Review Article

Forced degradation studies: Regulatory guidance, characterization of drugs, and their degradation products - a review

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ABSTRACT

Aim: The aim of this study is to consolidate the literature available on regulatory aspects and protocols for forced degradation studies of various drug substances and their products into a comprehensive review. **Background:** Forced degradation is a process in which different stress conditions are applied over drug substances and which in turn different degradation products are produced. These studies are mainly used for the determination of stability of molecule under accelerated conditions. It is known that regulatory documentation process, selection of proper storage and package conditions, and selection of formulation are dependent on the stability of molecules. **Objective:** The present review discusses about various regulatory aspects, methodology for forced degradation studies, and degradation profiles for various drugs. **Method:** In forced degradation process, the drug substance and drug products are subjected to severe accelerated conditions to determine their stability. For determination of specificity of stability methods, it is necessary to determine the stability under forced degradation conditions. **Conclusion:** For determination of degradation pathways and structural elucidation of degradants produced, these forced degradation studies are helpful. It is also used to select the storage conditions and improve the manufacturing process of formulations.

KEY WORDS: Characterization, Forced degradation studies, Method development, Regulatory guidance, Stability studies

INTRODUCTION

Forced degradation is a technique where different stress conditions are applied over drug substances and which in turn different degradation products are produced.[1] These studies are also called as stress testing or stress degradation studies. These methods are mainly used for the determination of stability of molecule under accelerated conditions.[2] It is known that regulatory documentation process, selection of proper storage and package conditions, and selection of formulation are dependent on the stability of molecules.[3] In forced degradation process, general conditions such as light, heat, humidity, and oxidation are accelerated individually or in combination with automated stress to accelerate the degradation of the molecule by physical or chemical means.[4,5] As per the International Committee for Harmonization (ICH) guidelines, the stability of the molecule, different degradative pathways, and validation of the developed stability procedures are studied using forced decomposition studies. The details of drug molecules that undergoes degradation and the different products that are formed with respect to time changes under the impact of different environmental parameters and understanding of stability data are well explained using the Food and Drug Administration (FDA) and ICH guidelines.[6,7]

Two kinds of studies, namely, long-term and accelarated stability studies have been reported. In case of long-term studies, the duration of study is about 12 months while accelerated stability studies take around 6 months. Intermediate stability studies are also conducted for 6 months at conditions milder than accelerated studies. In long-term studies, one can identify and separate the degraded products, but the main drawback is that the study takes more time. In forced degradation studies, generation of degradation

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products occur quicker than stability studies.[3]

Forced degradation studies act as a tool for the estimation of stability of the drug. Stability of the drug, which in turn affects the drug purity, potency, and safety can be determined by these forced degradation studies. Therefore, stability is considered as a critical parameter. Any alteration in stability can cause lowering of dose and thus make the dosage forms to be toxic.[1]

Degradation studies are important to determine the inference of degradation routes and stability of pharmaceuticals under various stress conditions. Characterization of the degradants produced is usually carried out according to ICH guidelines. Different analytical equipment are employed to determine the stability studies. For instance, high-performance liquid chromatography-ultraviolet (HPLC-UV) and HPLC-photodiode array detector (PDA) are two common equipment to study the stability indicating method (SIM) development and validation purpose, while LC coupled to mass spectrometry (LC-MS) has become the authentic technique for characterization of degradant products (DP). LC-MS has gained enormous importance due to its high DP sensitivity and selectivity and in addition also provides a detailed structural information about the different DP.[8]

NEED FOR FORCED DEGRADATION OF DRUGS

Studies on forced degradation of drug molecules are very important in the following aspects.[1-3]

1. To develop methods to determine stability.
2. To determine the degradation pathways.
3. For determination of intrinsic stability of drug in dosage forms.
4. To study the chemical properties of molecules.
5. For production of stable formulations.
6. To determine the structure of decomposition products.
7. To solve problems related to stability.
8. To generate a degradation profile under ICH conditions.

REGULATORY GUIDELINES

Several guidelines are mentioned about forced degradation. The ICH has given directions and guidelines for conducting these decomposition studies which are approved by other regulatory authorities. The European Medicines Agency (EMA), FDA, United States Pharmacopeia (USP), Japanese Pharmacopoeia (JP), and Agencia Nacional de Vigilancia Sanitaria (ANVISA) guidelines also explained about forced degradation studies.

