IJNRD.ORG ISSN : 2456-4184
INTERNATIONAL JOURNAL OF NOVEL RESEARCH AND DEVELOPMENT (IJNRD) | IJNRD.ORG
An International Open Access, Peer-reviewed, Refereed Journal

Degradation Profiling of Pharmaceuticals: A Review

N. M. Yenare , [2]B. K.Warkhade, [3]M. S. Charde, [4]R. D. Chakole,
Department of Pharmaceutical Chemistry,
Government College of Pharmacy, Vidyanagar Karad, Dist-Satara
Maharashtra, India, Pin : 415 124

***For Correspondance**
Ms. Nita Madhav Yenare
Government College of Pharmacy , Vidyanagar , Karad ,
Dist : Satara , Maharshtra , India , 415124

Abstract:

An epigrammatic impression of the most recent developments in analytical views of degradation profiling of pharmaceuticals, including active pharmaceutical ingredient, is described in this article. To give details on the processes and end results of degradation. This article offers a road map for when and how to conduct studies, helpful tools for planning tough scientific experiments, and instructions on how to record and disseminate results in order to achieve development and regulatory objectives. According to ICH recommendations, some factors might cause degradation, such as light, oxidation, dry heat, acidic, basic, hydrolysis, etc. The forced degradation experiments are best illustrated by ICH Q1A, QIB, and Q2B. The strategic ideas and developments in forced degradation studies are reviewed in this article. Studies on degradation are conducted at every stage of pharmaceutical research, production, and packaging. It aims to determine whether a method is stability indicating by assessing the degradation profile of an appropriate API and/or medications

Keywords: Degradation profiling, ICH guidelines, Force degradation, etc.

Introduction:

The terms "degradation profiling" and "quantitative determination of impurities and degradation product in bulk drug material and pharmaceutical formulation" are equivalent. A key aspect of the stability of drug candidate evaluation during preformulation. Through timely evaluation of a drug candidate's intrinsic stability features and purposeful stress application to produce degradation, these evaluations find to support further formulation development. Preformulation scientists use a variety of methods to achieve this goal, including increasing temperature, increasing humidity when appropriate (for example, when testing solid-state, chemical, and physical stability), subjecting materials to sheer or compressive forces (for example, when testing solid-state physical stability), exposing the test materials to different pH conditions, or using intense ultraviolet light (UV), visible light (for example, photostability), or by incorporating additional reactants such as acids, bases, and peroxides).

