Parenteral formulations

(Dosage Forms)

Solution
- Aqueous
- Oil based

Suspension
- Aqueous
- Oil based

Emulsion (o/w)
- Aqueous
- Oil based

Ready to use
Powders for reconstitution
Parenteral Solutions

Advantages

* Easy to formulate
* Uniform doses
* Suitable for all routes of administration (aqueous)
* Prolonged clinical effect (oily solutions, IM or SC routes)

Disadvantages

* Not for insoluble actives
* Not for depot effect
Formulation of Parenteral Solutions

1. Active drug
2. Solvent, co-solvent
3. Surfactants
4. Polymers
5. Preservatives
6. Buffer
7. Tonicity adjusters
8. Antioxidant
9. Chelating agents
10. Inert gases
Surfactants

• Surface-active agents enhance drug solubility to the required concentration to achieve solution clarity (> CMC).
• Surface-active agents may be incorporated into aqueous or oil-based vehicles for this purpose

Examples:

• Nonionic SAA (e.g. tweens, Poloxamers)
• Lecithin from soybean and egg yolk
Polymers

• Hydrophilic polymers to enhance drug solubility by complexation (polyvinyl alcohol).
Preservatives

- As a bacteriostatic to inhibit any microbes accidentally introduced while doses are being withdrawn.
- A must in multiple dose containers unless the drug itself is bacteriostatic.
- As adjuncts in aseptic filling.
- As adjuncts in intermittent heat sterilizations.
- Not permitted in single doses > 15 mL
- Not for routes reaching cerebrospinal fluid or intr-ocular.
- Not for oil-based parenteral products (due to the low water activity of this medium).
Preservatives

Examples:

• Benzyl alcohol (1-2%)
• Chlorobutanol (0.25-0.5)
• Phenylmercuric salts
• Esters of parahydroxybenzoic acid methyl & propyl parabens (0.2% w/v)
• Phenolic compounds
  - phenol (0.25–0.5% w/v)
  - chlorocresol (0.1–0.3% w/v).

Can cause convulsions in neonates

- Low aqueous solubility
- Low stability at high pHs
- Photosensitivity
- Incompatible with alkaline excipients
- Incompatible with polysorbate 80
Preservatives

Formulation considerations for the inclusion of preservatives into parenteral formulations

- They are reduced in presence of macro-molecules (polymers) due to binding.
- They are reduced in presence of surfactants due to micellar inclusion.
- They are reduced in presence of rubber closures and plastics due to sorption.
Buffers

Parenteral formulations should not vary significantly from physiological pH (about 7.4). Acidic or alkaline solutions may be needed to solubilize or stabilize drugs.

- **pH range**
  - IV: 3-10.5
  - Other routes: 4-9

- **Buffer capacity**
  - Sufficient to maintain proper product pH value during storage
  - Not very high to allow the body fluids to bring the pH of the solution close to the physiological pH after administration
Buffers can act as general catalysts (degradation of vitamin B1, increase with increase in citrate buffer concentration). Ionic strength contribution of the buffer systems can affect stability (HPO$_4^{-2}$ ion concentration increase the rate of hydrolysis of phenethicillin in its aqueous solution).
Tonicity adjusters

The osmotic pressure of blood is approximately 300 milliOsmoles/L

An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.
**Tonicity adjusters**

An isotonic solution is one that exhibits the same effective osmotic pressure as blood serum.

**Hypertonic**
- Slow SVP by IV route
- Central line IV administration
- SC
- IM if rapid action is required

**Isotonic**
- LVP by IV route
- IC
- IT
- PD

**Hypotonic**
- Adjusted to isotonicity:
  - sodium chloride
  - glucose
  - mannitol

In extreme dehydration, the plasma salt content may be very high, and it is then appropriate to use hypotonic solutions in a controlled fashion.
Antioxidants, Chelating agents and Inert gases

Oxidative degradation of drug in solution is mediated either by molecular oxygen or by free radicals and can be catalyzed by metals, heat, light and hydrogen ions.

Inert Gas

• Boiling the water
• Displacing the air in the solution with nitrogen
• Purging container N₂ or CO₂ before filling
• Topping off container with the gas after sealing
• Use glass-sealed ampoules
Oxidative degradation of drug in solution is mediated either by molecular oxygen or by free radicals and can be catalyzed by metals, heat, light and hydrogen ions.

**Antioxidants**
- With lower oxidation potential. They preferentially undergo oxidation
  - sulfite
  - bisulfite
  - metabisulfite
- **Antioxidants**
  - That terminate the propagation step in the free radical oxidation mechanism.
  - Butylated hydroxy toluene
  - Tocopherols
  - Ascorbic acid ester

**Conditions**
- high pH
- intermediate pH
- low pH values
Antioxidants, Chelating agents and Inert gases

Oxidative degradation of drug in solution is mediated either by **molecular oxygen** or by **free radicals** and can be catalyzed by **metals, heat, light** and **hydrogen ions**.

**Chelating agents**
- Sequester heavy metals to prevent the catalysis of oxidation reaction
- ethylenediamine tetra acetic acid derivatives and salts
- Citric acid
- Tartaric acid
Manufacturing Injectable solutions

Dissolving drug & additives
Adjusting pH
Aseptic filtration
Aseptic filling
sealing

Dissolving drug & additives
Adjusting pH
filling
sealing
Terminal sterilization?
(autoclaving/dry heat)
Parenteral Suspensions

Are sterile dispersed systems containing insoluble drug particles in either aqueous or vegetable oil vehicles.