ICH Guidelines

The ICH guidelines which discuss about forced degradation studies are ICH Q1A, Q1B, and Q2B, Q3A, Q3B, M4Q (R1).[1,9-11]

ICH Q1A – testing of stability for new drug molecules and their products

Intrinsic stability of drug is determined using these guidelines. Q1A Guidelines of Section 2.1.2 of Q1A guidelines. (under section ICH Q1A-testing of stability for new drug molecules and their products). These guidelines are helpful in designing methods for determining the stability of drugs. According to Q1A, degradation depends on respective drug molecules and the nature of drug products.[1] To conduct these forced decomposition analyses on drug substances and their products several accelerated conditions were mentioned. Those conditions were effects of temperature (>50°C), humidity (≥75% relative humidity), oxidation, photolysis, and diverse range of pH (solution/suspension).[9-11]

ICH Q1B – photostability testing of new drug substances and drug products

These methods are used to estimate the photostability nature of drug molecules normally in the development stage. These guidelines provide knowledge about how to assess the photostability of molecules that are under study for stability studies. Forced decomposition of drug molecules and their products were described in sections need of forced degradation of drugs and regulatory guidelines, respectively. Forced degradation studies find application for the detection of photolytic degradants in confirmatory studies.[1,6]

ICH Q2B – validation of analytical procedures: Methodology

The ICH Q2B guidelines provide information about the protocols to be followed for the validation of different analytical protocols. ICH Q2B, Part II, Section 1.2.2 explains about usage of samples for forced degradation studies. It emphasizes that the samples should be subjected to stress under different accelerating conditions such as humidity and heat and further used for the determination of specificity. In addition, these guidelines are useful for the quantitative determination of the degradants produced.[1,6]

ICH Q3A impurities in new drug substances

ICH Q3A guidelines provide information about the determination of contaminants present in new drug molecules. This section provides insights about different aspects such as the identification, types and specification of impurities, analytical protocols, and generation of reports. More importantly, if the impurities are either completely absent or present in trace amounts in batch of a new drug molecule is

considered helpful to ensure safety toward clinical studies.[1,6]

ICH Q3B impurities in new products

ICH Q3B provides information about analytical procedures. It is important for an analytical procedure to validate the specific or non-specific degradation products under various stress conditions.[1,6]

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

This document provides information about types of studies performed, procedures used, and outcomes of the studies. In conclusion, it provides the conditions for storage, storage life, and the probable date for reassessment. Section 3.2.S.7.3 covers the outcomes of stability analysis. Results should be given in a tabular, graphic, or narrative format and it also includes the analytical procedures along with the validation data.[1]

EMA Guidelines

It is a guideline used in chemistry of active substances. It covers the data for type of studies performed, procedures used, and outcomes thus obtained from the analysis. The Section 2.1.2 explains about the stability testing for API and dosage forms. It contains the data of retest date and expiry date of substances. Development of analytical method, validation of method, degradation pathways, and intrinsic stability are also determined. It also mandate on conducting stability studies for sensitive compounds such as photosensitive and hygroscopic drug.[1]

FDA Guidelines

FDA is providing guidelines for photostability analysis of newer drug molecules and their products (Q1B). According to the FDA, degradation studies should be conducted using normal development conditions. It covers the degradation pathway of samples when they exposed are to light. These guidelines help to develop SIM and also summarize the data of validation which are in turn helpful for confirmatory studies. These guidelines insist on the fact that there is no necessity to carry out the confirmatory studies for degradation products. According to the Section 211.166(a) (3), a SIM should be highly specific and must be able to quantify the amount of active ingredient present, the type of degradation products thus obtained with and other components present in dosage form without any interference under stress conditions. Stress conditions used for forced degradation studies are pH, temperature, and oxygen.[1]

USP Pharmacopoeia: Validation of Compendia Procedures

According to these guidelines, if degradation standards or contaminants are not available, the specificity can be estimated in comparison of the data with the results obtained from the analytes (containing the contaminants or degradative products) using an alternative procedure under the same accelerated conditions.[1]

Japanese Pharmacopoeia

It states that the proposed method should be specific, be able to identify and estimate the amount of analyte present in the sample. For comparative studies, if reference standard impurities are not available, samples will be exposed to stress conditions and degradation products may be used for further studies.[1]

National Health Surveillance Agency (ANVISA)

