Formulation of injections(Solution and suspension)

- **Solutions:**

✓A range of excipients may be included in parenteral solutions, including antioxidants, antimicrobial agents, buffers, chelating agents, inert gases, and substances for adjusting tonicity.

✓Antioxidants maintain product stability by being preferentially oxidized over the shelf life of the product.

✓Antimicrobial preservatives inhibit the growth of any microbes that are accidentally introduced while doses are being withdrawn from multiple-dose bottles and act as adjuncts in asepticprocessing of products.

✓It is Prepared by dissolving the drug and preservative, adjusting the pH and sterile- filtering the resultant solution through a 0.22 µm membranes filter. Drug solutions that resist heat are terminally autoclave sterilized after filling; this assures product sterility and package.

- **Suspension**

✓A suspension for injection consists of insoluble solid particles dispersed in a liquid medium, with the solid particles accounting for0.5-30% of the suspension. The vehicle may be aqueous, oil, or both.

✓Caking of injectable suspensions is minimized through the production of flocculated systems, comprising clusters of particles (flocs) held together in a loose open structure.

✓Excipients in injectable suspensions include antimicrobial preservatives, surfactants, dispersing or suspending agents, and buffers.

✓Surfactants wet the suspended powders and provide acceptable syringeability while suspending agents modify the viscosity of the formulation.

✓General steps in manufacturing:

- Sterilization and milling of active ingredient (s).
- Sterilization of vehicle.
- Aseptic wetting and dispersion of the active ingredient (s).
- Aseptic milling of the bulk suspension.
- Aseptic filling of the bulk suspension in suitable containers

Formulation of sterile powders

- ✓Due to instability in water, many drugs are formulated as drug powders to be reconstituted prior to administration. eg.Penicillins, barbiturates, benzocain. Sterile water for injection is supplied with dry powders to make “solutions / or suspensions for injections”. The obtained solution /suspension will meet with all the requirements of solution /suspension for parenteral. IV or IM route can give reconstituted solutions, however suspension is forbidden for IV administration.
- ✓Sterile powers are prepared by following methods.
- Sterile recrystallization:
- Lyophilization:
- Spray drying

- **Sterile Re-crystallization:** The drug is dissolved in a solvent and the obtained solution is sterilized through 0.22 µm membrane filter. A sterile anti-solvent is then added to crystalize the drug particles, which is filtered and dried aseptically.
  - **Advantages:** This method is Flexible and economic.
  - **Disadvantage:** This method represents variations from batch to batch and contamination.
- **Lyophilization:** In this method, a solid substance is separated from solution by freezing the solvent and evaporating the ice under vacuum. The obtained drug solution is sterile filtered into sterile trays, which are aseptically loaded into a freeze dryer. The solution is then frozen at -50°C and then dried by vacuum to separate the drug powder.
  - **Advantage:** This method involves removal of water at low temperatures.
  - **Disadvantage:**

i) In this method, the biological molecules are damaged by the stress associated with freezing, and drying.

ii) This method is expensive and time consuming

- **Spray drying:** In this method, the solution of the drug is sprayed into a dry chamber where it comes in contact with a hot steam of a sterile gas 80-100 °C temperature.
  - **Advantage:**

i) This method is Simple, Economical, scalable and faster.

ii) This method involves Coating of particles during drying prolonged release

  - **Disadvantage:**

i) In this method, the high processing temperatures and high shear forces can easily damage drugs.

ii) In this method, higher levels of drugs are lost in comparison to freeze-drying.

iii) This method has a limited solvent choice for a given drug.

iv) In this method, product cannot be prepared directly in vials or plates.

Formulation of large volume parenterals

- Large volume injections are intended to be administered by IV Infusion Fluids & are included in the group of sterile products & are known as large volume Parenterals.
- These consist of single dose injecting a volume of 100 ml or more than 100 ml sometimes additional drugs are added to them by either injecting svp to the administration sets or by piggyback method(small volume infusion of an additional drug is added to the intravenous delivery system).
- large volumeparenteral products include:

1) Infusion fluid(Basic nutrition -Dextrose inj, Fluid replacement therapy-Normal saline)

2) Total parenteral Nutrition solution(TPN)

3) Intravenous antibiotics

4) Dialysis fluid

5) Irrigation solutions

- Large volume parenterals should be terminally heat sterilized. Apart from water for injection as the main component, other ingredients that should be included are carbohydrates (e.g. dextrose, sucrose and dextran), amino acids, lipid emulsion, electrolytes (Nacl) and glycerol, sorbitol and mannitol.
- The LVP are mostly clear solutions, except for the oil- in –water emulsions. The emulsions for infusion are produced by highly specialized method as they are destabilized by heat. This result in many difficulties during production, thus the size of oil droplets should be controlled during heat sterilization.

Production of LVP:

i) The manufacturing and filling of LVP fluids into containers are carried out in a high standard clean room environment. High standards are required to prevent these products from getting contaminated with organisms, pyrogens and particulate matter.

ii) The fluids from a bulk container are filled into the product container using high speed filling machine. Before filling the fluid into the container, it is passed through an in-line membrane filter to remove the particulate matter.

iii) After filling, the neck of each glass bottle is immediately sealed with a tight fitting rubber closure held in place with a crimped aluminum cap.

iv) In case plastic bags are used, the pre-formed plastic bags are aseptically filled and heat-sealed immediately.

v) Blow –fill-seal system are adopted to minimizes the problems with product handling, cleaning and particulate contamination.

vi) The LVP products, including irrigation solution and dialysis fluids should be moist heat sterilized immediately after the containers are filled.

Lyophilization or freeze-drying

Lyophilization or freeze drying is a process in which water is removed from a product after it is frozen and placed under a vacuum, allowing the ice to change directly from solid to vapor without passing through a liquid phase. The process consists of three separate, unique, and interdependent processes like; Freezing, Primary drying (sublimation), and Secondary drying (desorption).

- **Advantages of Lyophilization**
- Ease of processing a liquid, which simplifies aseptic handling.
- Enhanced stability of a dry powder.
- Removal of water without excessive heating of the product.
- Enhanced product stability in a dry state.
- Rapid and easy dissolution of reconstituted product
- **Disadvantages**
- Increased handling and processing time.
- Need for sterile diluent upon reconstitution.
- Cost and complexity of equipment

Steps involved in formulation of Lyophilized products

- Dissolving the drug and excipients in a suitable solvent, generally water for injection (WFI).
- Sterilizing the bulk solution by passing it through a 0.22-micron bacteria-retentive filter.
- Filling into individual sterile containers and partially stoppering the containers under aseptic conditions.
- Transporting the partially stoppered containers to the lyophilizer and loading into the chamber under aseptic conditions.
- Freezing the solution by placing the partially stoppered containers on cooled shelves in a freeze-drying chamber or pre-freezing in another chamber.
- Applying a vacuum to the chamber and heating the shelves in order to evaporate the water from the frozen state.
- Complete stoppering of the vials usually by hydraulic or screw rod stoppering mechanisms installed in the lyophilizers. There are many new parenteral products, including anti-infectives, biotechnology derived products, and in-vitro diagnostics which are manufactured as lyophilized products.
- Additionally, inspections have disclosed potency, sterility and stability problems associated with the manufacture and control of lyophilized products