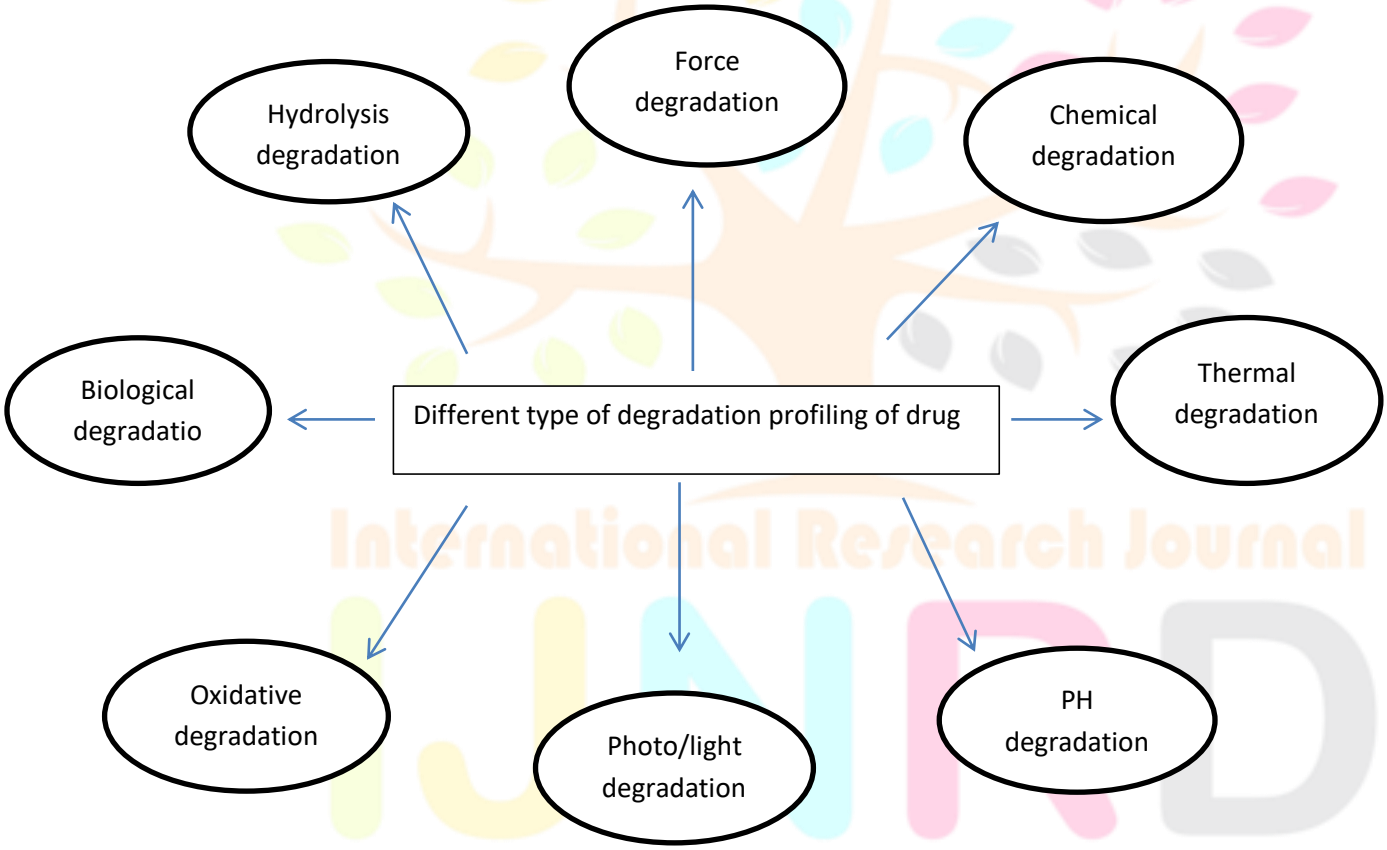

Figure 1: Different Type of Degradation Profiling Pathway

Studies on degradation will give prognostic data. When specific conditions exist, like hydrolysis in solution, it is possible to estimate shelf life rather accurately. It can be difficult to extrapolate stability under stress (such as oxidative testing) to regular storage settings in other situations. Although rank-order comparisons are frequently not only possible but also helpful for building subsequent formulations, stress testing is therefore a more qualitative than quantitative prediction tool. Early indications of drug candidate instability aid in the early detection of

potential development problems, the rapid development of prospective stabilisation decisions, and the suggestions of ways to improve the process of manufacture. Drug degradation is frequently caused by thermolytic, oxidative, and photolytic processes.

Degradation prediction tool:

CAMEO

Based on the conditions, reagents, and starting materials, the computer system CAMEO (Computer Aided Management of Emergency Operations) predicts the outcomes of chemical reactions. Important degradation conditions such as acidic/electrophilic, radical, and basic/nucleophilic are included in the studies. In addition, mechanical, photochemical, and oxidative/reductive reasons are provided for these responses. The CAMEO algorithms are usually applied to correct product mix forecasts that are inaccurate in anticipation of higher breakdown by product observations.

Degradation Studies of Drug and Drug Products:

Degradation is the main reason why drugs and medication products contain contaminants. The main causes of the drug and drug product's instability are the chemical and physical degradation that occur during manufacture when exposed to conditions including heat, humidity, solvent, pH, and light. These conditions also occur during isolation, purification, drying, storage, transportation, and formulation. To create stability-indicating assays for medications and pharmaceutical items, forced degradation investigations are carried out. Studies on degradation are conducted at every stage of pharmaceutical research, production, and packaging.

