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REVIEW OF FORCED DEGRADATION STUDIES ON THE DRUGS CONTAINING HETROCYCLIC COMPOUND

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ABSTRACT

Forced degradation studies are useful in the development of analytical methodology, as it is of help to obtain a better understanding of active pharmaceutical ingredient (API) and drug product (DP) stability, and also to get insight into degradation pathways and degradation products. Heterocyclic chemistry is a crucial branch of organic chemistry as evident that two thirds of organic compounds are heterocyclic. Under forced degradation studies, the hetero atoms and the carbocyclic rings in the structure aundergo degradation to a different product than the primary drug structure. To study these products, various analytical methods are utilized. The current review discusses forced degradation studies and their impact on heterocyclic compounds.

KEYWORDS

Heterocyclic Compound, ICH Guidelines, Forced Degradation and Analytical Method.

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INTRODUCTION

Forced degradation studies are widely recognized as, stress testing, stress studies, stress decomposition studies forced decomposition studies etc. Forced degradation involves degradation of drug products and drug substances at conditions more severe than accelerated conditions and thus generation of degradation products occur which can be studied to determine the stability of the molecule. It is defined as per ICH guidelines that stress testing is a method intended to identify the degradation products which further throws light on the intrinsic stability of the molecule and also to validate the stability indicating procedures used and establishing degradation pathways[1].

What are Heterocyclic compounds?

A cyclic organic compound containing all carbon atoms in ring formation is referred to as a carbocyclic compound. Compound containing one or more atoms other than carbon as a part of the ring system is considered to be a heterocyclic compound[2]. Nitrogen, oxygen and sulphur are the most common heteroatoms but heterocyclic rings containing other hetero atoms are also widely known. Heterocyclic compounds may be classified into aliphatic and aromatic. The aliphatic heterocycles include cyclic analogues of amines, ethers, thio-ethers, amides, etc. Particularly, their properties are influenced by the presence of strain in the ring. These compounds generally consist of small (3- and 4-membered) and common (5 to 7 membered) ring systems. The aromatic heterocyclic compounds, are those which possess a heteroatom in the ring and follow similar trend in terms of to properties as that of benzene. Heterocycles are present in a wide variety of drugs, most vitamins, many natural products, biomolecules, and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antidepressant, antimalarial, anti-HIV, antimicrobial, antibacterial, antifungal, antiviral, antidiabetic, herbicidal, fungicidal, and insecticidal agents[3].

OVERVIEW OF REGULATORY GUIDANCE

Forced degradation studies are described various International guidelines. The International committees for Harmonization of Technical Requirements for Registration of pharmaceutical Human use (ICH) has published a set of guidelines which have been discussed, agreed upon and adopted by the American, European and Japanese regulatory authorities[4].

The ICH guidelines that are applicable to forced degradation studies are:

- ICH Q1A – Stability Testing of New Drug Substances and Products[5].
- ICH Q1B – Photo stability Testing of New Drug Substances and Products[6].
- ICH Q2B – Validation of Analytical Procedures: Methodology[7].

OBJECTIVES OF FORCED DEGRADATION STUDIES

1. To establish degradation pathways of drug substances and drug products.
2. Differentiation of the 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 find the degradation mechanisms such as hydrolysis, oxidation, thermolysis or photolysis of the drug substance and drug product[1,8]
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 under ICH conditions similar to that of what would be observed in a formal stability study.
10. To solve stability-related problems[9.]

Origin of degradation products

Degradation is the main reason of appearance of impurities in drug substance or product. The chemical instability of the drug substance under the conditions of heat, humidity, solvent, pH, and light encountered during manufacture, isolation, purification, drying, storage, transportation, and/or formulation is main cause of its degradation. It is governed by inherent chemical stability of the drug substance. The major routes of degradation of any drug substance include hydrolysis, oxidation, heat and photolysis. The stress testing generates all possible degradation products that may form under different conditions[10].