It mentions about the requirements regarding stability and forced degradation. ANVISA was developed to promote public health and protect from risks caused by the production and use of various drug products. ANVISA coordinates states, districts, and municipalities, according to the Brazilian Unified Health System principles, so as to enhance the quality of life of the people.[1]

IMPORTANT FEATURES OF FORCED DEGRADATION STUDIES

Conduction of Forced Degradation Studies

Conducting forced degradation analysis for new drug substances is considered very important as it plays a vital role in the stability and shelf-life of the drugs. According to the FDA, Phase III regulatory submission is considered the right time to perform forced degradation studies. It was mentioned that under different stress conditions forced degradation studies will be conducted for single batches. The forced degradation studies can also be carried out after stability studies identification, quantification, and separation of degradants can be done. Pre-clinical and Phase - I clinical trials provide sufficient time for identification and structure elucidation of degradation products and help to improve the manufacturing process. During pre-clinical trials, determination of degradants and toxic components can be performed. The degradation analysis can be conducted during clinical development step where the comparison of results of pre-clinical to in-use stability stages can be accomplished. The guidelines also mention that the degradation studies can be performed during post-marketing period as well because new types of stresses and changes occurred during manufacturing processes can be determined.[12]

Degradation Limit

The regulatory agencies have defined the limits of degradation products in their guidelines. It is mentioned that 5–20% degradation is accepted for

validation of chromatographic assays. In case of small molecules, stability limit should be more than 90% and hence about 10% degradation is sufficient. In general, for monitoring drug product stability, spiked samples of mixture of known degradation products and drug substances are used, which ease out the process of determining the products that are observed during the degradation. If the drug sample displays any change in the physical and chemical nature, change in activity during the shelf life, then the drug molecule is considered to have undergone degradation. If no such degradation was observed, then either the study will be aborted or the respective drug sample will be subjected to additional stress to analyze the nature of secondary degradants that are expected to produce during the study. If any case only a little or no degradants are produced due to additional stress, then the drug substance will be exposed to excess energy to estimate the stability of molecules.[2,3]

Origin of Degradation Products

Degradation is considered as one of the chief sources for impurities. Under different stress conditions, namely humidity, heat, pH, isolation, storage, and transportation processes, drug molecules may undergo degradation because of chemical instability. Forced degradation can be carried out through various pathways including hydrolysis, oxidation, heat, and photolysis. It is also observed from different studies that under different stress conditions it is possible to produce all possible types of degradants.[10,11]

Selection of Degradation Conditions[1-3,5,8,10,12-17]

Earlier, intrinsic stability of drugs can be determined using normal conditions such as high temperature and pH. Later, the drug molecules were subjected to additional stress to study the stability. To study the degradation, the solution containing the drug sample was refluxed for a definite time. During this time, if any degradation products were observed, the process would be stopped; further isolation, identification, and characterization of the observed degradation products will be carried out. If no degradation was observed, the reaction time would be increased to observe any signs of degradation due to the extension of time. The frequently used forced degradation conditions are presented in Table 1 and Figure 1.

Hydrolysis

In hydrolysis, the drug reacts with water under different pH conditions (both acidic and alkaline). In general, the drug substances are treated with 0.1N hydrochloric acid or sulphuric acid or 0.1N sodium hydroxide at 50–60°C. The stability of molecule depends on the strength of acid or alkali used in the study. The strength of acid or alkali should be maintained between 0.1 N and 1 N solutions. Notably, the duration of the study should not exceed 7 days. After subjected to stress conditions, the samples should be neutralized with buffer or acid/base to avoid decomposition.

Oxidation

Most of the drug substances are found to be auto-oxidizers. They require free radical initiators for oxidation process. Hydrogen peroxide, trace level of impurities, and metal ions act as free radical initiators. This type of degradation involves the transfer of electrons. 0.1–3% of hydrogen peroxide is a common initiator for oxidation forced degradation studies. These studies should be conducted at 40°C for 1–7 days. If more than 20% degradants are produced, then it should be considered as abnormal.

Thermal condition

Several drugs are seen to be thermolabile in nature. By increasing the temperature, the rate of reaction also tends to increase which in turn leads to the production of degradation products. These studies should be conducted at 40–80°C. The duration of thermal stress studies usually lasts for 1–2 months and are conducted at 70°C and at high humidity. The drug molecules which are solid in nature are subjected to both dry and wet heat conditions, while liquids are exposed to dry heat for the shorter duration of time. Due to the elevated temperature, the drug molecule undergoes degradation and given by Arrhenius equation:

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

where k: Specific reaction rate, A: Frequency factor, Ea: Energy of activation, R: Gas constant (1.987 cal/deg/mole), and T: Absolute temperature in Kelvin.

