PARENTERAL PREPARATIONS

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Parenteral preparations are sterile preparations containing one or more active ingredients intended for administration by injection, infusion or implantation into human or animal bodies.

Classification of Parenteral Preparations in EP 6:

1) **Injections**: **Injections are sterile solutions, emulsions or suspensions.**

2) **Infusions**: **Infusions are sterile, aqueous solutions or emulsions with water as the continuous phase. They are principally intended for administration in large volumes.**

3)Concentrates for injections or infusions:

Concentrates for injections or infusions are sterile solutions intended for injection or infusion after dilution.

They are diluted to a prescribed volume with a liquid before administration. After dilution, they comply with the requirements for injections or for infusions.

4)Powders for injections or infusions:

Powders for injections or infusions are solid, sterile substances distributed in their final containers and which, when shaken with the prescribed volume of a sterile liquid rapidly form either clear and practically particle-free solutions or uniform suspensions.

After dissolution or suspension, they comply with the requirements for injections or for infusions.

5)Gels for injections: Gels for injections are sterile gels with a viscosity suitable to guarantee a modified release of the active substance(s) at the site of injection.

6)Implants: Implants are sterile, solid preparations of a size and shape suitable for parenteral implantation and release of the active substance(s) over an extended period of time. Each dose is provided in a sterile container.

Classification of parenterals according to their volume;

1) Large Volume Parenterals (LVP)

These are supplied for single-dose having more than 100 ml. These are delivered through the intravenous route.

Examples of LVPs:

-Calcium solutions
-Sodium chloride, Ringer's, sodium bicarbonate and other electrolyte solutions
-Dextrose (glucose) and other sugar solutions
-Amino acid, peptide and other protein-fraction solutions
-Solutions containing a combination of the above, sometimes with vitamins added
-Dextrans, and other plasma expanders

2) Small Volume Parenterals (SVP)

These are supplied in single or multiple doses. The volume is generally less than or equal to 100 ml.

Specific Routes of Administration of Parenterals

Three primary routes of parenteral administration are commonly employed:

-Intramuscular (i.m.)
-Intravenous (i.v.)
-Subcutaneous (s.c.)

Besides these three primary routes, additional ones are utilized under special circumstances: for example, subconjunctival, intraocular, intrathecal, intra-articular, and so on.

Primary Routes

1) Intramuscular (i.m.): Injection directly into the body of a relaxed muscle.

The intramuscular route provides a means for prolonged release of drugs formulated as aqueous or oily solutions or suspensions.

2) Intravenous (i.v.): Injections or infusions directly into a vein.

Intravenous administration of drugs, fluids, and/or electrolytes is one of the most common parenteral routes.

It is especially convenient for rapidly infusing large volumes of fluid.

3) Subcutaneous (s.c.): Injection into the loose connective and adipose tissue beneath the skin (dermis).

This route may be utilized if drugs cannot be administered orally because of lack of absorption from or inactivation by the contents of the gastrointestinal tract, if the patient is unable to ingest medications by mouth or if self-medication of parenteral (e.g., insulin) is desired.

Drugs are more rapidly and more predictably absorbed by this route than by the oral one, but absorption is slower and less predictable than by the intramuscular route.

Secondary Routes

Intraperitoneal (Intra-abdominal): **Injection or infusion directly into the peritoneal cavity via a needle or indwelling catheter or directly into an abdominal organ, such as the liver, kidney, or bladder.**

Intra-arterial: **Injection or infusion into an artery that leads directly to the target organ.**

Intra-articular: **Injection or infusion into the synovial sacs of various accessible joints.**

Intracardiac: **Injection directly into chambers of the heart.**

Intracisternal: **Injection directly into the cisternal space surrounding the base of the brain.**

Intrapleural: **Usually, a single injection into the pleural cavity.**

Intrathecal: **Injection or infusion directly into the lumbar sac (intrathecal) located at the caudal end of the spinal cord.**

Intrauterine: **Infusion or injection via a needle inserted percutaneously into the pregnant uterus.**

Intraventricular: **Injection or infusion directly into the lateral ventricles of the brain.**

Intradermal injections (ID or i.d.): **Intradermal injections are given into the skin between the epidermal and dermal layers. Volumes of up to 0.2 mL can be given by this route and absorption from the intradermal injection site is slow.**

Ophthalmic injections: **Ophthalmic injections are administered either around or into the eye; in the latter case, these are referred to as intraocular injections.**

☺ Advantages of Parenteral Administration

1. An immediate physiological response can be achieved if necessary, which can be of prime consideration in clinical conditions such as cardiac arrest, asthma, and shock.