DEGRADATION CONDITIONS

Hydrolysis condition

The most common degradation and chemical reactions thats occurs over a wide range of pH, is hydrolysis. The decomposition of a chemical

compound by reaction with water is called hydrolysis. In acidic and basic hydrolysis, the catalysis of ionisable functional groups present in the molecule occurs. When the drug interacts with acid and base forced degradation of a drug substance occurs. It produces primary degradants in the desirable range. For acidic hydrolysis hydrochloric acid or sulphuric acid are considered whereas sodium hydroxide is used for basic hydrolysis[11].

Oxidative condition

For oxidative forced degradation, oxidative reagent used is hydrogen peroxide. Apart from this, metal ions, oxygen, and radical initiators such as azobi-isobutyro-nitrile, AIBN are also used. Drug structure will allow selecting concentration and condition of oxidizing agent. An electron transfer mechanism occurs in oxidative degradation of drug substance[11].

Photolytic conditions

To demonstrate that a light exposure does not result in unacceptable change the photo stability testing of drug substances must be evaluated. Photo stability studies are performed to generate primary degradants of drug substance by exposure to UV or fluorescent conditions. Some recommended conditions for photo stability testing are described in ICH guidelines[9.] Functional groups like carbonyls, nitroaromatic, N-oxide, alkenes, aryl chlorides, weak C–H and O–H bonds, sulphides 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 sub- stances 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[9]. Effect of temperature on thermal degradation of a substance is studied through the Arrhenius equation: $k = Ae^{-Ea/RT}$, where k is specific reaction rate, A is frequency factor, Ea. is energy of activation, R is gas constant (1.987cal/degmole) and T is absolute temperature. Thermal degradation study is carried out at 40–80ºC [11].

Humidity

Humidity is the Key factor in establishing the potential degradants in the finished product and active pharmaceutical ingredient. For the establishment of forced degradation samples normally 90% humidity for duration of one week shall be recommended.

HOW HETEROCYCLIC COMPOUND GETS AFFECTED BY FORCED DEGRADATION

A stable drug product and drug substance is considered if it shows its stability at least for two years at 30±ºC and 65±5% RH (Relative Humidity) and six months at 40±2ºCand 75±5%RH i.e. ICH condition for stability testing.

The forced degradation study should encompass acid and base hydrolysis, photolysis, thermal, oxidation degradation. Any regulatory guidelines do not mention the pH. Condition for acid and base hydrolysis or the temperature for thermal degradation or concentration of an oxidising agent.

In photolysis

The rate of photo degradation depends upon the intensity of incident light and quantity of light absorbed by the drug molecule. Non-oxidative or oxidative photolytic reactions are the two methods of photolytic degradation. Dimerization, isomerization, rearrangements, cyclization, and decarboxylation etc are includes in the non-oxidative photolytic reaction. And while oxidative photolytic reaction occurs by two mechanism which are singlet oxygen ($1O_2$) or by triplet oxygen ($3O_2$) mechanism[12].

In thermal

Many APIs are sensitive to heat or tropical temperatures. For example, vitamins, peptides, etc. Different reactions like decarboxylation, pyrolysis, hydrolysis, isomerization, rearrangement and polymerization can occur by thermal degradation[12].

In oxidation

Many drug substances undergo autoxidation i.e. oxidation under normal storage condition and

involving ground state elemental oxygen. Therefore, it is an important degradation pathway of many drugs. Auto- oxidation is a free radical reaction that requires free radical initiator to begin the chain reaction. Hydrogen peroxide, trace level of impurities or metal ions in a drug substance act as initiators for auto-oxidation. The mechanism of oxidative degradation of drug substance involves an electron transfer mechanism to form reactive anions and cations. Amines, sulphides and phenols are capable of electron transfer oxidation to give N-oxides, hydroxylamine, sulphones and sulphoxide[12].

In hydrolysis

Hydrolytic study under acidic and basic condition involves catalization of ionisable functional groups present in the molecule[12].

Biochemical reactions can occur only in a certain way, whereas photochemical processes are less predictable, particularly when radicals are involved, which do not occur in the case of biochemical process[13,14]. Therefore, it can be expected that in the aquatic environment photo degradation will be more important mechanism of pharmaceuticals transformation[15,16], especially in case of compounds which contains aromatic rings, heteroatoms and other functional groups that can absorb the sunlight (direct photolysis) or react with active molecules •OH, $^1O_2$, ROO•, ^{3}DOM*, e^- generated by photosensitizers (indirect photolysis)[17,18].