Photolytic conditions

In photolytic degradation studies, the drug substances are exposed to UV or fluorescent conditions. In this study, the drug substances or drug products (solid/liquid) are exposed to the light source according to the ICH Q1B protocols. The commonly used radiation range for degradation studies is about 300–800 nm. In photolytic condition, the degradation occurs due to oxidation through free radical mechanism or non-oxidation process. Non-oxidative degradation process involves with isomerization, dimerization, etc., among others. On the other hand, oxidative photolytic reaction involves mechanism involving singlet/triplet oxygen states. Singlet oxygen reacts with unsaturated compounds to produce photooxidative decomposition products, while triplet oxygen follows free radical mechanism, to produce a peroxide. Notably, it is shown that light also catalyzes oxidation reactions. In non-oxidative process, several types of reactions are observed such as the homolytic breakage of C-X hetero bonds, deamination, and cleavage of C-S bonds are observed.

Table 1: Frequently used conditions for forced degradation studies

Type of degradation	Experimental conditions	Storage conditions	Sampling time (days)
Hydrolysis	Control API (no acid/base)	40°C, 60°C	1,3,5
	0.1M HCl	40°C, 60°C	1,3,5
	0.1M 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 (ABIN)	25°C, 60°C	1,3,5
	ABIN control	25°C, 60°C	1,3,5
Photolysis	Light 1 X ICH	NA	1,3,5
	Light 3 X ICH	NA	1,3,5
	Light 3 X ICH	NA	1,3,5
Thermolysis	Heat chamber	60°C	1,3,5
	Heat chamber	60°C/75°C% RH	1,3,5
	Heat chamber	60°C	1,3,5
	Heat chamber	60°C/75°C% RH	1,3,5

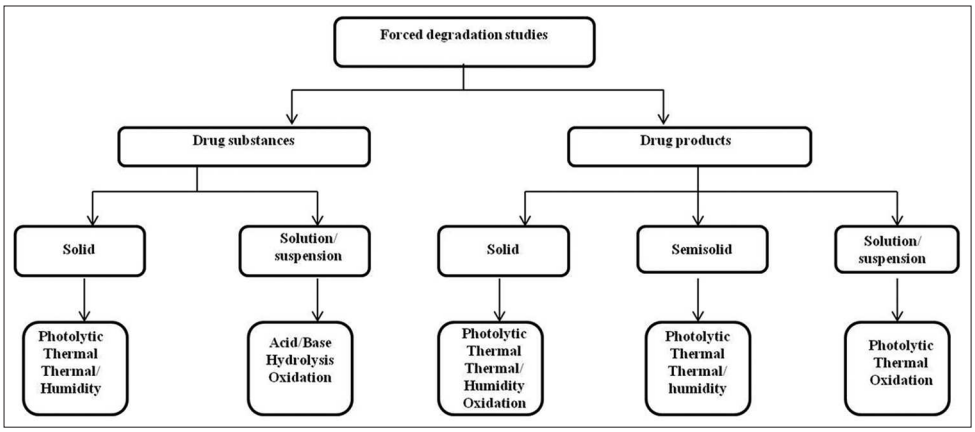

Figure 1: Schematic representation of degradation studies of drugs and drug products under different stress conditions

Humidity

Humidity plays an important role in degradation process. In forced degradation studies, the drug substance is exposed to 90% humidity for 1 week which tends to cause degradation. Humidity is one of the important parameters to establish the possible degradants in finished products and API.

FACTORS AFFECTING DEGRADATION

Following are the different factor which causes degradation of drug substances. They are:

Moisture

In the presence of moisture, water-soluble substances may get dissolved. This leads to physical and chemical changes within the molecule.

Excipients

It was observed that some excipients may contain high content of water. This moisture may lead to increased water level in formulation which later affects the stability of the drug. In some cases, chemical interactions that occur between the excipients and the drug material often results in decreased stability.

Temperature

Changes in temperature at times show deleterious effect on the stability of the drug. Increase in temperature usually causes increases 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 drugs are carried out using buffer solutions of pH with maximum stability.

Oxygen

Presence of oxygen increases the oxidation in some drugs. Drugs with increased rate of decomposition in the presence of oxygen are stabilized by purging nitrogen or carbon dioxide in the storage container.