2. Parenteral therapy is required for drugs that are not effective orally or that are destroyed by digestive secretions such as insulin, other hormones, and antibiotics.

3. Drugs for uncooperative, nauseous or unconscious patients must be administered by injection.

4. When desirable, parenteral therapy gives the physician control of the drug since the patient must return for continued treatment, also in some cases, the patient cannot be relied upon to take oral administration.

5. Parenteral administration can results in local effects for drugs when desired, as in dentistry and anesthesiology.

6. In a case in which prolonged drug action is wanted, parenteral forms are available, including the long-acting penicillins administered deep intramuscularly.

7. Parenteral therapy provides the means of correcting serious disturbances of fluid and electronic balances.

8. When food cannot be taken by mouth, total nutritional requirements can be supplied by the parenteral route.

☹ Disadvantage of Parenteral Administration

1. The dosage form must be administered by trained personnel and require more time than those administered by other routes.

2. Parenteral administration requires strict adherence to aseptic procedures, and some pain on injection is inevitable.

3. It is difficult to reverse its physiological effect.

4. Because of the manufacturing and packaging requirements, parenteral dosage forms are more expensive than preparations given by other routes.

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.**
- **Products should be isotonic.**
- **All products must be stable.**

Formulation of Injectable Dosage Forms

In the preparation of parenterals, the properties of the active substance(s), the type, the volume and the route of administration of dosage forms are important.

Points to consider when formulating of injectable dosage forms;

1) Physical and chemical properties of active substance(s),

2) Properties of vehicles (solvents and co-solvents in which the active substance will be dissolved/suspended/emulsified),

3) pH and osmolarity,

4) Structure of dosage form,

5) Excipients in the formulation.

1) Physicochemical properties of active substance(s):

- **Molecular structure and molecular weight,**
- **Particle size and shape,**
- **Solubility,**
- **Polymorphism,**
- **Hygroscopicity,**
- **Ionization constant,**
- **Optical activity,**
- **Melting point,**
- **Solvate formation,**
- **Stability,**
- **Color,**
- **Odor.**

2) Properties of Vehicles for Injections

Solvents

When preparing a parenteral dosage form, the active substance(s) and adjuvants need to be dissolved, suspended or emulsified in water for injection or in a suitable sterile anhydrous liquid or mixture thereof.

a) Water for injections

'Water for injections' is the most common vehicle used for parenteral products. Water for injections is a highly purified grade of water which is subject to pharmacopoeial standards with respect to production methods and purity.

b) Water-miscible solvents

For poorly soluble drugs in water, water-miscible non-aqueous solvents such as ethanol, glycerol or propylene glycol may be added as co-solvents to improve the solubility of drugs.

c) Water-immiscible solvents

Water-insoluble drugs may be administered parenterally by dissolving the drug in a suitable oil and forming an oil-in-water emulsion using a suitable emulsifying agent to stabilize the emulsion.

Such as arachis oil or sesame oil may be chosen as a vehicle for intramuscular injections, for drug release over a prolonged period of time (depot injections).

d) Solubilizing agents

The agents which help in dissolving or increase the drug solubility into the formulation are known as solubilizing agents.

Polyoxyethylene castor oil derivatives will solubilize hydrophobic drugs into aqueous solutions for injections and are used, for instance, for formulations of paclitaxel, diazepam and cisplatin.

5) Excipients

Excipients are used in parenteral preparations;

-To ensure continuity of stability and sterility,
-To increase physiological activity,
-For adjustment of isotonicity.

- **Antioxidants, reducers and chelating substances**
- **Antimicrobial agents**
- **pH setting and buffer solutions**
- **Isotonicity adjuster**
- **Surfactants**
- **Preservatives**

- **Antioxidant, antimicrobial and pH adjusting agents should not be used in infusions, intratechal, peridural, intracisternal, subcutaneus, intradermal and intraocular injections because they may cause toxic effects on injections.**

- **Coloring agents should not be added to the injectable dosage forms.**

Antioxidants and Chelating Agents

If the drug substance to be injected is prone to degradation by oxidation, a number of formulation processes and excipients can be used to reduce the rate of drug degradation in the product and thus improve the shelf-life or expiry date.

Vitamin C (ascorbic acid) and Vitamin E (alpha-tocopherol) can be used for this purpose.

