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Dosage Form Design

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1

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DRUG AND DRUG PRODUCT STABILITY ….

2

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Why Stability?

- Provide a evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as….. Temperature, Humidity and light.
- Establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions.
- Physical, chemical or microbiological changes might impact the efficiency and security of the final product

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Where and Why?

Stability Studies are preformed on ...

- **Drug Substances (DS)** ➔ The unformulated drug substance that may subsequently be formulated with excipients to produce the dosage form.
- **Drug Products (DP)** ➔ The dosage form in the final immediate packaging intended for marketing…….
- controlled and documented determination of acceptable changes of the drug substance or drug product

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Drug stability

- Is the extent to which a product retains within specified limits and throughout its period of storage and use (i.e., its shelf life) the same properties and characteristics that it possessed at the time of its manufacture.

- Stability studies conducted in the pre-formulation phase include:
  - Solid-state stability of the drug alone,
  - Solution phase stability,
  - Stability in the presence of expected excipients.

5

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Drug stability

- Pure drugs, solids, liquids, or gases are usually **more stable** than their formulations.
- Medicines decomposition happens **faster** because of: the presence of excipients, moisture and because of processing.
- If you take a bottle of an old sample of pure aspirin and smell it you can clearly feel the unmistakable odor of acetic acid because aspirin is decompose into acetic acid and salicylic acid.
- If you granulate aspirin and make it into tablets the rate of decomposition will be faster and if you formulate it into a suspension it will decompose totally in less than 25 days.

6

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What are changes?

- **Physical changes**
  - Appearance
  - Melting point
  - Clarity and color of solution
  - Moisture
  - Crystal modification (Polymorphism)
  - Particle size
- **Chemical changes**
  - Increase in Degradation
  - Decrease of Assay
- **Microbial changes**
- **Therapeutic.**
- **Toxicologic.**

7

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Mechanisms of Degradation

- Chemically, the most frequently encountered destructive processes are hydrolysis and oxidation.

Hydrolysis

- Solvolysis process in which (drug) molecules interact with water molecules to yield breakdown products.

- Example:
  - Aspirin + water ⟶ salicylic acid + acetic acid

8

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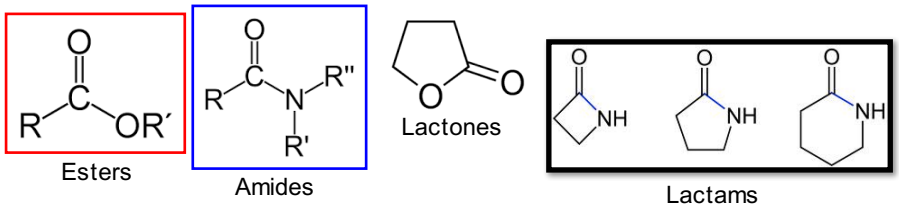
Hydrolysis

- Most important cause of drug decomposition.
  - because a great number of medicinal agents are esters or contain amides, lactones, and lactams, which are susceptible to the hydrolytic process.



Esters | Amides | Lactones | Lactams

9

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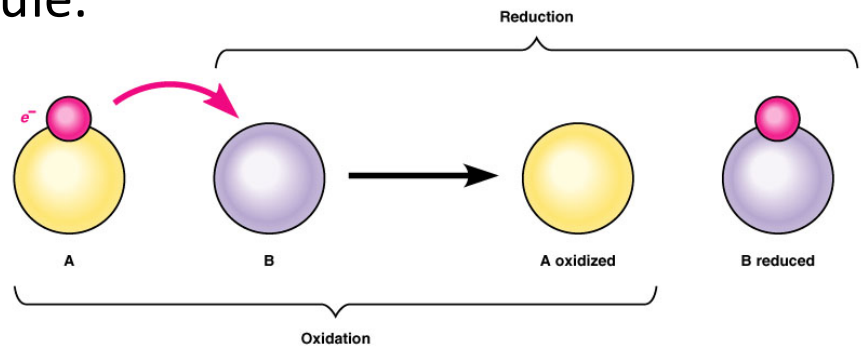
Oxidation

Oxidation is loss of electrons from an atom or a molecule.



10

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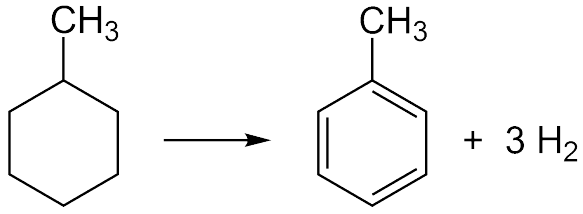
Oxidation

1. Oxidation is accompanied by an increase in the positive valence of an element,

- For example, Ferrous (+2) oxidizing to Ferric (+3).

2. Loss of hydrogen from a molecule



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11

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Oxidation

- Destroys many drug types including:
  - Aldehydes,
  - Alcohols,
  - Phenols,
  - Sugars,
  - Alkaloids,
  - Unsaturated fats.