Light

Some drugs are photolabile and tend to decompose when they are exposed to light. The susceptibility to

photolytic decomposition can be tested by comparing its stability in the presence of light and stability when stored under dark. It is to be remembered that the photolabile compounds should be stored in amber glass containers and should be stored in the dark.[16]

STABILITY INDICATING METHOD

FDA defines the stability indicated method as a quantitative method and monitors how the concentration of the drug will get affected with respect to change in time. The decrease in concentration of drug present and drug product will be determined. Notably, the concentration of the drug molecules are shown to vary during the degradation studies. It is observed that the concentration of the drug substance changes during the degradation studies; notably, no interference is observed from the excipients or other degradation products. Hence, the SIM helps in preformulation studies and also to predict the storage conditions of the drug.

RELATION BETWEEN FORCED DEGRADATION STUDIES AND STABILITY DATA

In forced degradation studies, several products are produced than normal stability testing. In stability testing, it becomes difficult to detect the actual degradation products because of its low potential. In this perspective, forced degradation studies minimize this problem. If no degradants was produced, then it can be considered that the drug substance is stable under given stress conditions and the protocol can be depicted to be a stability indicating process. Forced degradation analysis also helps to study the proper storage conditions of different pharmaceuticals. More importantly, forced degradation studies are useful in determining the degradation pathway of various drug substances.[9]

PREPARATION OF SAMPLE FOR FORCED DECOMPOSITION STUDIES

During forced decomposition and stability studies, active pharmaceutical ingredient is subjected to various stress under accelerated conditions such as photolytic, thermal, oxidative, and hydrolytic conditions. Due to stress conditions, several degradation products are expected to be produced, which can be compared to the degradative products (if any) that are obtained from regular storage conditions.[3]

Hydrolytic Conditions

Drugs molecules are dissolved in hydrochloric acid or sulfuric acid (0.1–1 M) in acid hydrolysis. In base hydrolysis drug molecules are dissolved in 0.1–1 M of potassium hydroxide or sodium hydroxide. Samples are subjected to stress for 2–7 days at room temperature. Stressed samples were neutralized with relevant acids or bases to prevent additional degradation.

Oxidation Conditions

Drug molecules are stressed with 0.1–3% hydrogen peroxide. Samples are stressed for not more than 7 days at room temperature and samples are neutralized with suitable agents.

Photolytic Conditions

Sample solutions that are subjected to photolytic stress by exposing them to as minimal as of 1.2 million × l h and 200 W h/m^2 light of 300–800 nm.

Thermal Conditions

Solids are exposed to wet heat and liquids are exposed to dry heat. Thermal stress conditions are applied for shorter period.

METHOD DEVELOPMENT AND OPTIMIZATION

Before developing a method, the first step is to determine the pKa value, log P, solubility, and λ_{max} of the respective drug. Development of a reverse phase method using HPLC is a common practice for the separation drugs. The commonly used solvents such as methanol, acetonitrile, and water are used as mobile phases in different combinations and proportions. With respect to the solubility profile of the drug, the organic phase such as methanol or acetonitrile is chosen. The choice of the mobile phase and its proportion is usually determined from earlier reports or by trial and error methods. At the onset of the experiment, the organic and aqueous phases are maintained at 50:50, and further optimization can be done on the proportions of the solvents for the mobile phase such that an ideal resolution of the peaks are obtained. In certain cases, buffers can be used for good baseline separation and peak symmetry. At times, the column temperature is adjusted to 30–40°C to get good reproducibility of the results. Degradant peaks are pushed in the chromatogram to get good resolution. Sometimes degradants peaks elute along with the drug peak or hidden by drug peaks, which in turn leads to peak purity analysis. Direct analysis can be done using HPLC that are equipped with PDA detectors. By changing the proportion of the mobile phase, it becomes easier to resolve and analyze the degradants peaks. The method developed is considered as homogeneous if the degradants peak is observed where the area under the curve of drug peak and its percentage are not affected. These degradants, which coelute with drug, are acceptable to some

extent provided; they were not observed in accelerated and long-term storage studies. Further, the method can be optimized by modifying the parameters such as the rate of flow of mobile phase, volume of sample injected, type of column used, and by changing the proportion of the mobile phase used in the analysis. After optimization of these parameters, the method developed for the study will be subjected to validation as per the ICH guidelines.[3]