1. Chemical Degradation

Any modification to a medicine's active ingredient or excipient, whether it be physical, chemical, microbiologic, or an alteration to its therapeutic characteristics, could cause the drug to become unstable. The majority of drug instability is caused by chemical reactions that lower potency, which is a well-known indicator of a substandard drug product. A medicine may break down into a harmful substance; pralidoxime, for instance, breaks down by parallel pH-sensitive pathways. A hazardous substance called cyanide is created at basic pH levels. For instance, epianhydrotetracycline, a tetracycline degradant, causes Fanconi syndrome. If materials deteriorate over time, significant changes in colour or smell may occur. For instance, the intensely red substance adrenochrome substances used as pharmaceuticals have diverse is an oxidize product of epinephrine. molecular structures and are hence subject to a wide range of degradation mechanisms. Various processes include hydrolysis, dehydration, isomerization, racemization, elimination, oxidation, photodegradation, and complex reactions with excipients and

other drugs are examples of potential degradation pathways. If we might predict a drug's chemical instability based on its molecular structure, such information would be highly helpful.

2. Hydrolysis degradation

For the majority of parenteral products, the drugs comes into touch with water, and even in solid dosage forms, moisture is frequently present, albeit in minimal quantities. As a result, one of the most frequent reactions involving drugs is hydrolysis. When it comes to medicinal compounds with ester and amide functional groups in their structure, hydrolysis is frequently the primary pathway for degradation. Procaine, aspirin, chloramphenicol, atropine, and methylphenidate were some examples.

3 Photodegradation

In the field of pharmaceutical drugs and drug product photostability studies are essential stages in the development of the dosage form containing the bioactive. To ensure the manufactured drug products' quality, efficacy, and safety during formulation, storage, and usage, photostability tests are carried out. The medication's functional groups are essential for the photoreactivity of the medicine. In one such work, the photophysical process is described along with its connections to the photochemical kinetic reactions. These studies describe the numerous methods for drug photodegradation as well as the biological effects of light's impact on drug degradation. For assessing pharmaceuticals and drug products for photostability, there are ICH guidelines. The photostability of a drug is described as the response of the drug or drug product to exposure to solar, UV, or visible light in the solid, semisolid, or liquid state that results in a physical or chemical change.

Photodegradation reactions include pharmacological responses that result in the production of free radicals or photosensitization reactions caused by intermolecular energy transfer in the presence of light through excitation and/or absorption. In addition to secondary chemical reactions, which produce the final products, photo degradation reactions also include primary photochemical reactions. Photochemistry can explain how photochemical processes affect the drug's stability and effectiveness. Different processes and products might result from the photochemical reactions that lead to the breakdown of medicinal compounds. The nature of the medication and the types of photochemical processes involved must be thoroughly understood in order to elucidate these mechanistic routes. Such reactions can be impacted by physical properties like light absorption, pKas, solubility, and the presence of particular functional groups. The elements that determine the speeds and mechanisms of the underlying photochemical reactions are necessary for the assessment of a drug's photostability.

The quantity and wavelength of incident photons both affect a drug's rate of photodegradation. For instance, nifedipine's photodegradation rate was related to the quantity of incident photons. Nifedipine tablet photodegradation peaked at 420 nm. Another illustration is the difference between the rates of sulfisomidine

discolouration in tablets exposed to ultraviolet light versus mercury lamp radiation. The spectral characteristics of the medication as well as the spectral distribution of the light source have a significant impact on drug photodegradation. Under a mercury lamp, which is a reliable supply of UV energy, sulpyrine discolouration is a significant process, while it is minimal under a fluorescent lamp, which mostly emits visible light. An exposure to light can cause a drug or drug product to undergo photolytic breakdown. Light absorption causes photolytic degradation to begin; as a result, temperature has very little of an impact. Photolytic degradation is common, and studies have produced evidence to help identify potential degradant;

4. Oxidation degradation

It is possible to oxidise under an oxygen environment or with the help of peroxides. A more accurate model is the use of oxygen. Acceleration initiatives of free radicals can be employed to speed up oxidation. Typically, all initial oxidation degradation products seen in real-time stability are produced by a free radical initiator and peroxide. So, during all phases of development, free radical and/or hydrogen peroxide conditions are highly advised. Use a suitable solvent to dissolve the API under solution state stress conditions, and then add 5–20 mol% of a free radical initiator while maintaining atmospheric pressure. The reaction can be carried out in a reaction vessel pressurised with molecular oxygen at a pressure of 50 to 300 psi to improve the solubility of oxygen in the solution. The apparatus is also heated to quicken deterioration.

