,3 isomers
16	Lansoprazole	This drug in acid hydrolytic condition, one degradation product was produced & it was identified as 1-methyl-10-thioxo-10H-4a, 5, 9b-triaza-indeno [2, 1-a] inden-2-one.
17	Piracetam	This drug stable under all condition except base stress condition .In base condition, one degradation product was occurred.
18	Dexlansoprazole	This drug under the oxidation stress condition, one degradation product was produced & characterized by 1-(1H- benzo[d]imidazole-2-yl)-2, 3-dimethyl-4-(2, 2, 2-trifluoroethoxy) pyridine-1ium.
19	Deflazacort	In base condition, the drug was readily degraded & produced and 21 hydroxy deflazacort (21-OH-DFZ) as degradation product.
20	Nevirapine	This drug degradation was observed in both heat & acidic condition. At acidic condition, 2-(3-amino-4-methylpyridine-2-ylamino) nicotinic acid impurity was occurred.
21	Cedritoren pivoxil	This drug stable under the thermal & photolytic stress conditions, and also unstable at hydrolytic condition, 7 two degradant were produced.
22	Sofosbuvir	This drug stable under the thermal condition; susceptible to oxidative, photolytic & hydrolytic condition.
23	Enflurane	This drug under base stress condition, N-acetyl-L-cysteine S-conjugates impurity was produced.
24	Paliperidone	This drug degradation observed at acid & base hydrolysis; 3-(1-allyl-1, 4-dihydropyridin-4-yl)-5fluorobenzo isoxazole, and 5-(2-(4-(5-fluorobenzo isoxazol-3yl) piperidin-1yl) ethyl)-6-methylpyrimidin-4-(3H)-one were the degradation products produced under hydrolysis condition.
25	Metoclopramide	This drug is a photosensitive. Under the uv radiation, degradation reaction such as dechlorination & hydroxylation were occurred.
26	Curcumin	This drug is labile to base condition & able to withstand under the acidic, photolytic, oxidative, and thermal stress condition. In base condition, 8 degrading were occurred.
27	Flupirtine maleate	This drug at hydrolysis condition , 3 degradant were produced & identified as (2amino6 [(4fluorobenzy)amino]pyridine-3-yl}carbamic acid,N-(4-fluorobenzyl)pyridine-2,3,6-triamine & 5-[(4flourobenzyl) amino]-1,3-dihydro-2H-imidazo[4,5-b] pyridine-2-one
28	Fidarestat	This drug is able to withstand under thermal & photolytic stress condition. These drug also unstable at hydrolysis & oxidative stress condition
29	Ezetimibe	This drug is stable at thermal, oxidative& photolytic condition, 4 degradant were produced at hydrolytic condition.
30	Abacavir sulfate	This drug degradation observed under oxidative & acid stress; in acid hydrolysis, C8H10N6 impurity was while C14H18N6O3 & C11H14N6O were produced at oxidative stress condition
31	Finofibrate	This drug is under hydrolysis & oxidative condition, drug undergoes degradation process. 4 degradation products were occurred.
32	Gefitinib	This drug degradation observed at hydrolysis & oxidative condition; and also unstable at thermal condition.
33	Emtricitabine	This drug significantly degraded under oxidative& acidic stress condition; 3 major degrading were produced.
34	Nintedanib	This drug is stable at thermal & photolytic condition; labile to hydrolytic & oxidative condition; and in acid condition, 2 degrading, alkaline condition 1 degradation product, & oxidative condition 1 degradant were produced.
35	Agomelatine	This drug is stable at thermal & photolytic condition; and also unstable at hydrolytic & oxidative.
36	Hydrochlorothiazide	This drug at under hydrolytic condition, 2 degrading was produced.

Conclusion

Forced degradation studies provides information about degradation pathways and degradation product of active ingredient and its help to elucidate the structure of the degradants products. Forced degradation studies may or may not produce in storage condition, but they are used to select the suitable storage condition. It will help to develop SIM (Stability indicating method). This forced degradation provide the information will in turn help improve the formulation manufacturing process & determine the storage condition as no specific set of condition is applicable to all drug substances and products and regulatory guidance does not specify about the condition to be used. The aim of any plan used for forced degradation is to produce the desire amount of degradation i.e. 5-20%. This review article has been summarized to the best, to provide information about different regulatory guidance's available for forced degradation studies, this method also perform stress testing studies under different accelerated condition, and stability & degradants produced under different stress testing condition for various drugs.

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