Degradation Pathway of Pharmaceutical Dosage Forms

Mahmad Awaiz M. Shaikh[1], Deepak A. Joshi[2], vidyasagar Gali[3], Shyamlila B. Bavage[4], Nandkishor B. Bavage[5]

[1]*B.Pharmacy Final Year Student, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

[2]*Assistant Professor, Department of Pharmaceutics, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

[3]*Principal of B.Pharmacy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

[4]*Vice Principal of B.Pharmacy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

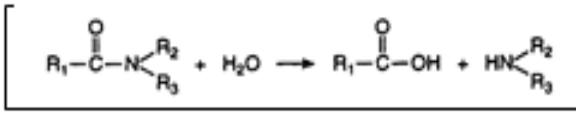
[5]*Principal of D.Pharmacy, Latur College of Pharmacy Hasegaon, Tq. Ausa, Dist. Latur-413512, Maharashtra, India*

Abstract- **In the formulation of drug dosage forms, stability consideration for the active pharmaceutical ingredients (API) and the excipients is critical. This is because degradation process leads to loss of efficacy, making the drug in a specific packaging not to remain in the specified chemical, physical, microbiological, therapeutic and toxicological specifications. Guillory and Poust (2002), Barnes (2013).Therefore, understanding the degradation pathways in order to achieve stability of both the drug substance and drug products is a key quality goal. Porter (2013)**

TYPES OF DEGRADATION PATHWAY

Pharmaceutical products tend to deteriorate on storage, even though it is expected to retain acceptable chemical, physical and microbiological stability. Barnes (2013)

- To get desired effect from any pharmaceutical product is has to be stable throughout its shelf life.
- Drug substances used as pharmaceuticals have diverse molecular structures; therefore, they are susceptible to different kinds of degradation pathways. Yoshioka S. and Stella J. (2002)



- Degradation of drugs occur through three principal pathways namely

1. Chemical Degradation
2. Physical Degradation
3. Microbial Degradation.

CHEMICAL DEGRADATION PATHWAY

Barnes (2013), David and Alexander (2008), Yoshioka S. and Stella J. (2002) Guillory and Poust (2002).

- Hydrolysis/Solvolysis
- Oxidation
- Photolysis
- Polymerization
- Dehydration
- Isomerisation
- Racemization
- Optical Isomerization
- Geometrical Isomerization
- Hydration
- Decarboxylation
- Chemical Incompatibilities.

HYDROLYSIS / SOLVOLYSIS

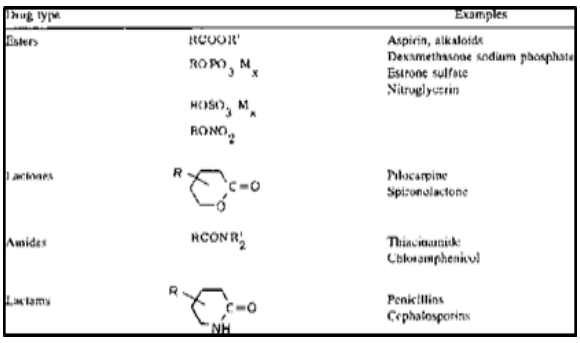
- Hydrolysis is one of the most common reactions seen with pharmaceuticals, since water is part of many products and moisture is everywhere. Yoshioka S. and Stella J. (2002)
- Hydrolysis reactions usually depend on PH and temperature, in the presence of either hydronium

ion or hydroxide ions as catalyst. Bokser and O'Donnell (2012)

- The degradation rate depends on the substituents R1 and R2, in that electron- withdrawing groups enhance hydrolysis whereas electron-donating groups inhibit hydrolysis. Substituted benzoates having an electron-withdrawing group, such as a nitro group, in the para position of the phenyl ring (R1) exhibit higher decomposition rates than the unsubstituted benzoate. On the other hand, the decomposition rate decreases with increasing electron-donating effect of the alkyl