Hydrogen peroxide reagent (up to 3%) can be used for peroxide conditions. According to API solubility, it might be essential to add an appropriate co-solvent, as was previously stated. of DP studies where hydrogen peroxide is a contaminant of an excipient, hydrogen peroxide stress testing might be helpful.

Placing the API (as is) in suitably closed containers filled with an oxygen headspace as opposed to argon or nitrogen control headspace will allow you to examine solid-state stress situations. Depending on the API sensitivity to heat, the sample may also be heated for a specific length of time or temperature to hasten the rate of degradation. For substances in later stages of research with greater time and resources available to devote to mechanistic knowledge, the following oxidation conditions can be used. When metal ions are added to API solutions, it may be determined whether there is a propensity for catalytic oxidation of the API. APIs and formulation excipients frequently contain iron and copper ions. In a Fenton-type reaction, transition metal ions can also decrease peroxide to produce hydroxyl radicals. Additionally, light can influence oxidation processes. The more reactive singlet oxygen species can be created when light that a photosensitizer absorbs reacts with molecular oxygen.

Catechol like adrenaline and methyldopa are easily converted to quinones by oxidation. 5- Amino salicylic acid is subjected to oxidation, resulting in quinoneimine, which is then broken down into polymeric molecules.

Due to their complexity, oxidative degradation reactions typically do not adhere to the Arrhenius relationship. Different processes, including electrophilic/nucleophilic, electron transfer reactions, and autoxidation, can be used to oxidise medicines. The acknowledged justification for the validation of chromatographic assays is the 5%–20% oxidative degradation of pharmacological compounds.

5. Thermolytic degradation

The Arrhenius relationship is typically followed by processes that are heated or at high temperatures and these processes are referred to as thermolytic degradation. The term "thermolytic" is being used broadly here because it can refer to any degradation mechanism where a high temperature accelerates the rate of deterioration. The most frequent drug degradation routes are hydrolysis reactions, which are a subgroup of thermolytic degradation reactions; they will be covered individually. The generation of esters and amides, rearrangement, isomerization and epimerization, cyclization, decarboxylation, hydration and dehydration, dimerization and polymerization, among others, are other thermolytic degradation mechanisms.

6. pH-Degradation

Drug degradation studies must include pH-Degradation Profiles as an essential component. They offer suggestions for pharmacologically active substance breakdown pathways from a theoretical perspective. They might offer practical guidance for the ideal formulation and storage conditions of pharmaceutical products that comprise these active ingredients. When dissolved in aqueous solutions, the majority of pharmaceuticals are involved in protolytic equilibria. The pH degradation profiles of the relevant medicines are made more difficult by these protolytic equilibria. We presented a general methodology for the interpretation of pH-degradation profiles in 1988.

7. Forced degradation

Degradation routes, the drug's inherent stability, and the verification of stability-indicating analytical techniques. The findings of one-time forced degradation experiments should allegedly be included in Phase 3 INDs (Investigational New Drugs), according to a draught guidance paper. Data from forced degradation investigations, such as forced degradation products, degradation reaction kinetics, structure, mass balance, and drug peak purity, are necessary for NDA (New Drug Application) registration. Information regarding API degradation pathways is provided by this forced degradation study. Stress testing is another name for forced deterioration tests, which are also carried out to aid in the development of analytical methods.

One of the keys to IND and NDA registration documents is forced degradation and impurity profiling. The investigation on impurity and deterioration profiles has been summarised in a number of books [11–12] and review articles [13–16]. Aiming to examine the analytical trends for forced degradation studies and impurity profiling of

active pharmaceutical ingredients and pharmaceutical medication product with this viewpoint in mind, the current work.

