Stability of Drugs

Stability of drugs (Cont.)

- **Definition:** Drug stability means the ability of the pharmaceutical dosage form to maintain the physical, chemical, therapeutic and microbial properties during the time of storage & usage by patients.
- Measured by the rate of changes that take place in pharmaceutical dosage forms.
- **Expiry date**: means that drug can not be used after this date because the conc. of drug decreased & become lower than therapeutic conc.
- **Instability** may causeUndesired change in performance; i.e. dissolution/bioavailability

Factors affecting Drug Stability

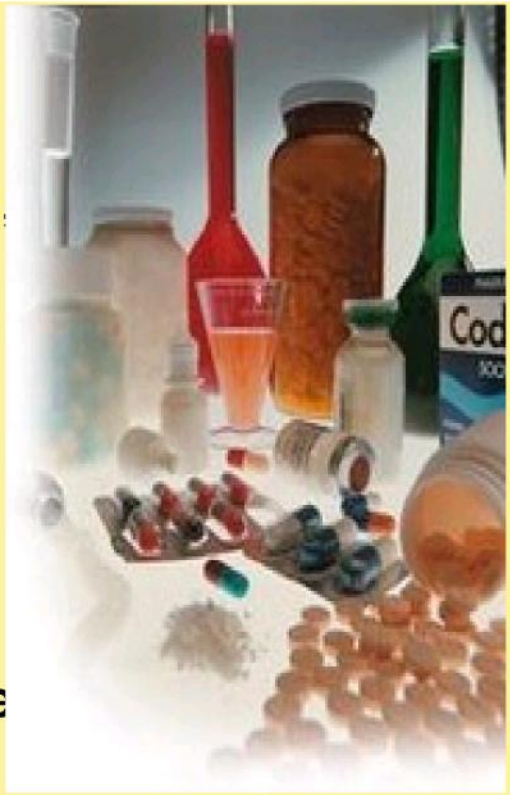
Environmental factors

1-Temperature

- 1. high temperature accelerate oxidation, reduction & hydrolysis reaction which lead to drug degradation.

2- Drugs or excipients in the dosage form

- **Particle size of the basic drug**
- **pH of the vehicle .**
- **Acidic & alkaline pH influence the rate of decomposition of most drugs.**
- **Many drugs stable between pH 4 and 8.**

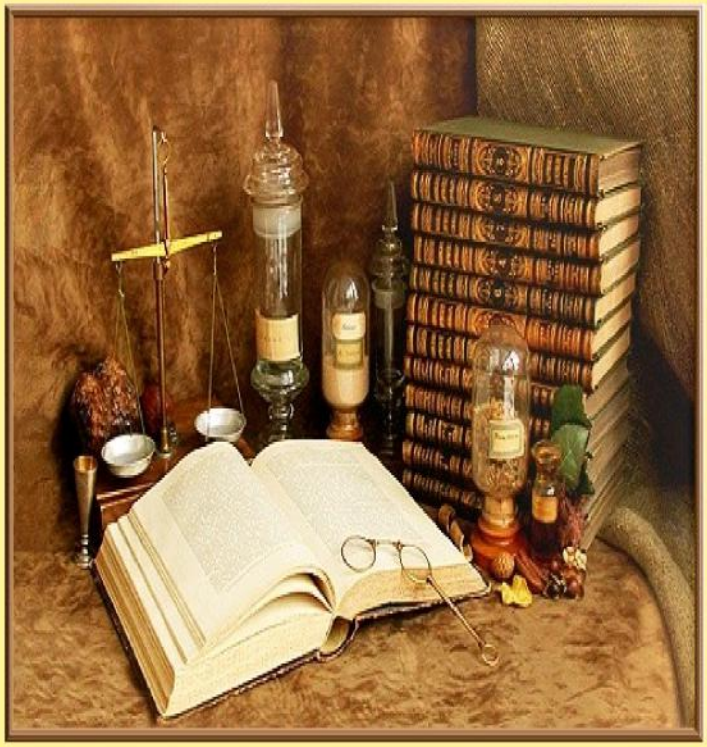


Factors affecting Drug Stability(Cont.)

- **3. Moisture:**
- Water catalyse chemical reactions as oxidation, hydrolysis & reduction + promotes microbial growth
- **4. Light:** affect stability through its energy or thermal effect.
- **5. Pharmaceutical dosage forms:** solid dosage forms more stable than liquid dosage forms
- **6. Concentration:** rate of drug degradation is constant for the solutions of the same drug with different conc.
- **7. Drug incompatibility:** reactions between components of dosage form or between components and cover of container.
- **8. Oxygen:**
- Exposure of drug formulations to oxygen affects stability .