Ascorbic acid is used in aqueous parenteral products at a concentration of 0.01–0.1% w/v. Ascorbic acid can also be used to adjust the pH of the formulation.

Alpha-tocopherol is highly lipophilic and can be used in oil based parenteral products usually in the range of 0.001–0.05% v/v.

Butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT) are structurally similar antioxidants used in parenteral preparations either separately or in combination. For intramuscular injections they are usually used at a concentration of 0.03% w/v and for intravenous injections 0.0002–0.002% w/v is used.

The most commonly used antioxidants are the sulphite salts. Sodium metabisulphite is used at concentrations between 0.01–0.1% w/v and also has some preservative properties. It is used as an antioxidant for acidic parenteral products.

If the product is of neutral pH sodium bisulphite is used, whereas sodium sulphite is used as an antioxidant in alkali parenterals.

Chelating agents are used to remove toxic metals, such as copper, iron, and zinc that generally catalyze oxidative degradation of drug molecules.

Examples of chelating agents used in parenteral products include: citric acid at concentrations between 0.3–2.0% w/v and derivatives of ethylenediaminetetraacetic acid (EDTA) at concentrations between 0.0005–0.01% w/v.

Citric acid can also be used to adjust the pH of formulations and EDTA compounds possess preservative properties.

Antimicrobial Agents

Antimicrobial agents (preservatives) are added to injections which are designed for multiple use to inhibit the growth of any microorganisms that may be inadvertently introduced into the product during repeated use by the patient or healthcare professional.

Preservatives may be added to single-dose parenteral products that are not terminally sterilized.

☠ Preservatives should not be added to large volume parenterals (infusions), or products intended for intraspinal or intraocular injection.

pH Adjustment and Buffers

Buffers are added to a formulation to adjust and stabilize pH and optimize drug solubility and stability, for parenteral preparations, it is desirable that the product pH be close to physiologic pH.

Injectable products should have a pH value between 3.0 and 9.0 prior to administration. pH values above or below this range are too corrosive and will cause tissue damage at the site of injection.

Changes in pH may arise due to interactions between an ingredient in the formulation and the container, or from changes in storage temperature.

Buffer ingredients commonly used in parenteral products include citric acid, sodium citrate, sodium acetate, sodium lactate and mono and dibasic sodiumphosphate.

Tonicity Adjusting Agents

Parenteral formulations should be isotonic with human plasma so as to avoid damage to the tissues. However, not all drugs at their recommended dosage are isotonic with blood, thus requiring the addition of a tonicity adjusting agent to the formulation.

An aqueous solution of sodium chloride at a concentration of 0.9% w/v or 9 g per L has a measured osmolarity of 286 mmol per L and is isotonic (meaning has the same osmotic pressure with human plasma, which has an osmolarity of between 280–295 mmol per L).

- **An isotonic solution refers to a solution having the same osmotic pressure with bodily fluids or plasma.**

A hypotonic solution refers to a solution that has a lower osmotic pressure than that of bodily fluids or plasma.

A hypertonic solution refers to a solution that has a higher osmotic pressure than that of bodily fluids or plasma.

If a hypotonic solution is administered intravenously, water will pass into the red blood cells, causing them to swell and possibly burst (haemolysis).

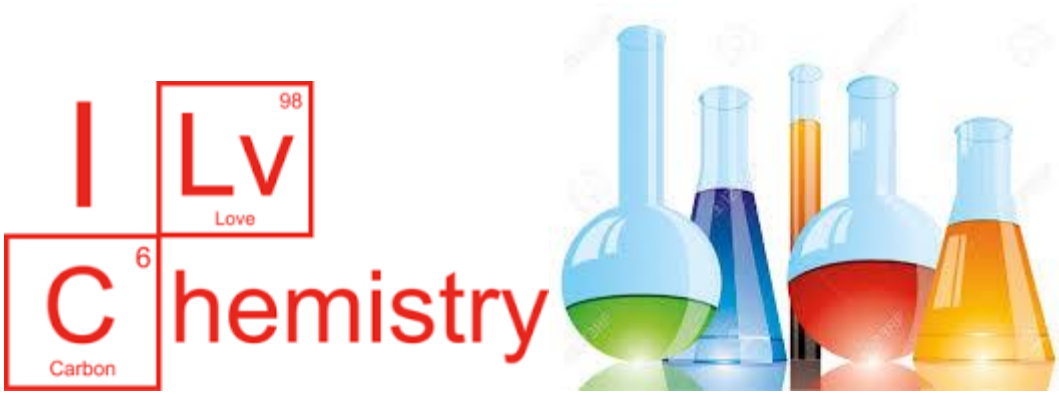
If a hypertonic solution is administered intravenously, water is drawn from the cells in an attempt to dilute the solution, causing them to shrink (granulation).