Objective of stress degradation

- To create pathways for the breakdown of drug compounds and drug products.
- To comprehend the chemical characteristics of the medication molecule
- Clarification of the degradation product's structure.
- To address issues with stability
- To determine a pharmacological substance's inherent stability in the formulation.
- to identify the mechanisms of degradation, such as hydrolysis, oxidation, photolysis, and thermolysis
- To separate degradation products produced by drug products in a formulation from those produced by non-drug products.
- To produce stability revealing a method's nature that has been developed.
- To create formulations that is more stable. It also aids in figuring out when a specific formulation will expire.
- To create a deterioration profile that resembles what would be seen in an official stability study under ICH conditions.

Outcomes of forced degradation studies Forced degradation studies

- Determination of likely degradant,
- Determination of degradation pathways,
- Determination of intrinsic stability of the drug molecule,
- Determination of validated stability indicating analytical methods.

Regulatory guidelines

Forced degradation researches were advised by many international standards. Sometimes ICH guidelines only apply to new product marketing applications and do not include the portion during clinical development.

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

1. **ICH Q1A**: Stability Testing of New Drug Substances and Products,

   Recommendations for conducting studies on drug substances and drug products under configurations that may cause forced degradation (Stress testing). The advice is to carefully examine the findings of oxidation, photolysis, humidity (75% relative humidity), and temperature (above that for accelerated testing, i.e., >50 C). When evaluating a solution or suspension, a wide pH range should be taken into account.

2. **ICH Q1B**: Force degradation research, photo stability testing of new drug substances, and exposure limits are not specified. Photo stability testing can be done on solids or in solutions or suspensions.
3. **ICH Q2B**Analytical procedure validation. Provides direction for confirming the analytical methods. Section B 1.2.2 (impurities not accessible) suggests using samples from forced degradation trials to demonstrate specificity. 'Specificity' is a crucial consideration in determining whether the analytical approach is stability signaling.
4. **ICH Q3A (R2):** Identification of each impurity is necessary in order to consider chemical and safety implications. Chemical possibilities include a succinct description of analytical techniques, report preparation, cataloguing of impurities in the specification, and classification and identification of impurities. The safety prospects include detailed instructions for classifying contaminants that were absent or present in very small quantities in a batch of a new medicinal ingredient.

Force degradation process flow map

1. PREDICT DEGRADATION

Predict most likely degradant using the degradation database, CAMO and organic chemistry

⇩

2. DESIGN PROTOCOL

Develop forced degradation protocol based on the chemistry (CAMO) of the API/ drug product

⇩

3. PERFORM EXPERIMENTS

Sample at appropriate points using 'reasonable' stress conditions.

⇩

4. CHALLENGE METHODOLOGY

Perform HPLC screening of the degradation samples using suitable screening methodology.

⇩

5. EVALUATE PURITY/POTENCY

Obtain purity/potency data including mass balance where appropriate. Determine purity of the main band using diode array and LC-MS.

⇩

6. SELECT KEY DEGRADANTS/TRACK PEAKS

Determine the key degradant (primary degradant; 10% of total degradation). Track key degradants across orthogonal methods.

⇩

7. IDENTIFY DEGRADANTS

Utilize LC-MS,LC-NMR,TLC,Pre-LC,Column chromatography and synthesis to identify unknown

⇩

8. DOCUMENT DEGRADANTS AND MECHANISMS

Prepare reports and share degradation structures, mechanisms, in a degradation database.

Degradation Conditions

Conditions Usually Applied For Forced Degradation Studies:

Degradation type	Experimental Conditions	Storage Conditions	Sampling time(Days)
Hydrolysis	Control API	40^0C, 60^0C	1,3,5
	0.1 M HCl	40^0C, 60^0C	1,3,5
	0.1M NaOH	40^0C, 60^0C	1,3,5
	Acid/ base Control	40^0C, 60^0C	1,3,5
	Ph. : 2,4,6,8	40^0C, 60^0C	
Oxidation	3%H_2O2	25^0C, 60^0C	1,3,5
	Peroxide Control	25^0C, 60^0C	1,3,5
	Azobisisobutyronitrile (AIBN)	40^0C, 60^0C	1,3,5
Photolytic	Light 1^xICH	NA	1,3,5
	3^x ICH	NA	1,3,5
	Light	NA	1,3,5
Thermal	Heat Chamber	60^0C	1,3,5
	Heat Chamber/RH	60^0C/75%RH	1,3,5
	Heat Chamber	80^0C	1,3,5

API

The API should degrade by roughly 5-20% under the given stress levels or be at a suitable upper limit under those conditions. The precise parameters (intensity and duration) will be chosen based on the chemical properties of the API. The unstressed sample (control) and the corresponding blank should be contrasted with the stressed sample. A chemical might not always breakdown under a specific stress scenario. In these situations, it is advisable to stop stressing.