Types of stability studies

- Physical stability
- Chemical
- Microbiological



Physical stability

- **Physical stability implies that:**

- **The formulation is totally unchanged throughout its shelf life and has not suffered any changes by way of appearance, organoleptic properties, hardness, brittleness, particle size .**

- **It is significant as it affects:**
  - **pharmaceutical elegance**
  - **drug content uniformity**
  - **drug release rate.**

Physical stability

- **Physical instabilities possibilities are:**
- **1. Crystal formation :.**
- Polymorphism phenomena(eg; Chloramphenicol change of amorphous to crystalline form.
- **2. Loss of volatile subs. from pharm. dosage forms**
- Eg; Aromatic waters, Elixirs. Spirits
- **3. Loss of water: in Saturated sol., Emulsions, Creams Humectants as hydrophilic subs added e.g; Glycerin**
- **4. Absorption of water: (Powders: Liquification ,Suppositories which base made from Glycerin, Gelatin, becomes jelly-like appearance**

Physical stability (Cont.)

Formulation	Likely physical instability problems	Effects
Oral solutions	1- Loss of flavour 2- Change in taste 3- Presence of off flavours due to interaction with plastic bottle 4- Loss of dye 5- Precipitation 6- discoloration	Change in smell or feel or taste

Physical stability (Cont.)

Formulation	Likely physical instability problems	Effects
Parenteral solutions	1. Discoloration due to photo chemical reaction or oxidation 2. Presence of precipitate due to interaction with container or stopper 3. Presence of "whiskers" 4. Clouds due to: (i) Chemical changes (ii) The original preparation of a supersaturated solution	Change in appearance and in bio-availability

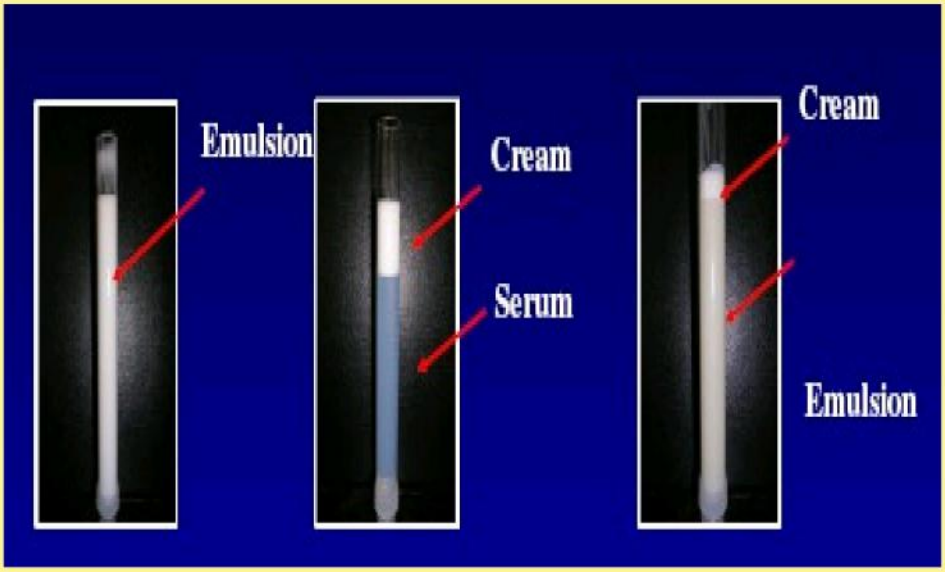
Physical stability (Cont.)

Formulation	Likely physical instability problems	Effects
Suspensions 	1- settling 2- caking 3- crystal growth	1-Loss of drug content uniformity in different doses from the bottle 2- loss of elegance.

Physical stability (Cont.)

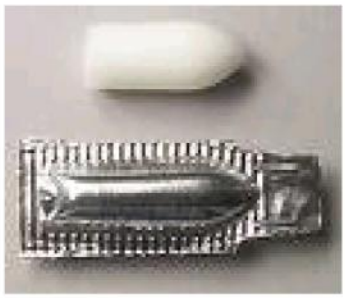
Formulation	Likely physical instability problems	Effects
Emulsions 	1- Creaming 2- coalescence	1- Loss of drug content uniformity in different doses from the bottle 2- loss of elegance

Physical stability (Cont.)