- The active drug undergoes decomposition with the solvent (aqueous and non-aqueous) present, in which the solvent acts as nuclophiles attacking the electropositive center in the drug molecules. Barnes (2013), Bokser and O'Donnell (2012)
- Drugs with the following functional groups: esters, amides, lactones or lactams, Imides, may be susceptible to hydrolysis.
- Esters e.g. Aspirin, cocaine, procaine, nitroglycerine, methyldopa.
- Amides: Acetaminophen, chloramphenicol, indomethacin and sulfacetamide all produce an amino acid through hydrolysis of their amide bond. Barnes (2013), David and Alexander (2008), Bokser and O'Donnell (2012)
- Barbiturates, hydantoins, and imides contain functional groups related to amides but tend to be more reactive. Barbituric acids such as barbital, phenobarbital, amobarbital, and metharbital undergo ring-opening hydrolysis. Yoshioka S. and Stella J. (2002)

SOME GROUPS OF DRUGS THAT UNDERGO HYDROLYSIS. GUILLORY AND POUST (2002)



OXIDATION

- Oxidation reaction is the greatest cause of chemical degradation.
- It involves most often, increase in the number of carbon to oxygen bonds in a molecule or reduction of C-H bonds. Sometimes molecular oxygen is involved at room temperature. This reaction is known as auto-oxidation.
- Barnes (2013), Bokser and O'Donnell (2012) Three primary mechanisms exist for oxidative degradations:
  a. Nucleophilic and electrophilic oxidations are typically mediated by peroxides.
  b. Electron transfer process via catalysis by transition metal such as Cu ions. 0.0002M Cu2+ has shown to increase the rate of vitamin C oxidation by a factor of 105.
  c. Autoxidation involves free-radical initiated chain reactions. A single free- radical can cause oxidation of many drug molecules.

Some functional groups subject to oxidation are phenols, aldehydes, alcohols and unsaturated fats and oils. Guillory and Poust (2002

Auto oxidation process includes:

a. Initiation:
   In • + RH "In − H + R •
b. Propagation:
   R • + O2 "ROO • (fast)
   ROO • + RH "ROOH + R • (rate-limiting)
c. Termination:
   R • + R • "R − R
   R• + ROO • "ROOR. Zhou (2009), Barnes (2013)

In order to reduce degradation by oxidation, nitrogen and carbon dioxide are often used to replace the airspace in pharmaceutical dosage forms. Bokser and O'Donnell (2012)

PHOTODEGRADATION

- Degradation of light sensitive drugs or excipients by room or sunlight.
- Guillory and Poust (2002), Sumie and Valentino (2002).
- Photo degradation occurs when molecules absorb light wavelength, especially 300 – 400

nm. UV light causes more damage than red or orange light and shorter wavelengths because more damage than longer ones. Barnes (2013), David and Alexander (2008).

- Photodecomposition involves oxidation mechanism, although others like polymerization or ring opening may occur. Once initiated can progress in the absence of light in a chain reaction.
- It occurs during manufacture, storage and during the use of the product.
- In susceptible compounds, photodecomposition creates free radical intermediates, which can perpetuate chain reactions. Barnes (2013), Bokser and O'Donnell (2012)
- To avoid photochemical reactions, photolabile formulations are packaged in coloured containers.
- Yellowish green glass is best protector against UV radiation; amber colour gives only a little protection from infrared radiation.
- The addition of an antioxidant like sodium thiosulfate or sodium metabisulfite hinders the photo degradation of sulfacetamide. Bokser and O'Donnell (2012)
- Nifedipine, nicardipine, nitroprusside, chlorthalidone, acetazolamide, retinol, riboflavin, furosemide and phenothiazines are very labile to photo- oxidation. Bokser and O'Donnell (2012), Barnes (2013), Yoshioka S. and Stella J. (2002), Guillory and Poust (2002)
- Photochemical reactions are common in steroids. Guillory and Poust (2002)

POLYMERISATION

- This is the process by which two or more identical molecules combine together to form a much larger and more complex molecule. The reactants are called monomers and the products are called polymers.
- Eg Aminopenicillin, such as ampicillin sodium in aqueous solution and also formaldehyde.
- Formaldehyde solution may result into a formation of white deposit when kept in cold. David and Alexander (2008)

- In order to avoid polymerisation on storage, glutaraldehyde needs to be formulated at an acidic pH, where the process does not occur. Barnes (2013)

ISOMERIZATION

Isomerization is the process of conversion of a drug into its optical or geometric isomers. The isomers are often of different therapeutic activity. There are two types of isomerization

