PARENTERAL PREPARATIONS

INTRODUCTION

- Parenteral (Gk, *para enteron*, beside the intestine) dosage forms differ from all other drug dosage forms, because they are injected directly into body tissue through the primary protective systems of the human body, the skin, and mucous membranes. They must be exceptionally pure and free from physical, chemical, and biological contaminants. These requirements place a heavy responsibility on the pharmaceutical industry to practice current good manufacturing practices (cGMPs) in the manufacture of parenteral dosage forms and on pharmacists and other health care professionals to practice good aseptic practices (GAPs) in dispensing parenteral dosage forms for administration to patients.

INTRODUCTION

- Certain pharmaceutical agents, particularly peptides, proteins, and many chemotherapeutic agents, can only be given parenterally, because they are inactivated in the gastrointestinal tract when given by mouth. Parenterally-administered drugs are relatively unstable and generally highly potent drugs that require strict control of administration to the patient. Due to the advent of biotechnology, parenteral products have grown in number and usage around the world.

Characteristics of parenteral dosage forms

- Parenteral products are unique from any other type of pharmaceutical dosage form for the following reasons:
- All products must be sterile.
- All products must be free from pyrogenic (endotoxin) contamination.
- Injectable solutions must be free from visible particulate matter. This includes reconstituted sterile powders.
- Products should be isotonic, although strictness of isotonicity depends on the route of administration.
- Products administered into the cerebrospinal fluid must be isotonic.
- Ophthalmic products, although not parenteral, must also be isotonic. Products to be administered by bolus injection by routes other than intravenous (IV) should be isotonic, or at least very close to isotonicity.
- IV infusions must be isotonic.

Characteristics of parenteral dosage forms

- All products must be stable, not only chemically and physically like all other dosage forms, but also ‘stable’ microbiologically (i.e., sterility, freedom from pyrogenic and visible particulate contamination must be maintained throughout the shelf life of the product).
- Products must be compatible, if applicable, with IV diluents, delivery systems, and other drug products co-administered.

CLASSIFICATION

Injections may be classified in six general categories:

- 1. Solutions ready for injection
- 2. Dry, soluble products ready to be combined with a solvent just prior to use
- 3. Suspensions ready for injection
- 4. Dry, insoluble products ready to be combined with a vehicle just prior to use
- 5. Emulsions
- 6. Liquid concentrates ready for dilution prior to administration

Components

- Components of parenteral products include the active ingredient, formulation additives, vehicle(s), and primary container and closure. Establishing specifications to ensure the quality of each of these components of an injection is essential. Secondary packaging is relevant more to marketing considerations, although some drug products might rely on secondary packaging for stability considerations, such as added protection from light exposure for light-sensitive drugs and antimicrobial preservatives.

SOLVENTS AND VEHICLES

WATER AND AQUEOUS VEHICLES

- Water for injection
- Sterile water for injection
- Bacteriostatic water for injection
- Sodium chloride injection
- Bacteriostatic sodium chloride injection

Non-aqueous solvents

Fixed vegetable oils

Alcohols

ADDED SUBSTANCES

- **Preservatives**

- Agents containing mercury in concentration not more than 0.01%
- Cationic surfactants
- Alcohols up to 2%
- Phenols up to 0.5%
- Others

ADDED SUBSTANCES

- **Antioxidants**

Water soluble

- Sulfurous acid salts
- Ascorbic acid isomers
- Thiol derivatives

Oil soluble

- Propyl gallate
- Butylated hydroxyanisole
- Ascorbyl palmitate
- a- Tocopherol

ADDED SUBSTANCES

- **BUFFER SYSTEMS**

pH	Buffer system	Concentration (%)
3.5-5.7	Acetic acid-acetate	1-2
2.5-6.0	Citric acid- citrate	1-5
6.0-8.2	Phosphoric acid-phosphate	0.8-2
8.2-10.2	Glutamic acid- glutamate	1-2

PREPARATION

- Primary washing and sterilization
- Compounding
- Terminal sterilization

CONTROL/TESTS

- Particulate contamination
- Sterility
- Bacterial endotoxins and pyrogens
- Uniformity of dosage units
- Uniformity of content
- Uniformity of mass

LABELLING

- Name and concentration of active substances
- Name and concentration of any added antimicrobial preservatives
- Route of administration
- Shelf- life
- Batch number

REQUIREMENTS FOR PARENTERAL PREPARATIONS

- Sterile
- Apyrogenic
- Pure
- Stable
- Isohydric
- Isoviscous
- Isotonic

Containers and closures

- Injectable formulations are packaged into containers made of glass or plastic. Container systems include ampoules, vials, syringes, cartridges, bottles, and bags.

Containers and closures

- Ampoules are all glass, whereas bags are all plastic. The other containers can be composed of glass or plastic and must include rubber materials, such as rubber stoppers for vials and bottles and rubber plungers and rubber seals for syringes and cartridges.
- Irrigation solutions are packaged in glass bottles with aluminum screw caps.
- Further, the integrity of the container/closure system depends on several characteristics, including container opening finish, closure modulus, durometer and compression set, and aluminum seal application force

Containers and closures

- **Small volume parenterals (SVPs)**
- Ampoules
- Glass vials sealed with rubber stoppers
- Plastic ampoules (blow-fill-seal)
- Pre-filled syringes
- Needle-free injection