Coalescence

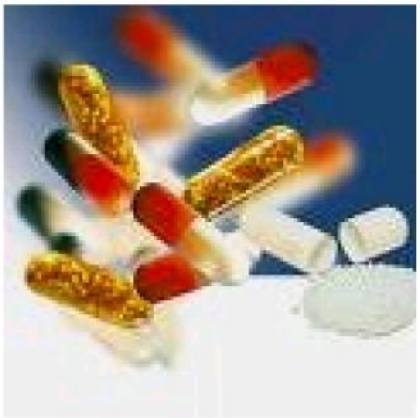
Physical stability (Cont.)

Formulation	Likely physical instability problems	Effects
Semisolids (Ointments & suppositories)	1. Changes in: a) Particle size b) Consistency	1-Loss of drug content uniformity
	2. Caking or coalescence	2- loss of elegance
	3. Bleeding	3-change in drug release rate.

Physical stability (Cont.)

Formulation	Likely physical instability problems	Effects
Tablets 	Change in: a) Disintegration time b) Dissolution profile c) Hardness d) Appearance (soft and ugly or become very hard)	Change in drug release

Physical stability (Cont.)

Formulation	Likely physical instability problems	Effects
Capsules 	Change in: a) Appearance b) Dissolution c) Strength	Change in drug release

Chemical stability

- **Chemical stability implies:**
  - **The lack of any decomposition in the chemical moiety that is incorporated in the formulation as the drug, preservatives or any**
    - **This d**

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Mechanisms Of Degradation

1- Hydrolysis:

- Hydrolysis means “splitting by water”
- Some Functional Groups Subject to Hydrolysis

Drug type	Examples
Esters	Aspirin, alkaloids - Nitroglycerin Dexmethasne sodium phosphate
Lactones	Pilocarpine - Spironolactone
Amides	Chloramphenicol
Lactams	Penicillins - Cephalosporin's
Imides	Glutethimide

Mechanisms Of Degradation

2- Oxidation

- **Oxidation** of inorganic & organic compounds explained by a loss of electrons & the loss of a molecule of hydrogen
- **Some Functional Groups Subject to Autoxidation**

Functional group	Examples
Catechols	Catecholamines (dopamine)
Ethers	Diethylether
Thiols	Dimercaprol (BAL)
Thioethers	Chlorpromazine
Carboxylic acids	Fatty acids

Mechanisms Of Degradation

3- Photolysis

- **Photolysis** means: **decomposition by light**
- E.g. **Sodium nitroprusside** is administered by IV infusion for management of acute hypertension.
- If the solution is protected from light, it is stable for at least 1 year;
  - if exposed to normal room light, it has a shelf life of only 4 hours.

Mechanisms Of Degradation

- Relationship between wavelength and associated energy of various forms of light.

Type of radiation	Wavelength	Energy
U.V.	50 – 400	Kcal mol-1
Visible	400 – 750	287 – 72
I.r.	750 – 10,000	36 - 1

- Conventional tungsten filament light bulbs are safe & do not contribute to photolysis.

Mechanisms Of Degradation

- **Photolysis is prevented by:**
- 1- suitable packing in amber coloured bottles
- 2- cardboard outers
- 3- aluminium foil over wraps

- **Factors Affecting Rates Of Degradation:**

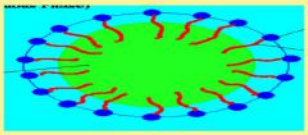
1- Ph

- The acidity or the alkalinity of a solution has a profound influence on the decomposition of drug compound.
- Aspirin buffered sol. maximum stable at a pH of 2.4, above a pH of 10 the decomposition rate rapidly increases.
- pH also influence the rate of oxidation. The system is less readily oxidized when the pH is low

Factors Affecting Rates Of Degradation

2- Complexation:

- Complex formation reduce the rate of hydrolysis & oxidation.
- E.g. caffeine complexes with local anesthetics, such as benzocaine, & procaine to cause a reduction in their rate of hydrolytic degradation.