CHARACTERIZATION OF DEGRADANTS

Earlier reports have shown that multiple analytical techniques are available to isolate, identify, and characterize the impurities that are produced in the degradation studies even at a very low concentration. The degradants isolated in the study were identified and characterized by hyphenated methods such as LC–MS and LC–nuclear magnetic resonance spectroscopy (LC–NMR).[3] More importantly, the structural characterization of the degradants/impurities become necessary as they play a vital role in the determination of shelf-life stability. Detection of impurities can be done by thin layer chromatography (TLC), electrophoresis, colorimetric, and gel filtration techniques, while separation and isolation of degradants in pure form can be done using reversed-phase HPLC, TLC, gas chromatography, and supercritical fluid chromatography. Notably, the determination of degradants pathways is carried out using LC-MS/MS technique. The degradative pathways can be determined on the basis of fragmentation patterns that are observed. After determination of degradant pathways, structure elucidations of degradants are done by synthesizing or isolating methods and further characterized by employing LC-MS, LC-UV, and LC-NMR techniques.[1,3,6,12]

Several studies were conducted based on forced degradation of drug molecules. The characterization of degradants produced was determined using advanced analytical techniques such as LC-MS, LC-NMR, and LC-MS/MS methods. From the earlier reports, the forced degradation studies of different drug molecules, the stability profile, degradants produced, and storage requirements for the drug molecules are summarized as follows:

1. Aceclofenac: Aceclofenac is stable at dry heat or below 80°C and in the absence of light.[18]
2. Diacerein: Diacerein was unstable at alkaline hydrolysis, photolytic, and thermal conditions. It remains stable under acid hydrolytic and oxidative stress conditions.[19]
3. Proteins: Unstable at photolytic conditions. Secondary packing is necessary to protect from light.[20]
4. Idarubicin: Drug degradation occurs in hydrolysis and oxidative stress conditions. In oxidative stress and alkaline hydrolysis, two degradants were produced, and in acid hydrolysis, one degradant was produced. These degradants were characterized by LC-MS-TOF and were found to be desacetylidarubicin hydroperoxide, desacetylidarubicin, and deglucosaminylidarubicin.[8]
5. Valsartan: Drug is unstable at acid stress conditions and produced three degradation products.[21] 2-methyl-N-{[2'-(1H-tetrazol-5-yl)biphenyl-3-yl]methyl}propan-1-amine and N-methyl-N-{[2'-(1H-tetrazol-5-yl)biphenyl-3-yl]methyl} butanamide were produced due to oxidation stress.[22]
6. Piroxicam and meloxicam: Two drugs were stable at thermal stress and unstable at hydrolytic, oxidative, and photolytic stress conditions.[23]
7. Tetrabenazine: In alkaline conditions, poor degradation was observed, but in acidic conditions, more degradation had occurred.[24]
8. Wheat straw: At higher temperatures, aromatic aldehydes were produced as degradants.[25]
9. Anastrozole: In base hydrolysis and oxidative stress, drug molecule degraded and two degradants were produced. These impurities were characterized as 2,2'-(5-((1H-1,2,4-triazol-1-yl)methyl)-1,3-phenylene)bis(2-methylpropanoicacid) (Diacid) and 2-(3-((1H-1,2,4-triazol-1-yl)methyl)-5-(2-cyanopropan-2-yl)phenyl)-2-methylpropanoicacid (monoacid).[26]
10. Ivabradine: Drug was unstable at acid–base hydrolysis conditions and five degradation products were produced under hydrolytic conditions.[27]
11. Amlodipine besylate: Drug was stable at thermal stress conditions; in acidic stress two degradants, in basic stress four degradative products, and in oxidative stress conditions one degradation product were produced.[28]
12. Lisinopril: Unstable at acid hydrolytic conditions and four degradation products were produced.[29]
13. Midazolam maleate: Drug was unstable at hydrolytic and thermal stress conditions.[30]
14. Saikosaponin: Under acid hydrolysis, two degradants were produced; impurities characterized as SS-B2 and hydroxysaikosaponin A.[31]
15. Moxidectin: Drug showed good stability at thermal stress conditions; under alkaline hydrolysis, two degradants produced which were characterized as 2-epi and Δ2,3 isomers.[32]
16. Lansoprazole: In acid hydrolytic conditions, one degradation product was produced and was identified as 1-methyl-10-thioxo-10H-4a,5,9b-triaza-indeno[2,1-a]inden-2-one.[33]
17. Piracetam: Stable at all conditions except alkaline stress conditions. In alkaline conditions, one degradation product was observed.[34]
18. Dexlansoprazole: In oxidation stress condition, one degradation product was produced and characterized to be 1-(1H-benzo[d] imidazol-

