Drug Stability

- ***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 and usage by the patient.
- It is measured by the rate of changes that take place in the pharmaceutical dosage forms.
- ***Expiry date:*** means that drug can not be used after this date because the concentration of drug is decreased and become lower than therapeutic concentration. In addition, some products of drug degradation are toxic and harmful to patients.
- Note! After the opening of the drug container, the expiry date will be shorter as a result of the decreased concentration of drug during usage and the effects of external factors. Example:
  1. Eye drops: can be used for one month after opening the droppers
  2. Syrups and suspension of antibiotics: can be used for one week by storage in room temperature and for two weeks by storage in 4C˚.
  3. Tablets and capsules remain stable in the package but after removal the expiry date will change
  4. Ampoules: must be used immediately but the vials (multidose) are stable for 24 h for the presence of preservatives.

- ***Factors affecting drug stability:***
  1. *Temperature*: high temperature accelerate oxidation, reduction and hydrolysis reaction which lead to drug degradation
  2. *pH*:
     - Acidic and alkaline pH influence the rate of decomposition of most drugs.
     - Many drugs are stable between pH 4 and 8.
     - Weekly acidic and basic drugs show good solubility when they are ionized and they also decompose faster when they are ionized.
     - So if the pH of a drug solution has to be adjusted to improve solubility and the resultant pH leads to instability then a way out of this tricky problem is to introduce a water-miscible solvent into the product. It will increase stability by:
       - suppressing ionization
       - reducing the extreme pH required to achieve solubility
       - enhancing solubility and
       - reducing the water activity by reducing the polarity of the solvent. For example, 20% propylene glycol is placed in chlordiazepoxide injection for this purpose.

- Reactions catalyzed by pH are monitored by measuring degradation rates against pH, keeping temperature, ionic strength and solvent concentration constant. Some buffers such as acetate, citrate, lactate, phosphate and ascorbate buffers are utilized to prevent drastic change in pH.
- Sometimes pH can have a very serious effect on decomposition. As little as 1 pH unit change in pH can cause a change of ten fold in rate constant. So when we are formulating a drug into a solution we should carefully prepare a pH – decomposition profile and then formulate the solution at a pH which is acceptable physiologically and stability-wise also.

3. *Moisture*:
    a. Water catalyses chemical reactions as oxidation, hydrolysis and reduction reaction
    b. Water promotes microbial growth
4. *Light:* affects drug stability through its energy or thermal effect which lead to oxidation
5. *Pharmaceutical dosage forms*: solid dosage forms are more stable than liquid dosage forms for presence of water.
6. *Concentration*: rate of drug degradation is constant for the solutions of the same drug with different concentration. So, ratio of degraded part to total amount of drug in diluted solution is bigger than of concentrated solution.

Stock solutions: are concentrated solutions which diluted by using (i.e. syrup 85%)
at high concentration the stability is high

7. *Drug incompatibility*: reactions between components of pharmaceutical dosage forms it self or between these components and cover of the container .
8. *Oxygen:* exposure of drug formulations to oxygen affects their stability

- ***Three stabilities of drug must be considered::***
    1. Physical stability
    2. Chemical stability
    3. Microbiologicall stability

A. Physical stability:

Physical instabilities possibilities are:

1. Crystal formation in pharmaceutical preparations:
   Causes:

a. Polymorphism phenomena: i.e. Chloramphenicol (change of amorphous to crystalline form.
b. Saturated solution: by different temperature precipitation of solute may occur.
c. In suspension: when very fine powder is used a part of suspending agent will dissolve then precipitate as crystal.

2. Loss of volatile substances from pharmaceutical dosage forms:
   Examples:
   a. Aromatic waters
   b. Elixirs
   c. Spirits
   d. Some types of tablets which contain aromatic water (Nitroglycerin tablets)

3. Loss of water:
   This can be seen in the following dosage forms:
   a. Saturated solution: by loss of water they become supersaturated and precipitate as crystals is formed
   b. Emulsions: Loss of water lead to separation of the two phases and change to other type
   c. Creams: especially oil/water, they become dry by loss of water
   d. Pastes
   e. Ointments: especially aqueous base ointments

Humectants is added to the previous dosage forms which defined as hydrophilic substances added to aqueous phase to absorb water from atmosphere and prevent its loss from the dosage forms.
Examples: Glycerin

4. Absorption of water:
   This phenomena can be seen in the following pharmaceutical forms:
   a. Powders: Liquification and degradation may occur as a result of absorption of water
   b. Suppositories which base made from hydrophilic substances as Glycerin, Gelatin, poly ethylene glycol.
      The consistency of these forms becomes jelly-like appearence