1. Acid

Examples of acids (0.1–1 mol/L solution) are HCl and H2SO4. Studies ought to be conducted in a solution condition. It may be necessary to add a suitable co-solvent, change the solution pH to the acidic range, or run the APIs as suspensions for some APIs that are only partially soluble or insoluble in the stated acidic solution. When selecting the proper co-solvent, particular attention should be made to the API structure (i.e., avoid using alcohols

for acidic circumstances due to their reactivity). Under acidic conditions, dimethylsulfoxide, acetic acid, and propionic acid are helpful. Depending on the API sensitivity to heat, the sample may also be heated for a specific period of time or temperature to hasten the rate of degradation.

2. Base

Mostly selecting bases are NaOH, LiOH or KOH (0.1–1 mol/L solution). And evaluate in the solution state. For certain APIs which are partially soluble or insoluble in the described basic solution, addition of an appropriate co-solvent, or adjustment of solution pH may be required to achieve dissolution; or the APIs can be run as suspensions. Glyme and 1, 4-dioxane also shows reactions in basic conditions so as per acknowledge we conditions set. Sample heated for a defined time/temperatureto study degradation at accelerate state, depending on the API stability and sensitivity toward heat.

3. Thermal/humidity

It is advised to run thermal/humidity conditions below the critical thermal/humidity that induces the phase change if the forced degradation thermal/humidity settings result in a phase shift. To determine a suitable temperature and the maximum time for thermal degradation investigations, consider Arrhenius kinetics. The length of time that the study's simulation of controlled room temperature storage requires can be estimated using an appropriate assumption of activation energy. Using accelerated storage temperatures typically more than 50 °C and N75% relative humidity, solid state stability can be assessed. The API sensitivity determines how long an exposure lasts.

4. Photostability

Follow the ICH photostability recommendations when conducting experiments. The ICH guidelines state that while the exposure levels must be justified, "the design of the forced degradation experiments is left to the applicant's discretion." The suggested exposures for confirmatory stability experiments are an integrated near UV energy of not less than 200 W-h/m2 and a total illumination of not less than 1.2 million lux hours. In order to ensure that the samples are sufficiently exposed for forced degradation investigations, the exposure time should be at least twice as long as the ICH exposure time. Acetonitrile is the go-to co-solvent for solution experiments. Methoxy radicals generated by exposure to light can cause methanol to develop more artefact degradation byproducts.

Force degradation study of ibuprofen

Specifications for system suitability. Throughout the forced-degradation investigation, all run sequences satisfied the requirements for system appropriateness.

- **Acid stress**. Under acid stress, IBP in bulk-drug assay preparations did not degrade. With FPPA, MPPA, and 4-IBAP as the primary degradation products, IBP showed some degradation in tablet test preparations when subjected to acid stress.
- **Base stress**. Because the IBP-free acid that generated in the acidic extraction solution was precipitated by the addition of base stress, substantial precipitation occurred when sodium hydroxide was added to the assay preparations designated for base stress. Due to this, research on this stress has been stopped and no findings are reported.
- **Oxidation Stress**. Using commercial 30% hydrogen peroxide, samples were subjected to oxidative stress, resulting in a final sample concentration of 10% hydrogen peroxide. After 216 hours, 4-IBAP was the main degradation product, accounting for 2% of the bulk drug and 1.2% of the tablet preparations of stress exposure . IBP was marginally more likely to degrade in bulk medication than in tablet forms under oxidation stress.
- **Temperature stress**. Preparations of sample tablets and bulk medications were heated to 80 C for 244 hours. IBP degradation ranged from 2.9 to 11.4% in bulk medication samples, and from 21.5 to 39.9% in IBP tablet formulations (at 1.3 and 1.4 min).
- **Light stress**. An adequately illuminated light cabinet. Under laboratory window lighting, IBP did not deteriorate. In a light cabinet that is frequently used for accelerated stability storage conditions, samples were then exposed to light.