2-yl) -2,3- dimethyl-4-(2, 2, 2-trifluoroethoxy) pyridine-1-ium.[35]

19. Deflazacort: In alkaline condition, the drug was readily degraded and produced and 21-hydroxy deflazacort (21-OH-DFZ) as degradation product.[36]
20. Nevirapine: Degradation was observed in both heat and acidic conditions. Under acidic condition, 2-(3-Amino-4-methylpyridine-2-ylamino) nicotinic acid impurity was observed.[37]
21. Cefditoren pivoxil: Stable at thermal and photolytic stress conditions, unstable at hydrolytic conditions, and two degradants were produced.[38]
22. Sofosbuvir: Stable at thermal conditions; susceptible to oxidative, photolytic, and hydrolytic conditions.[39]
23. Enflurane: Under alkaline stress condition, N-acetyl-L-cysteine S-conjugates impurity was produced.[40]
24. Paliperidone: Drug degradation occurred at acid and alkaline hydrolysis; 3-(1-allyl-1, 4-dihydropyridin-4-yl)-5-fluorobenzo [d] isoxazole, 5-fluoro-3-(piperidin-4-yl) benzo[d] isoxazole, and 5-(2-(4-(5-fluorobenzo[d] isoxazol-3-yl)piperidin-1-yl)ethyl)-6-methylpyrimidin-4-(3H)-one were the degradation products produced under hydrolysis condition.[41]
25. Metoclopramide: It is a photosensitive drug. Under UV radiation, degradation reactions like dechlorination and hydroxylation were observed.[42]
26. Curcumin: Curcumin is labile to alkaline conditions and able to withstand at acidic, photolytic, oxidative, and thermal stress conditions. In alkaline conditions, eight degradants were observed.[43]
27. Flupirtine maleate: Under hydrolysis conditions, three degradants were produced and identified as{2-amino-6-[(4-fluorobenzyl)amino]pyridin-3-yl}carbamic acid, N -(4-fluorobenzyl)pyridine-2,3,6-triamine, and 5-[(4-fluorobenzyl)amino]-1,3-dihydro-2H-imidazo[4,5-b]pyridin-2-one.[44]
28. Fidarestat: Drug is able to withstand under thermal and photolytic stress conditions. Unstable at hydrolysis and oxidative stress conditions.[45]
29. Ezetimibe: Stable at thermal, oxidative, and photolytic conditions; four degradants were produced at hydrolytic conditions.[46]
30. Abacavir sulfate: Drug degradation occurred under oxidative and acid stress; in acid hydrolysis, $C_8H_{10}N_6$ impurity was produced while $C_{14}H_{18}N_6O_3$ and $C_{11}H_{14}N_6O$ were produced under oxidative stress condition.[47]
31. Fenofibrate: Under hydrolysis and oxidative conditions, drug undergoes degradation process. Four degradation products were observed.[48]
32. Gefitinib: Degradation occurred at hydrolysis and oxidative conditions; unstable at thermal conditions.[49]
33. Emtricitabine: Significantly degraded under oxidative and acidic stress conditions; three major degradants were produced.[50]
34. Nintedanib: Stable at thermal and photolytic conditions; labile to hydrolytic and oxidative conditions; in acid conditions, two degradants, basic condition one degradation product, and oxidative condition one degradant were produced.[51]
35. Agomelatine: Stable at thermal and photolytic conditions; unstable at hydrolytic and oxidative conditions.[52]
36. Hydrochlorothiazide: Under hydrolytic conditions, two degradants were produced.[53]

CONCLUSION

The forced decomposition studies provide a means to estimate the stability of drug stability and aids in the identification of the degradants produced. Degradants produced in forced degradation studies may or may not produce in storage conditions, but they are used to select appropriate storage conditions. It will help to develop SIM. Using this information, manufacturing process can efficiently be carried out and the drug preparations can be stored under most suitable storage conditions. This review has been summarized to the best, to provide knowledge about various regulatory guidances available for forced degradation studies, methods to perform stress studies under various accelerated conditions, and stability and degradants produced under various stress conditions for several drugs.

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