Examples of drugs containing heterocyclic compound which gets affected by forced degradation

Rosuvastatin (class of statin) undergoes alkaline degradation. The carboxylic group present in the chemical structure of rosuvastatin is highly responsible for degradation. Lactonization of β-hydroxy acid and lactone ring formation takes place at same time. Ezetimibe also has undergone alkaline degradation and the phenolic hydroxyl group present in the chemical structure may be responsible for it[19].

In Paclitaxel (class of taxanes) major degradation take place in acidic condition (0.1N HCl). 7th position of paclitaxel, is a possible site for acid catalysed cleavage. Oxetane ring present at 7th position gets cleaved by acidic catalysed condition and also hydrolysis of ester group occurs forming a degradant product of paclitaxel as showed in Figure No.2.

Amlodipine (a long-acting calcium channel blocker):- Study revealed that the main photoproduct of amlodipine, its pyridine derivative, exhibited a stronger toxic potential than the parent drug in *Ceriodaphnia dubia*[21].

Riboflavin (vitamin B2) is the most classic example for photo stability studies and also its degradation in aqueous and organic solvents and is degraded into various photoproducts on exposure to light. These products include formylmethylflavin (FMF), lumichrome (LC), lumiflavin (LF), carboxymethyl Flavin (CMF), 2, 3-butanedione, a β-keto acid and a dike to compound[21-42] (see Figure No.3)

The thermal degradation of piroxicam carried out at pH range 2.0-12.0 followed first-order kinetics. The thermal degradation of piroxicam represents a bell-shaped pH-rate profile in the pH range 2.0-12. Showing the pH of maximum degradation around 6.0, which then slows down due to ionization of the molecule. Such curves indicate the presence of two ionisable groups in the molecule and the most reactive species is the non-ionized form[43] (see Figure No.4).

Selection of analytical method for identification and characterization of drug product

To make drugs serve their purpose in the estimation of drugs various chemical and instrumental methods were developed at regular intervals. The impurities may build up in these pharmaceuticals at various stages of their development, transportation and storage which make the pharmaceutical unsafe for administration and thus they must be detected and quantified. Therefore, analytical instrumentation and methods play an important role. The current review focuses on the function of the analytical instrumentation and the analytical methods in assessing the quality of the drugs.

Reverse-phase high-performance liquid chromatography (HPLC) generally is a preferred method of analysis for stability indicating assay.

RP-HPLC is preferred method because of its compatibility with aqueous and organic solutions, highly precise, good sensitivity, and ability to detect polar compounds.

A gradient elution may be carried out to determine highly polar compounds eluting early and most retained non-polar compounds for method development.

Stress sample preparation should be similar to the sample preparation mentioned in the analytical procedure. For acid and base hydrolysed samples neutralization or dilution of samples are necessary. To determine the origin of peaks, chromatographic profiles of stressed samples should be compared to those of relevant blanks (containing no active and unstressed samples). The selected analytical method should be sensitive and be able to identify 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. Based on stability results in accordance with ICH requirements, degradation product identification and characterization shall be performed[43-48].

For characterization and identification of the degradation products, conventional methods (e.g., column chromatography) or hyphenated techniques (e.g., LC MS, LC NMR) can be used. It should be noted that structural characterization of degradation products is necessary for those impurities that are formed during formal shelf-life stability studies. To detect spectral non-homogeneity the detector should contain 3D data capabilities such as diode array detectors or mass spectrometers. For major impurities /degradants, use the analytical mode and check the mass numbers or develop chromatographic conditions suitable to LC-MS and identify the mass of major degradant which are found to be forming greater than 1.0% during stress studies. Try to establish the structures of the major degradant, if possible and compare the synthetic process for justification. It is possibility to checking peak profile for multiple wavelengths by Diode array detection. The diode array arises has a limitation when the UV profiles are similar for analyte peak and impurity or degradant peak and the noise level of the system is high to mask the co-eluting impurities or degradants. Similar molecular weights and functional groups compounds such as diastereoisomers may exhibit similar UV profiles. Therefore, attempts must be made to modify the chromatographic parameters to achieve necessary separation. An optimal wavelength should be selected to detect and quantitation of all the potential impurities and degradants Use of more than one wavelength may be necessary, if there is no overlap in the UV profile of an analyte and impurity or degradant peaks[49-53].