3- Surfactants:

- Nonionic, cationic and anionic surfactants when added to sol. containing drugs form micelle & drug particles become trapped in the micelle.
- The hydrolytic group as OH cannot penetrate this micelle cover & reach drug particles,so hydrolysis rate decrease

Factors Affecting Rates Of Degradation

- **4- Presence of heavy metals:**
  - **Heavy metals, such as copper, iron, cobalt and nickel increase the rate of formation of free radicals and enhance oxidative decomposition.**
- **5- Light and humidity:**
  - **Light, especially ultraviolet light enhances photolysis and humidity enhances hydrolytic decomposition.**

Stabilization of drugs against hydrolysis, oxidation and photolysis

- **1- Temperature:**
- **All the drug products are stored at suitable temperatures to avoid thermal acceleration of decomposition.**
- **3 varieties of temp. suggested for storage of drug products. Room temp, cool storage & cold storage.**
- **2- Light:**
- **Light sensitive materials are stored in ambered colour bottles.**
- **3- Humidity:**
- **Packing materials are chosen (usually glass & plastic) to prevent exposure of drug products to high humid condition.**

Stabilization of drugs against hydrolysis, oxidation and photolysis

Antioxidants commonly used for

Aqueous systems

- Sodium metabisulfite
- Sodium thiosulfate
- Ascorbic acid

Oil systems

- Ascorbyl palmitate
- Butylaled hydroxy toluene
- Butylated hydroxy anisole

Stabilization of drugs against hydrolysis, oxidation and photolysis

- **4- Oxygen:**
- Proper packing keeping the oxygen content of sol. less & leaving very little head space in the bottle above the drug products are methods to fight against oxidation.
- **5- Chelating Agents:**
- Chelating agents form complexes with heavy metal ions & prevent them from catalyzing oxidative decomposition
- E.g. ethylenediamine tetracetic acid (EDTA) derivatives & salts, citric acid and tartaric acid.
- **6- Solvents:**
- By addition of a suitable solvent hydrolysis rate may be decreased.

Microbiological stability

- **Microbiological stability implies that:**
- **The formulation has not suffered from any microbiological attack& is meeting the standards with respect to lack of contamination/sterility.**
- **Sources of Microbial Contamination:**

Water	**gram-negative groups: Pseudomonas, Xanthamonas, Flavobacterium**
Air	**Mould spores: Penicillium, Aspergillus** **Bacterial spores: Bacillus spp. Yeasts**
Raw materials	**Micrococci**

Microbiological stability

- **Sources of Microbial Contamination:**

Starches	**Coli forms**
Pigments	**Salmonella**
Gums	**Actinomyces**
Animal products	**Salmonella, Coliforms**
Personnel	**Coliforms, Staph, Sterpt.**

To prevent contamination to the formulation during storage

(1) Suitably designing the containers

(2) Usually using single dose containers

(3) Sticking to proper storage conditions

(4) Adding an antimicrobial substance as preservative.

Preservatives used in Pharmaceutical Preparations

Preparation	Preservative	Conc. (% w.v)
Injections	Phenol	0.5
	Cresol	0.3
	Chlorocresol	0.1
Eye drops	Chlorhexidine acetate	0.01
	Benzalkonium chloride	0.01
Mixtures	Benzoic acid	0.1
	Methyl paraben	0.1
	Alcohol	12-20
Creams	Parabens	0.1-0.2
	Chlorocresol	0.10
Tablets	Methylparaben	0.1

Packaging And Stability

- **The immediate container & closure are particularly important in affecting product stability.**

Packaging And Stability

Glass

- Glass is resistant to chemical & physical change and is the most commonly used material.

Limitations	Overcome
1. Its alkaline surface	use of Borosilicate glass
2. Ions precipitate insoluble crystals from glass	the use of buffers
3- Permits the transmission of light w. accelerate decomposition.	Amber coloured glass

Packaging & Stability

- Plastics
  - The problems with
    - 1. Migration of drug through the plastic into the environment.
    - 2. Transfer of environmental moisture, oxygen, and other elements into the pharmaceutical product.
    - 3. Leaching of container ingredients into drug.
    - 4. Adsorption of the active drug or excipients by the plastic.

Packaging And Stability

- Various alloys & aluminium tubes utilized as containers for emulsions, ointments, creams and pastes.
- Limitation: They may cause corrosion and precipitation in the drug product.
- Overcome: Coating the tubes with polymers may reduce these tendencies.

Packaging And Stability

- **Rubber**

- **Rubber also has the problems of extraction of drug ingredients and leaching of container ingredients.**

- **The pretreatment of rubber vial stoppers and closures with water and steam reduces potential leaching.**