Optical isomerism: Divided into

- Racemization: like epimerization, it is a reversible conversion between optical isomers also known as enantiomers. Thalidomide is racemic. The R-thalidomide causes birth defect while the S-thalidomide is active against morning sickness. Eg are Penicillins, cephalosporins, benzodiazepines.
- Epimerization: in compounds having more than one asymmetric carbon atom in the molecule. Pilocarpine epimerises by base catalysis. Tetracyclines (to epitetracycline) and ergortamine manifest epimerization by acid catalysis. Yoshioka S. and Stella J. (2002), Barness (2013)
- Geometric isomerism: Forms CIS and Trans isomers of the compounds. E.g. vitamin A forms the cis–trans isomers. David and Alexander (2008), Barnes (2013)

OTHERS

- • DEHYDRATION: is the elimination of a water molecule from the molecular structures. Found in the degradation of prostaglandin E2 and tetracycline There is formation of a double bond that participate in electronic resonance with neighbouring functional groups. Guillory and Poust (2002)
- DECARBOXLATION: Occurs sometimes in drugs with carboxylic acid groups. It is not a common. It is a chemical process that releases carbon dioxide. β-Keto decarboxylation can occur in some solid antibiotics with a carbonyl group on the β-carbon of a carboxylic acid or a carboxylate anion. Decarboxylations also occur in the following antibiotics: carbenicillin sodium,

carbenicillin free acid, ticarcillin sodium, and ticarcillin free acid. Bokser and O'Donnell (2012)

- CHEMICAL INCOMPARTIBILITIES: occur between APIs and also between API and excipient. Guillory and Poust (2002)

PHYSICAL DEGRADATION

- Polymorphism
- Particle size
- Vaporization
- Evaporation
- Temperature
- Efflorescence
- Hygroscopy
- Deliquscence

POLYMORPHISM

- POLYMORPHS are different crystal forms of the same compound caused by exposure to changes in temperature, pressure, relative humidity, drying, granulation, milling and compression. Barnes (2013)
- Polymorphs differ in their crystal energy, in solubility, dissolution rate and melting point. The metastable seeks to revert to the most stable form. Steroids, sulphamides and barbiturates are

ADSORPTION; PARTICLE SIZE

ADSORPTION: Drug-plastic interaction has been a major challenge when drugs are stored in plastics materials. This compromises the preservative content and predisposes the drug to microbial degradation.

- Up to 50% of nitroglycerin that was stored in PVC infusion for seven days at room temperature. This phenomenon is due to adsorption. Guillory and Poust (2002)
- PARTICLE SIZE affects solubility and dissolution, and absorption rate, also, the flowability of pwder.
- Decrease in particle size increases surface area of the drug
- Suspension and emulsion are more stable at lower particle size.

VAPORIZATION, EVAPORATION AND TEMPERATURE

- Volatile components such as alcohol, ether, ketones, aldehydes iodine, volatile oils, camphor and cosolvent of lower molecular weight etc., escape from formulation through vaporization, even at room temperature, leading to drug loss.
- Such product should be placed in well closed containers, at proper temperature. Eg. Nitroglycerin, chloroform and volatile oil. Guillory and Poust (2002), Barness (2013)
- Evaporation of water from liquid preparation will cause the drug concentration to change with the possibility of crystallization, if the solubility of the drug in the solvent is exceeded. Water loss from emulsion will cause it to crack or suspension to cake.
- Increase in temperature degrades thermo-labiles, it enhances degradation chemically and physically. Guillory and Poust (2002)

EFFLORESCENCE, HYGROSCOPY, DELIQUESCENCE AND EFFERVESCENCE

- Efflorescence is the process where some drugslose water to the atmosphere resulting in increased concentration of the drug.
- Saturated solution becomes supersaturated, crystallization.
- Hygroscopic: Drugs absorb water from the atmosphere causing physical degradation, e.g. glycerol and plant extract.
- Deliquescent e.g. absorbs water from the atmosphere and turns to liquid. CaCl2, potassium citrate, ammonium chloride.
- Effervescence powders and tablets will deteriorate if stored in moist atmosphere.