12

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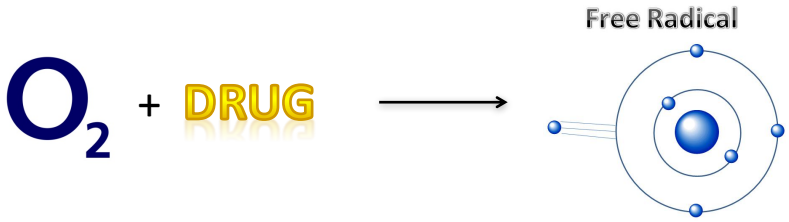
Pharmaceutical autoxidation

- Atmosphering oxygen reacts with drug molecule resulting in free radical.



13

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Pharmaceutical autoxidation

- Atmosphering oxygen reacts with drug molecule resulting in free radical.
- Free radical oxidizes further drug molecules.

14

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Drug and drug product stability

- Steps should be taken to reduce or prevent deterioration due to hydrolysis, oxidation, and other processes.
- Many environmental conditions enhance or catalyze deterioration including light, heat, oxidizing agents, presence of divalent metal ions, etc..

15

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H W

- Amide drug was formulated as:

1. Powder for reconstitution just before administration.
2. Solution dosage form.

- Do you think that both of DFs are susceptible to hydrolysis and oxidation? Why?

16

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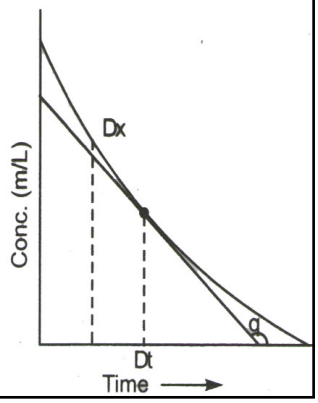
Rate reactions

- Is a description of the drug concentration with respect to time.

Zero order rate:

- Loss of drug is independent on concentration of reactan
- Rate is constant with respect to time.
  - $K_0 = -dC/dt$
  - $T_{0.5} = 0.5\ C_0/K_0$



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Example

- A drug suspension (125 mg/mL) decays by zero-order kinetics with a reaction rate constant of 0.5 mg/mL/hour. What is the concentration of intact drug remaining after 3 days, and what is its $t_{1/2}$?

  - C = −(0.5 mg/mL/hour) (72 hour) + 125 mg/mL
  - C = 89 mg/mL after 3 days
  - $t_{½}$ = 1/2 (125 mg/mL)/(0.5 mg/mL/hour)
  - $t_{½}$ = 125 hours

18

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First order rate reactions

- Loss of drug is related to concentration.
- $KC = -dC/dt$
- $logC = \frac{-Kt}{2.303} + \log Co$
- $t_{1/2} = \frac{0.693}{K}$

19

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Example

- An ophthalmic solution of a mydriatic drug at 5 mg/mL exhibits first-order degradation with a rate constant of 0.0005/day. How much drug will remain after 120 days, and what is its half-life?
  - ln C = −(0.0005/day) (120) + ln (5 mg/mL)
  - ln C = −0.06 + 1.609
  - ln C = 1.549
  - C = 4.71 mg/mL
  - $t_{½}$ = 0.693/0.0005/day
  - $t_{½}$ = 1,386 days

20

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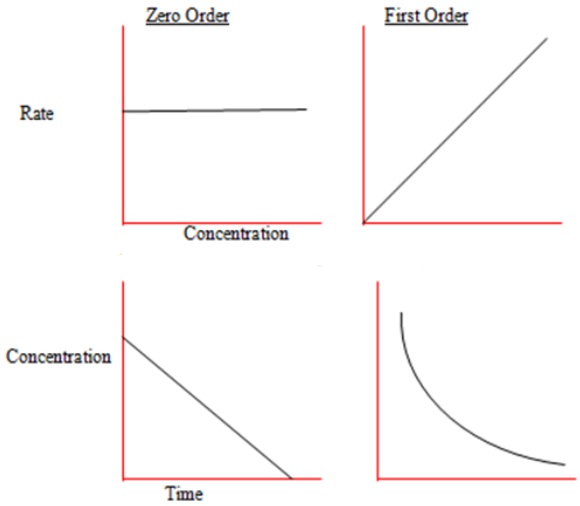
First order VS Zero order



21

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Enhancing stability of drug products

- Excipients can be added to enhance stability.
  - Mainly against hydrolysis and oxidation.

Hydrolysis:

- Reduction or elimination of water from the pharmaceutical system.
  - Replacing water by alcohol, propylene glycol, or glycerin
- Preparation of solid dosage form.
- Protecting the product from humidity.
  - Applying a water- proof protective coating over tablets, like by using shellac.
  - Keeping the drug in a tightly closed container.
- Suspending the drug in a non-aqueous vehicle rather than dissolving it in aqueous solvent.

22