  Acetone (1%) was added to samples as a sensitizer in anticipation of IBP's slow disintegration in a light cabinet and to hasten degradation. IBP degradation was 30%, thus researchers looked into how UV stress affected degradation. IBP significantly deteriorated in both the bulk-drug and tablet test preparations, with degradation rates of 70% and 98% (by area percent) in 380 hours, respectively. This discrepancy suggests that one or more excipients may have acted as photosensitizers (indirect photolysis), which allowed for a higher level of IBP degradation in tablet extract preparations.

Conclusion:

The current study provides a thorough update on recent developments in the analytical aspects of impurity profiling and degradation of pharmaceuticals, including active pharmaceutical ingredients (APIs) and drug products. Forced degradation studies are a well-known method for creating degradation pathways, identifying the products of active ingredient degradation, and elucidating the structure of degradants. The chemical and physical stability analysis of drug ingredients and drug products is made considerably by forced degradation experiments. This helps to establish the manufacturing and storage conditions for drug formulations as well as the expiration date. Information can be collected using many hyphenated analytical procedures in combination with one another.

Acknowledgement:

The authors are thankful to AICTE New Delhi for regarding the financial support during M.pharm studies tenure. Also thankful to principal of Government College of Pharmacy, Karad for allowing to publish this article and other facilities.

References:

1.Zhou, Deliang, William R. Porter, and Geoff GZ Zhang. "Drug stability and degradation studies." Developing solid oral dosage forms. Academic Press, 2017. 113-149.

2.Alsante, Karen M., et al. "The role of degradant profiling in active pharmaceutical ingredients and drug products." Advanced drug delivery reviews 59.1 (2007): 29-37.

3 Maheshwari, Rahul, et al. "Stability and degradation studies for drug and drug product." Dosage Form Design Considerations. Academic Press, 2018. 225-257.

4. Van der Houwen, O. A. G. J., et al. "Systematic interpretation of pH-degradation profiles. A critical review." International journal of pharmaceutics 155.2 (1997): 137-152.

5.Rawat, Trivikram, and I. P. Pandey. "Forced degradation studies for drug substances and drug products-scientific and regulatory considerations." Journal of pharmaceutical Sciences and research 7.5 (2015): 238.

6.Farmer, Sherri, et al. "Forced degradation of ibuprofen in bulk drug and tablets." Pharmaceutical technology 28.42 (2002): 13.

7.Jain, Deepti, and Pawan Kumar Basniwal. "Forced degradation and impurity profiling: recent trends in analytical perspectives." Journal of pharmaceutical and biomedical analysis 86 (2013): 11-35.

8. Iram, Farah, et al. "Forced degradation studies." Journal of Analytical & Pharmaceutical Research 3.6 (2016): 73.

9. Kats, Michael. "Forced degradation studies: regulatory considerations and implementation." (2005).

10. Reynolds, Dan W., et al. "Conducting forced degradation studies." Pharm Technol 26.2 (2002): 48-56.

11. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH harmonised tripartite guideline Q1B stability testing: photostability testing of new drug substances and products; 1996.

12. Baertschi, Steven W. "Analytical methodologies for discovering and profiling degradation-related impurities." TrAC Trends in Analytical Chemistry 25.8 (2006): 758-767.

13. ICH Q3C (R3) (2002) Impurities: Guidelines for Residual solvents (Step 5), International Conference on Harmonization.

14. 9. Sándor_Görög. ” Critical review of reports on impurity and degradation product profiling in the last decade” TrAC Trends in Analytical Chemistry
Volume 101, April 2018, Pages 2-16

15. Pan, Changkang, et al. "The use of LC/MS, GC/MS, and LC/NMR hyphenated techniques to identify a drug degradation product in pharmaceutical development." Journal of pharmaceutical and biomedical analysis 40.3 (2006): 581-590.