MICROBIOLOGICAL DEGRADATION

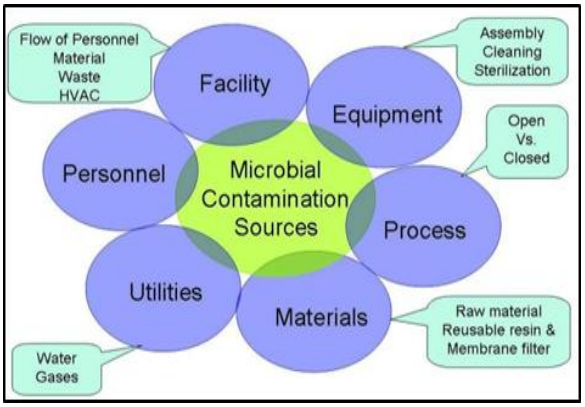
- Micro-organisms are everywhere: air, food, water and humans, raw materials and finished products. Suvarna K, Lolas A, Hughes P, & Friedman R.L, (2011)
- Degradation due to micro-organisms can render the product harmful to the patient or have an

adverse effect on the product properties. Eissa M.E and Mahmoud A.M (2015).

- Once opened, a product degrades microbiologically shortening the shelf life, except there is addition of preservatives.
- Injectable need to be used immediately the container is opened. Barness (2013), Survarna et al (2011).

SOURCES OF MICROBIAL CONTAMINATION

Suvarna et al. (2011)



REFERENCES

[1] Barnes A.R (2013). Product stability and stability testing, in Aulton's Pharmaceutics: The Design and Manufacture of Medicines, 4th Edition. Editors: Michael Aulton and Kevin Taylor . eBook ISBN: 9780702062520. Imprint: Churchill Livingstone. P650-662. Published Date: 18th June 2013

[2] Bokser A.D and O'Donnell P.B (2012): Stability of Pharmaceutical Products in Remington, Essentials of Pharmaceutics. Edited by Felton L.A. Published by Pharmaceutical Press 2012. Printed in USA. ISBN 978 0 85711 105 0

[3] David A and Alexander T. F.(2008): Drug stability, in Physical Pharmacy.P29-42. Published by the Pharmaceutical Press Grayslake, IL 60030-7820, USA © Pharmaceutical Press 2008. ISBN 978 0 85369 725 1

[4] Eissa M.E and Mahmoud A.M (2015). Development of methods for microbial recovery: Pharmaceutical dosage forms including drugs with antimicrobial properties (study iii) in European Journal of Pharmaceutical and Medical Research 2015, 2(4), P537-549.

[5] Guillory K.J and Poust R.I (2002): Chemical Kinetics and drug stability, in Modern Pharmaceutics, 4th Edition, Revised and expanded. Edited by Banker G.S and Rhodes G.T. Published by Marcel Dekker inc. ISBN: 0-8247-0674-9. Printed in USA.

[6] Porter W.R. (2013). Degradation of Pharmaceutical Solids Accelerated by Changes in Both Relative Humidity and Temperature and Combined Storage Temperature and Storage Relative Humidity Design Space for Solid Products. Journal of Validation Technology, 2013, Volume 19 Number 2.

[7] Yoshika S and Stella J. V. (2002) Yoshioka S and Valentino J. S. (2002): Chemical Stability of Drug Substances in Stability of Drugs and Dosage Forms. Kluwer Academic Publishers 2002. Printed in USA. eBook ISBN: 0-306-46829-8. Print ISBN: 0-306-46404-7. P4-135

[8] Suvarna K, Lolas A, Hughes P, & Friedman R.L, (2011) Case Studies of Microbial Contamination in Biologic Product Manufacturing in American Pharmaceutical review, January/February 2011. P50-56.

[9] Yoshioka S and Stella J. V. (2002): Physical Stability of Drug Substances in Stability of Drugs and Dosage Forms. Kluwer Academic Publishers 2002. Printed in USA. eBook ISBN: 0-306-46829-8. Print ISBN: 0-306-46404-7. P139-145

[10] Zhou, D .2009. Understanding Physicochemical Properties for Pharmaceutical Product Development and Manufacturing II: Physical and Chemical Stability and Excipient Compatibility. Journal of Validation Technology, summer 2009. P36-40