They usually contain 0.5 - 5 % solids, however certain antibiotic parenterals may contain up to 30% solids. Particle size less than 5 µ,
Parenteral Suspensions

Important properties of the parenteral suspension for the formulation development

**Syringeability:** It is the ability of a parenteral suspension to pass easily through a needle, especially during the transfer of product to the syringe prior to injection (ease of withdrawal, clogging and foaming tendencies, and accuracy of dose measurements)

**Injectability:** The performance of the suspension during injection (force or pressure required, evenness of flow and clogging)
Parenteral Suspensions

Advantages

* For insoluble & poorly soluble drugs
* Increase chemical stability of drugs (↑ resistance to hydrolysis & oxidation)
* More prolonged release from injection site than solution (a depot effect)
Parenteral Suspensions

Advantages

Disadvantages

* Difficult formulation & manufacturing
* Risk of non-uniformity of dose
* Problems of physical stability
* Patient discomfort during injection
* Limited to SC and IM routes
Formulation of Parenteral Suspensions

1. Active drug
   - insoluble
   - poorly soluble

2. Solvent
   - WFI
   - vegetable oil
   - wetting powders

3. Surfactants
   - prevent crystal growth
   - to provide acceptable syringeability

4. Suspending/flocculating agents
   - Gelatin
   - Na CMC

5. Preservatives
   - For aqueous suspensions only

6. Buffer
   - For aqueous suspensions only

7. Tonicity adjusters
   - prevent pain, irritation and tissue damage at the site of administration

8. Antioxidant
   - Drugs are more chemically stable in the solid state

9. Chelating agents

10. Inert gases
Manufacturing of Injectable suspensions

Drug

Sterilization

? Aseptic sterile powder addition

Vehicle + excipients

Sterilization

? Aseptic Dispersion

Aseptic mixing/milling

Aseptic filling
Manufacturing of Injectable Suspensions

**In situ sterile crystallization**

- Drug solution in organic solvent
  - Sterilization (filtration)
- Counter solvent
  - Sterilization (filtration)
- Vehicle + excipients
  - Sterilization (filtration)

**In-situ Crystallization**

- Aseptic organic solvent removal
- Aseptic addition
- Aseptic mixing/milling
- Aseptic filling
Preparation of Sterile Solids

1. Sterilization of bulk conventionally prepared solids

- Dry heat (for stable drugs only)
- Gamma Radiation
- Ethylene oxide gas (limited due to safety considerations)
Preparation of Sterile Solids

2. Aseptic recrystallization of solids

Drug solution in organic solvent

Sterilization (filtration)

Counter solvent

Sterilization (filtration)

In-situ Crystallization

Aseptic filtration

Drying
Preparation of Sterile Solids

2. Aseptic recrystallization of solids

Advantages

* The method is economic and flexible

Disadvantages

* Variation in density of products from batch to batch
* Color development in drugs sensitive to iron.
Preparation of Sterile Solids

3. Bulk aseptic lyophilization

Removal of water (sublimation) from frozen solution under reduced pressure
Preparation of Sterile Solids

3. Bulk aseptic lyophilization

Advantages

* For heat sensitive drugs.
* Product of more rapid solubility is obtained.
* Reduced levels of particulate contamination.
* Elegant appearance product.

Disadvantages

* Difficulty of achieving a product when a crystalline form is required.
* Relatively high expenses.
Preparation of Sterile Solids

3. Bulk aseptic spray drying

Drug solution or slurry is sprayed

Solvent evaporation

Drug powder

Steam of hot sterile gas
Preparation of Sterile Solids

3. Bulk aseptic Spray drying

Advantages

* For heat sensitive drugs.
* Uniform particle size and density of the product.
* Good flowability of the product.
* Low levels of particulate matter contamination.
* Low price and time consuming.
Parenteral Powders

Are dry powders to be converted into solution or suspensions by adding a specified amount of a vehicle before used.

Advantages
* For unstable drugs

Disadvantages
* Less convenient for patient & health care professional
Formulation of Parenteral Powders

- Dug alone
- Drug + excipients

Examples:
- Solubilizer
- Buffer
Preparation of Sterile Powders

Aseptic sterile powder fill

Vial aseptic lyophilization
Chylomicra: natural-borne fat-globules (0.5 – 1) µm circulating in the blood stream after oral intake of fat.
Parenteral Emulsions

Advantages

- Are carriers for poorly water-soluble, oil-soluble drugs
- For unstable drugs (reduce drug hydrolysis)
- Provide parenteral nutrition
- For controlled drug delivery
- Targeting to the mononuclear phagocyte system (RES)
- Reduce adsorption of drugs on infusion sets
- Lower drug-toxicity compared with solubilised form
- As x-ray and ultrasonic contrast-emulsions
- As blood-substitutes (perfluorocarbon-emulsions)
Parenteral Emulsions

Advantages

Disadvantages

* Difficult formulation & manufacturing
* Problems of physical stability
**Formulation** of Parenteral Emulsions

1. **Active drug**
   - oil-soluble drugs
   - Poorly water-soluble

2. **Emulsifiers**
   - Poloxamer 188
   - Tween 80
   - lecithin

3. **Aqueous Phase**
   - WFI

4. **Oily Phase**
   - Vegetable oil

5. **Buffer**
   - pH = 6-7 to reduce the rate of oil hydrolysis and free fatty acid formation

6. **Tonicity adjusters**

7. **Antioxidant**

8. **Chelating agents**

9. **Inert gases**
Manufacturing of Injectable Emulsions

Oily phase + Lecithin

\[ \triangle 70-80^\circ C \]

Preparation of Coarse Emulsions

Aqueous phase + excipients

High shear mixers

20 \( \mu m \)

High-Pressure Homogenisation

0.5 – 1 \( \mu m \)

Filling

Sterilisation? by Autoclaving