Forced Degradation Studies in Stability-Indicating Method Development

Changes in the chemical, physical, and microbiological properties of drug product must be able to monitor by stability indicating method.

The ability of the method to monitor a change in the chemical properties of the drug over time, invariably calls for a forced degradation (stress testing) study to be done on the drug substance and drug product.

Forced degradation on the drug and formulations will also provide other information as follows:

1. Determination of degradation pathways of drug substances and drug products;
2. Discernment of degradation products in formulations that are related to drug substances versus those that are related to non-drug substances (e.g., excipients);
3. Structure elucidation of degradation products;
4. To determine the intrinsic stability of a drug substance molecule in solution and solid state; and
5. Reveal the thermolytic, hydrolytic, oxidative, and photolytic degradation mechanism of the drug substance and drug product[54,55].

Table No.1: Conditions used for forced degradation studies

S.No	Degradation type	Experimental Condition	Storage condition	Sampling time
1	Hydrolysis	Control API (no acid or base) 0.1M	40º C, 60º C	1,3,5
		HCl	40º C, 60º C	1,3,5
		0.1 M NaOH	40º C, 60º C	1,3,5
		Acid control (no API)	40º C, 60º C	1,3,5
		Base control (no API)	40º C, 60º C	1,3,5
		pH: 2, 4, 6, 8	40º C, 60º C	1,3,5
2	Oxidation	3%H2O2	25ºC, 60º C	1,3,5
		Peroxide control	25ºC, 60º C	1,3,5
		Azobisisobutyronitrile (AIBN)	40ºC, 60º C	1,3,5
		AIBN control	40ºC, 60º C	1,3,5
3	Photolysis	Light 1 × ICH	NA	1,3,5
		Light 3 × ICH	NA	1,3,5
		Light control	NA	1,3,5
4	Thermal	Heat chamber	60º C	1,3,5
		Heat chamber	60º C/75% RH	1,3,5
		Heat chamber	80º C	1,3,5
		Heat chamber	80º C/75% RH Room temp.	1,3,5
		Heat control		1,3,5