- **A <u>hypotonic solution</u> can be made isotonic by adding an adjusting substance.**

- **The osmotic pressure adjustment of each injection solution is not required. But; large volume solutions and solutions given with intrathecal, peridural and intracisternal routes must be isotonic.**

- **Inert and non-toxic substances for the osmotic pressure adjustment of injection solutions, mainly sodium chloride and dextrose are used.**

IZOOSMOTIC-IZOCRYOSCOPIC-IZOTONIC SOLUTIONS



Raoult's Law

According to the Raoult's Law; the vapor pressure of a solution is proportional to the molar fraction of the liquid in the solution.

If the number of molecules in the dissolved solid increases, the liquid fraction decreases and the vapor pressure decreases. The Raoult's law for ideal solutions is described by the following equation:

$$P_1 = X_1 \cdot P^\circ_1$$

P_1: Partial pressure of solvent

X_1: Mole fraction of solvent

P°_1: Vapor pressure of pure solvent

Osmosis is the diffusion of water molecules from a dilute solution to a more concentrated solution across a selectively permeable membrane.

The pressure needed to stop the osmotic flow is the osmotic pressure.

P = n / V x R T I

P: Osmotic pressure
n: Mole value of solid (m/m_A)
V: Volume
R: Gas content (0.082 L.atm/mol (K°))
I: Ionization coefficient for electrolyte

I_{NaCl} $Na^+ + Cl^- = 2$

n / V = M

$I_{dekstroz}$ = 1

M: Molarity

Calculation of Freezing Point

$$P = R\,T \times \Delta T / K$$

ΔT: Freezing point

K: Cryoscopic constant (1.86)

RT: 0.082 x (0 + 273)= 22.4 atm

$P = 22.4 \times \Delta T / 1.86$

$P = 12 \times \Delta T$

Freezing point of blood serum : - 0.52 C°

$\Delta T = K \times M \times I$ (I: Ionization coefficient for electrolyte)

Calculations for preparation of isotonic solutions

1) Freezing point depression method

Freezing point data (ΔT) can be used in isotonicity calculations.

The freezing point of both blood and lacrimal fluid is -0.52°C.

Thus, a pharmaceutical solution that has a freezing point of -0.52°C is considered isotonic.

Example: The freezing point of 1% solution of calcium gluconate is -0.091 ° C. How many percent of calcium gluconate is isotonic?

1%	-0.091°C
X	-0.52°C

X= 5.8% w/v

Example: **How many grams of sodium chloride is required to prepare 100 mL of a 1% atropine sulfate solution isotonic?**

Freezing point of 1% atropine sulfate solution = -0.073°C
Freezing point of 1% NaCI solution = -0.576°C
Freezing point of plasma = -0.52°C

0.52-0.073 = 0.447 °C

%1 NaCl 0.576°C

X 0.447 °C

X= 0.78 g NaCl

If 0.78 g of NaCl is added and the volume of the solution is completed to 100 mL, a 1% isotonic atropine sulfate solution is prepared.

Example: How many grams of sodium chloride is required to prepare 100 ml of a 1% procaine hydrochloride solution isotonic?

F.P. of 1% w/v solution of procaine HCl is	**0.122**
F.P. of a 1% w/v solution of NaCl is	**0.576**

0.52-0.122 = 0.398 °C

%1 NaCl	**0.576**
X	**0.398**

X=0.69 g NaCl

2) İsotonic solutions are calculated by the following formula

W = 0.52 – a / b

W: The weight (in grams) of adjusting agent in 100 mL of the final solution

a: The freezing point of 1% solution of the active substance multiplied by the percentage of the substance in the formula

b: Freezing point of 1% solution of the adjusting agent

Freezing point of plasma = -0.52 °C

Freezing point of 1% NaCl solution = -0.576 °C

The freezing point of a solution can be found by the Raoult formula.

$$\Delta T = K \times M \times I$$

$$\Delta T = K \times \frac{g \times 1000}{MW \times V} \times I$$

ΔT: Freezing point depression of solution according to water (for 100 mL)
K: Cryoscopic proportional constant (1.86 for water)
I: Number of ion of substance
g: Weight of substance (g)
MW: Molecular weight of substance
V: Volume of solution (mL)