5. Change in crystalline form:
   • Example: Cocoa butter which is capable of existing in four polymorphic forms.

B. Chemical stability:

- It is discussed in chemical incompatibility unit

C. Microbiological stability:

1. Contamination from microorganisms is a big problem for all formulations containing moisture but it can be a bother in solid dosage forms also if some natural polymers are used because many natural polymers are fertile sources of microorganisms.
2. In the type of hygienic manufacture carried out today where "Quality Assurance" is a prerequisite as per the GMP procedures, there are definite procedures to prevent microbial contamination in all formulations.

- ***Sources of Microbial Contamination:***

1. Water
2. Air
3. Raw materials, containers and closures
4. Personnel
5. Instruments and apparatus

Sources of microbial contaminations

Water	Low demand gram-negative groups: Pseudomonas, Xanthamonas, Flavobacterium, Achromobacter
Air	Mould spores: Penicillium, Mucor, Aspergillus Bacterial spores: Bacillus spp. Yeasts
Raw Materials	Micrococci
Earths	Anaerobic spore formers: Clostridium spp
Pigments	Salmonella
Starches	Coliforms
Gums	Actinomyces
Animal products	Salmonella, Coliforms
Personnel	Coliforms, Staphylococci, Sterptococci, Coryembacteria

Packaging And Stability

- Packaging of the drug product is very important when its stability is being considered.
- The immediate container and closure are particularly important in affecting product stability.
- Glass, plastic, rubber (natural and synthetic) and metal are the four types of containers commonly utilized for packing drug products.

1. Glass

- Glass is resistant to chemical and physical change and is the most commonly used material, but it has the limitations of :
    1. Its alkaline surface may raise the pH of the product.
    2. Ionic radicals present in the drug may precipitate insoluble crystals from the glass
    3. The clarity of the glass permits the transmission of high energy wavelength of light which may accelerate decomposition.
- All these limitations are overcome by the technologists in the following way:
    1. the first problem is overcome by the use of Borosilicate glass which contains fewer reactive alkali ions
    2. Treatment of glass with chemicals or the use of buffers helps in overcoming the second problem
    3. Amber coloured glass which transmits light only at wavelengths above 470 nm is used for photolytic drug products.

2. Plastics

- Plastics include a wide range of polymers of varying density and molecular weight, each possessing different physicochemical characteristics. The problems with plastic are:
    1. Migration of the 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 the drug.
    4. Adsorption or absorption of the active drug or excipients by the plastic.
- For all these problems the solution is to suitably pretreat the plastic chemically. The drug product packed in the final container must be tested for stability.

3. Metals

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

4. Rubber

- Rubber also has the problems of extraction of drug ingredients and leaching of container ingredients described for plastics.
- The use of neoprene, butyl or natural rubber, in combination with certain epoxy, Teflon or varnish coatings reduces drug-container interactions.
- The pretreatment of rubber vial stoppers and closures with water and steam removes surface blooms and also reduces potential leaching

Preservatives

- Extremely hygienic manufacture ensures a product that is free of contamination in the case of all non-sterile preparations and a sterile preparation in the case of all parenterals.
- There are two strategies followed in the manufacture of microbiologically stable, acceptable pharmaceutical preparations:
  1. The first step is to prevent contamination of the product.
  2. The second is to formulate the final product so that it is hostile to microorganisms and it is usually done by the addition of preservatives.
- For sterile preparations there is either a terminal sterilization process or a closely controlled aseptic manufacturing procedure. In every case the final product is so made to protect the product during storage and minimize contamination while the product is in use.
- When discussing microbiological stability we have to discuss parenterals as one class and the rest of the formulations as one class.
- Parenterals are either terminally sterilized or manufactured by an aseptic manufacturing procedure. To prevent contamination to the formulation during storage and use many steps are taken such as:
  1. suitably designing the containers,
  2. usually using single dose containers,
  3. sticking to proper storage conditions and
  4. adding an antimicrobial substance as preservative.