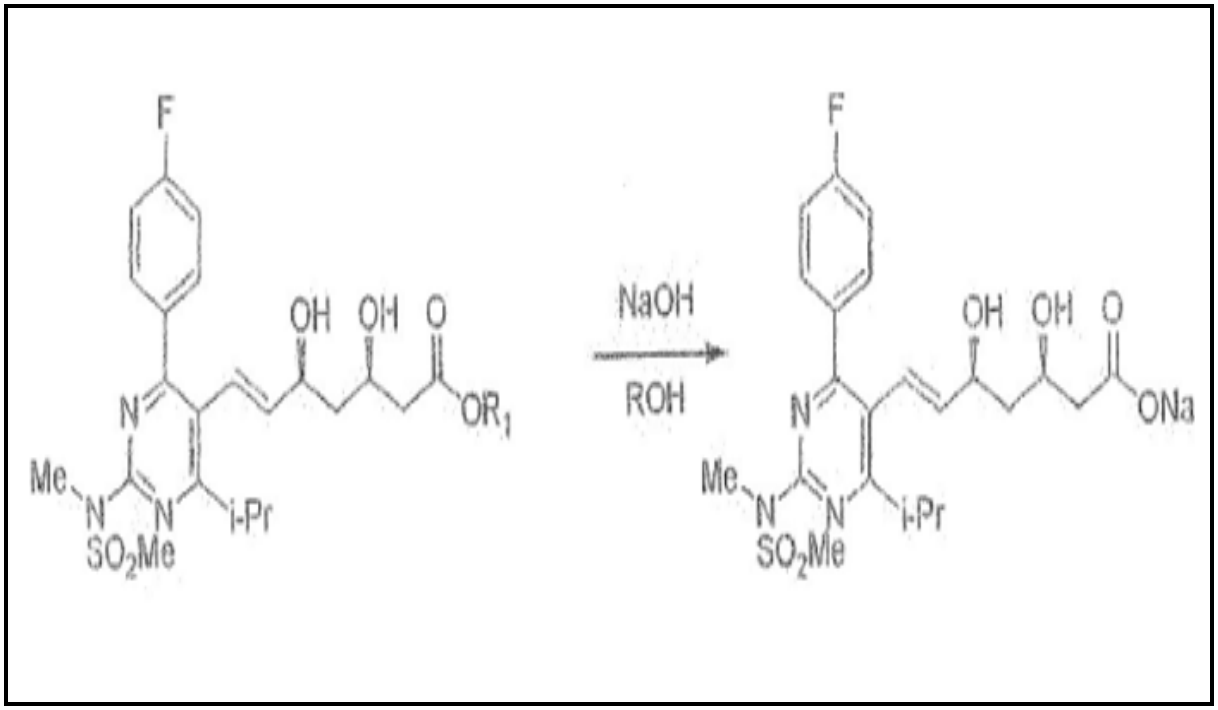

Figure No.1: Alkaline degradation of Rosuvastatin

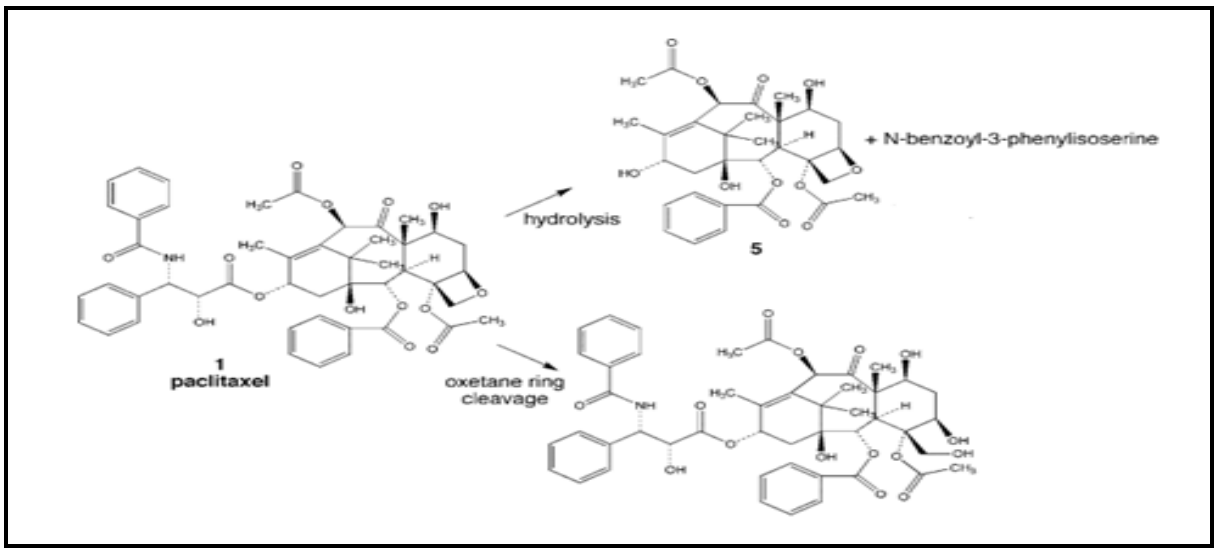

Figure No.2: Acidic and Hydrolytic degradation in Paclitaxel

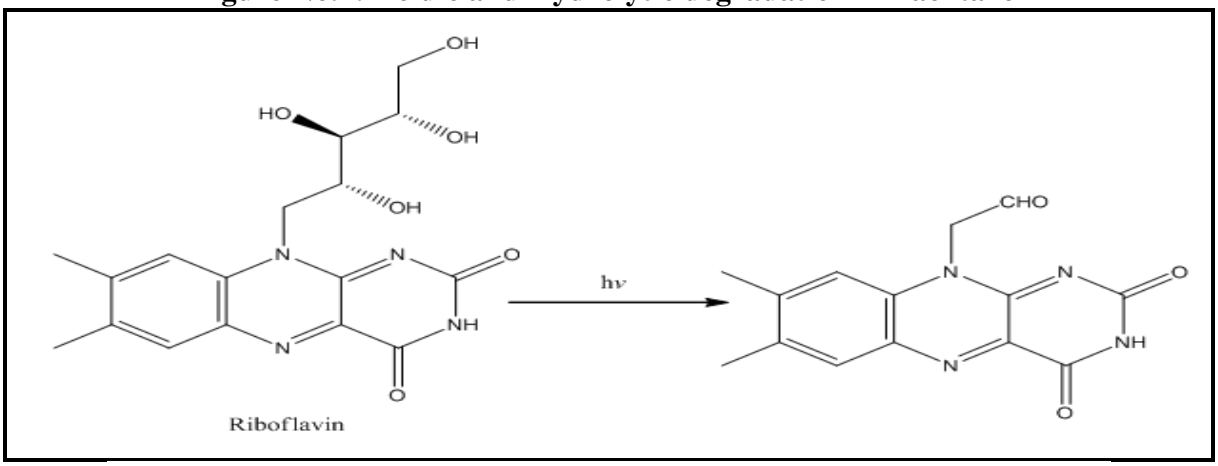

Figure No.3: Photolysis of Riboflavin to form for mylmethyl flavin (FMF)

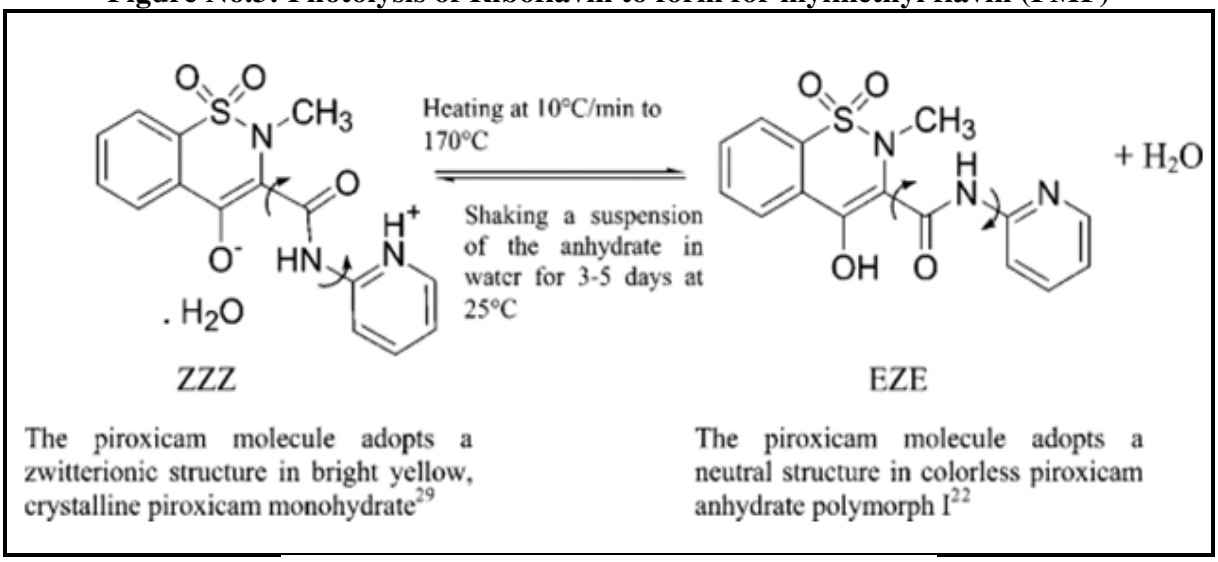

Figure No.4: Thermal degradation of Piroxicam

CONCLUSION

In drug development process, forced degradation studies plays a vital role as it provides knowledge about the degradation chemistry of drug substances and drug products. Heterocyclic compounds which are mainly present in drug chemistry are more prone to forced degradation by hydrolysis, thermal, photolysis, oxidation reaction and forms a degraded product. Proper selection of analytical method is important to detect and quantify the impurities and degradative product by chromatographic profile or UV spectrum etc.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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