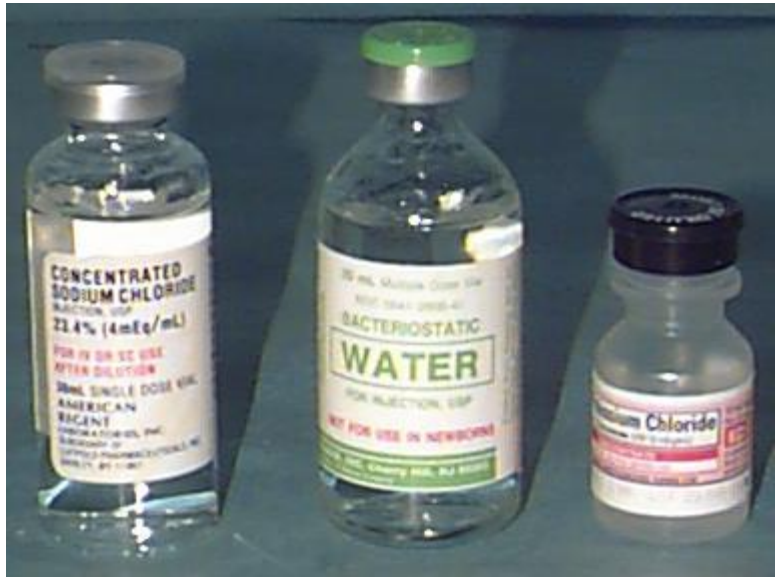
Containers and closures

- Small volume parenterals (SVPs)
- Ampoules
  – heat sealed after filling
- Glass vials sealed with rubber stoppers
- Plastic ampoules (blow-fill-seal)
- Pre-filled syringes
  – reducing the degree of manipulation required
  – facilitating administration in an emergency situation
- Needle-free injection

Containers and closures

Large volume parenterals (LVPs)

- Glass bottles sealed with rubber stoppers
- Plastic bags



CALCULATION INVOLVED IN PREPARATION OF ISOTONIC PARENTERAL SOLUTIONS

- **Freezing point depression** (colligative properties)
- - 0.52 is the freezing point of both blood serum and lacrimal fluids
- Rault equitation

$$\Delta Tm = \frac{Km * m(g) * i * 1000}{V(ml) * Mr} \Rightarrow m(g) = \frac{\Delta Tm * V(ml) * Mr}{Km * 1000}$$

ΔTm- freezing point depression (°C)
Km- molar constant of freezing depression point of water (-1.86°C l/mol)
m- weight of substance in isotonization solution (g)
i- number of dissociated ions in the electrolyte
Mr- molecular weight
V- volume of solution for isotonization

CALCULATION INVOLVED IN PREPARATION OF ISOTONIC PARENTERAL SOLUTIONS

- **D- value (tabular value)**

- Freezing point depression of electrolytes

- Proportional of concentration of dissolved substance

CALCULATION INVOLVED IN PREPARATION OF ISOTONIC PARENTERAL SOLUTIONS

- NaCl equivalent
- Weight of NaCl in grams dissolved in 1000 ml of water, which gives the same freezing point depression like 1 gr of the active substance, dissolved in equal volume of distillated water

$$X = \frac{Cx * V}{100} - \frac{a*E}{Ax}$$

- X- weight (g) of the substance for isotonization
- Cx- weight of the solution required for isotonization of 100 ml water
- V- volume of solution required for isotonization
- a- weight of the active substance
- E- NaCl equivalent of active substance
- Ax- NaCl equivalent of substance for isotonization (for NaCl=1)

CALCULATION INVOLVED IN PREPARATION OF ISOTONIC PARENTERAL SOLUTIONS

- V- value

Tabular value which represents the volume of water in ml, which needs to be added of 0.3 g of active substance in order to prepare isotonic solution

V-value ⟶ 0.3g active substance

x ml water ⟶ x g active substance

CALCULATION INVOLVED IN PREPARATION OF ISOTONIC PARENTERAL SOLUTIONS

- **Example:**

How much NaCl (g) is required for isotonization of 0.1 % 1000 ml solution of procaine hydrochloride?

1. Freezing point depression method:

$\Delta Tm=?$

- Mr(procaine hydrochloride)= 282.78 g/mol
  - 0.1g ⟶ 100ml
  - X g ⟶ 1000ml
  - X= 1 gr

$$\Delta Tm = \frac{Km*m(g)*i*1000}{V(ml)*Mr}$$

$$\Delta Tm = \frac{-1.86*\ 1g*2*1000}{1000ml*282.78g/mol}$$

$\Delta Tm=0.0131$

0.52 - 0.0131 = 0.5069

0.9% → 0.52

X% → 0.5069

X=0.877%

0.877g → 100ml

X g → 1000ml

X= 8.775g NaCl

- **D- value**

D-value (procaine hydrochloride 1%)=0.122

0.122 → 1%

X → 0.1%

X= 0.0122 ΔTm

0.52-0.0122=0.507

0.9% → 0.52

X% → 0.507

X=0.877%

0.877g → 100ml

X g → 1000ml

X= 8.775g NaCl

- **E- value (NaCl equivalent)**

E-value (procaine hydrochloride)=0.21

$$X = \frac{Cx * V}{100} - \frac{a*E}{Ax} \qquad X = \frac{0.9*1000ml}{100} - \frac{0.21*1}{1}$$

<u>8.79g NaCl</u>

- **V- value**

V-value (procaine hydrochloride)=7

7ml ⟶ 0.3g

Xml ⟶ 1g прокаин хидрохлорид

X= 23ml

1000ml - 23ml = 977 ml

0.9g ⟶ 100ml

X g ⟶ 977ml

X=8.79g NaCl