Example:

Made calculation necessary to make 100 mL isotonic solution containing 0.5% anhydrous calcium chloride.

$$\Delta T = K \times \frac{g \times 1000}{MW \times V} \times I$$

$$= 1.86 \times \frac{1 \times 1000}{110.99 \times 100} \times 3$$

= 0.5 (hypotonic)

W= 0.52-a/b

= 0.52-(0.5x0.5)/0.576

= 0.47 g NaCl

Example: **Calculate weight of NaCl necessary to prepare isotonic solution of 1% Cocain HCl solution.**

W=(0.52-a)/b

Cocain HCl Δt:0.090 **(0.52-0.090x1)/0.576= 0.746 g NaCl**

NaCl Δt:0.576

Example: Find the proportion of sodium chloride required to render a 1.5% solution of procaine hydrochloride isotonic with NaCl.

F.P. a 1% W/V solution of procaine HCl is 0.122.

W= (0.52-a)/b

= (0.52-0.122x1.5)/0.576

= 0.585 g

Example: Find the amount of sodium chloride necessary to be included in 100 ml of 0.3 per cent solution of zinc sulfate so that, on dilution with an equal quantity of water.

Zinc sulfate Δt:0.086 NaCl Δt:0.576

$$\frac{(0.52)-(0.3/2 \times 0.086)}{0.576} = 0.88 \text{ g (100 mL)}$$

0.88 x 2= 1.76 g NaCl

3) Sodium chloride equivalent method

The sodium chloride equivalent, of a drug is the amount of sodium chloride that has the same osmotic effect as 1 gram of the drug.

Calculations for determining the amount of sodium chloride or other inert substance to render a solution isotonic simply involve:

a. **Multiplying the quantity of each drug in the prescription by its sodium chloride equivalent.**
b. **Calculating the amount of sodium chloride that renders the whole prescription volume isotonic.**
c. **Subtract the value in step (a) from that in step b give the amount of sodium chloride must be added.**
d. **If the isotonicity is to be adjusted with some other inert substance the calculated NaCl amount in the previous step is converted to the inert substance using its NaCl equivalent value.**

Example:

A solution contains 1.0 g ephedrine sulphate in volume of 100 ml. What quantity of sodium chloride must be added to make the solution isotonic?

How much dextrose would be required for this purpose?

The quantity of the drug is multiplied by its sodium chloride equivalent E, giving the weight of sodium chloride to which:

1. **The quantity of drug is equivalent in osmotic pressure to:**

   1.0 g x 0.23 = 0.23 g of NaCl $E_{\text{ephedrine sulphate}} = 0.23$

1. **The total sodium chloride required for isotonicity is 0.9 g/100 ml (the prescription volume).**
2. **The amount of NaCl required to be added to adjust the isotonicity of the prescription:**

   0.9 - 0.23 = 0.67 g of NaCl must be added.

The sodium chloride equivalent of dextrose is 0.16.

1 g dextrose	**0.16 g NaCl**
X	**0.67 g**

X= 4.2 g dextrose

Example:

Rx	E
Ephedrine hydrochloride……..1.2 g	0.28
Chlorbutanol…… ….. ……..0.3 g	0.18
Dextrose ……..y.m.	0.16
Water for injection ……ym…….60 mL	

for 60 mL; 1.2 x 0.28 = 0.34 g NaCl

0.3 x 0.18 = 0.05 g NaCl

\+ ---------- 0.39 g (for 60 mL)

$0.9x0.6 = 0.39 + 0.16xD$

$0.54-0.39 = 0.16xD$

$D = 0{,}9375 \approx 0.94$ g dextrose

4. White-Vincent method:

1. This method involves the addition of water to the drugs to make an isotonic solution.
2. Followed by the addition of an isotonic or isotonic-buffered diluting vehicle to bring the solution to the final volume.

$$V = W \times E \times 111.1$$

V: The volume of water needed to prepare the isotonic solution (mL)
W: Amount of substance (g)
E: NaCl equivalent of substance

Example: Show the calculations required to prepare 30 mL of 2% isotonic phenylbutazone sodium solution.

($E_{\text{Phenylbutazone sodium}} = 0.18$)

V = W x E x 111.1

W

100 2

30 X= 0.6 g

V= 0.6 x 0.18 x 111.1

=12 mL amount of water needed to prepare the isotonic solution

30 – 12 = 18 mL %0.9 NaCl

100 mL 0.9 g

18 mL X= 0.162 g NaCl