- ***Preservatives used in pharmaceutical preparations***
  - The following gives a list of usual preservatives used in pharmaceutical preparations:

Preparation	**Preservative**	**Concentration** % w/v
Injections	Phenol	0.5
	Cresol	0.3
	Chlorocresol	0.1
	Phenylmrcuric nitrate	0.001
	Benzyl alcohol	1.0
Eye drops	Phenylmercuric nitrate or acetate	0.002
	Chlorhexidine acetate	0.01
	Benzalkonium chloride	0.01
Mixtures	Chloroform	0.25
	Benzoic acid	0.1
	Methyl paraben	0.1
	Alcohol	12-20
	Sulphur dioxide	400 parts/10^6
Creams	Parabens	0.1-0.2
	Chlorocresol	0.1
	Dichlorobenzyl alcohol	0.05-0.2
	Cetyltrimethyl ammonium bromide	0.01-0.1
	Phenylmercuric nitrate	0.001
Tablets	Methylparaben	0.1

  - Parenterals and ophthalmic preparations have to be totally free from microorganisms i.e. they have to be sterile.

- This requirement is met by:
    1. placing a suitable preservative or combination of preservatives wherever required in the products
    2. storing the products properly
    3. stoppering them properly and by following proper aseptic procedures during administration and during any admixture procedures followed prior to administration.
- In spite of all these precautions if any microbial growth takes place and is observed the product is condemned and the entire batch from which the product has come is recalled.
- The storage of these products is done under conditions recommended by WHO which prescribe temperature, humidity, cleanliness as well as colour of the walls of the room.
- Non-sterile preparations have less stringent requirements regarding exclusion of microbes. They need not be sterile but it has to be shown that some specifically named organisms are not present in them.

The instability possibilities in different formulations

1. Oral solutions

Instability problems

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

Effects

Change in smell or feel or taste

Steps to prevent instability

Use of proper excipients and suitable packing materials

2. Parenteral solutions

physical instability occurs due to:

1. Interaction of the contents with the container.
2. Changes in Chemical composition.

Instability problems

1. Discoloration due to photo chemical reaction or oxidation. Ex: thiamine hydrochloride
2. Presence of precipitate due to interaction with container or stopper.
3. Presence of “whiskers”. If some small pinholes are present in the ampule due to improper sealing the solution wicks out, the liquid evaporates and the solid settles on the outside. It further helps in wicking out more solution and long lines of crystals form on the outside of the vial which are called whiskers. This may happen due too small hole (<0.5 μm) going undetected or the crack developing during storage.
4. Clouds: A cloud will appear in the product due to:
    a. Chemical changes (an ester eg.: polysorbate may hydrolyse producing an acid which is poorly soluble)
    b. Solubility product may be exceeded.
    c. The original preparation of a supersaturated solution or the use of a metastable form (ex: calcium gluceptate).

Effects

Change in appearance and in bioavailability.

Steps to prevent instability

1. Use of antioxidants (0.5%) Acetylcystane or 0.02 – 1% Ascorbic acid) or Chelating agents (0.01 – 0.075 sodium edetate) to prevent discoloration.
2. Change in stopper or material of the container will eliminate the problem.
3. Checking of the manufacturing process Increasing solubility by the use of cosolvents (eg: polyethylene glycol) or by other methods such as micellar approach or complexation will reduce clouding.

3. Suspensions

This instability occurs due to:

a. Particle diameter
b. Concentration of resuspending agent
c. Viscosity of surrounded media
d. Temperature
e. pH
f. Presence of microbes

Instability problems

1. Settling
2. Caking
3. Crystal growth

Effects

Loss of drug content uniformity in different doses from the bottle and loss of elegance.

Steps to prevent instability

Design of product based on proper pre-formulation studies.

4. Emulsions

This instability occurs due to:

a. Droplet diameter
b. Viscosity
c. Difference in Density
d. Temperature
e. pH
f. Presence of microbes

Instability problems

1. Creaming
2. Cracking

Effects

Loss of drug content uniformity in different doses from the bottle and loss of elegance.

Steps to prevent instability

Design of product based on proper pre-formulation studies.

5. Semisolids (Ointments and suppositories)

Instability problems

1. Changes in:

a. Particle size

b. Polymorphic state, or hydration or solvation state

c. Consistency

d. drug release rate

2. Caking or coalescence.

3. Bleeding

Effects

Loss of drug content uniformity, loss of elegance and change in drug release rate.

Steps to prevent instability

Design of product based on proper pre-formulation studies.

6. Tablets

Instability problems

Change in

a. Disintegration time

b. Dissolution profile

c. Hardness

d. Appearance

Effects

Change in drug release

Steps to prevent instability

Design of product based on proper pre-formulation studies.

7. Capsules

Instability problems

Change in

a. Appearance

b. Dissolution

c. Strength

Effects

Change in drug release

Steps to prevent instability

Design of product based on proper pre-formulation studies