LARGE VOLUME PARENTERAL PREPARATIONS

Large volume parenterals (LVPs or large volume injections) are aqueous solutions usually supplied in volumes of 100 ml to 5 000 ml.

LVPs are typically used to provide fluid replacement therapy.

Routes of administration may include intravenous, intraperitoneal, or subcutaneous.

Some examples of LVPs include solutions containing:

- **Sodium bicarbonate**
- **Electrolytes**
- **Dextrose (glucose) and other sugars**
- **Amino acids, peptides and other protein-fractions**
- **Vitamins, minerals**
- **Dextrans, and other plasma expanders**

Electrolyte Solutions

They are used when the electrolyte, acid and base balance of blood change and to improve blood volume.

Na^+ is important in providing osmotic pressure,
K^+ is important in providing acid-base balance,
Ca^{++} is important in blood clotting,
Cl^- and HCO_3^- are important in providing acid-base balance.

Disruption of balance of these ions disrupts cell functions.

Examples: Ringer's Solution (USP 27), Lactated Ringer Solution (USP 27)

Milliequivalent (mEq)

The concentration of electrolytes in the blood is expressed in milliequivalents.

To make the electrolyte solutions isotonic, the ionic concentrations of the solutions should be calculated.

In plasma;

Cation	Anion
361 mg/100 mL	7464 mg/100 mL
155 mEq/L	155 mEq/L

$$mEq = \frac{g/L}{\text{Molecular weight}} \times 1000 \times \text{Valence of ion} \times \text{Dissociated ion number}$$

Na^{+}	1	1
Ca^{+2}	2	1
Cl^{-}_{2}	1	2

Example: **Calculate the mEq values of anions and cations in a solution containing 20 mg $CaCl_2.2H_2O$ in 100 mL.**

100 mL 20 mg **MA $CaCl_2.2H_2O$=147**

1000 mL X=200 mg=0.2 g

$$\text{mEq Ca} = \frac{0.2 \times 1000 \times 2 \times 1}{147} = 2.72 \text{ mEq/L}$$

$$\text{mEq Cl} = \frac{0.2 \times 1000 \times 1 \times 2}{147} = 2.72 \text{ mEq/L}$$

Nourishing Solutions

They contain protein, amino acid, oil (sunflower and soybean oil), glucose, electrolyte and vitamins.

Examples:

-2-5-10-20-50% isotonic glucose/fructose/protein hydrolysate solutions

-Oil/water type emulsions (high calories)

-Vitamin E (Antioxidant)

-85% amino acid emulsions

-10% oil emulsions

Plasma Expanders

They are used temporarily when blood transfusions can not be made to the patient.

Dextrans:

-Dextran 40 (Mw 35000-45000)
10% dextran 40 solution in 5% glucose or 0.9% NaCl solution

-Dextran 70 (Mw 63000-77000)
6% dextran 70 solution in 5% glucose or 0.9% NaCl solution

Human Serum Albumin:

Albumin is a plasma protein.

Albumin protects the blood volume with high water retention capacity in the plasma and also provides 80% of the osmotic pressure.

It temporarily completes blood volume in shock and bleeding.

It is prepared by fractionation of blood, plasma and serum.

Plasma Protein Fraction:

It consists of albumin and globulins obtained by fractionation of blood, plasma and serum.

It contains some electrolytes such as sodium, potassium and chloride.

Because it is a good protein source, it is used in feeding.

STERILIZATION

Sterilization

Sterilization can be defined as any process that effectively kills or eliminates transmissible agents (such as fungi, bacteria, viruses and prions) from a surface, equipment, foods, medications, or biological culture medium.

Terms Commonly Used in Sterilization

Sterilization Assurance Level (SAL=10^{-6})

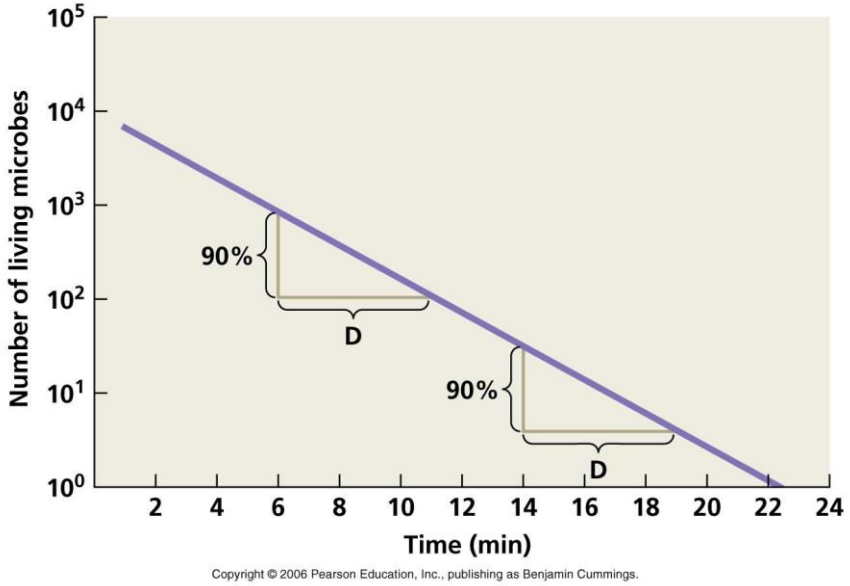
A sterility-assurance level (SAL) is defined as the probability of an item being nonsterile after it has been exposed to a validated terminal sterilization process.

At present, a sterility assurance level (SAL) of 10^{-6} is generally accepted for pharmacopoeial sterilization procedures, i.e., a probability of not more than one viable microorganism in an amount of one million sterilised items of the final product.

D-value

D-value is indicative of the resistance of any organism to a sterilizing agent.

For radiation and heat treatment, D-value is the time taken at a fixed temperature or the radiation dose required to achieve a 90% reduction in viable count.

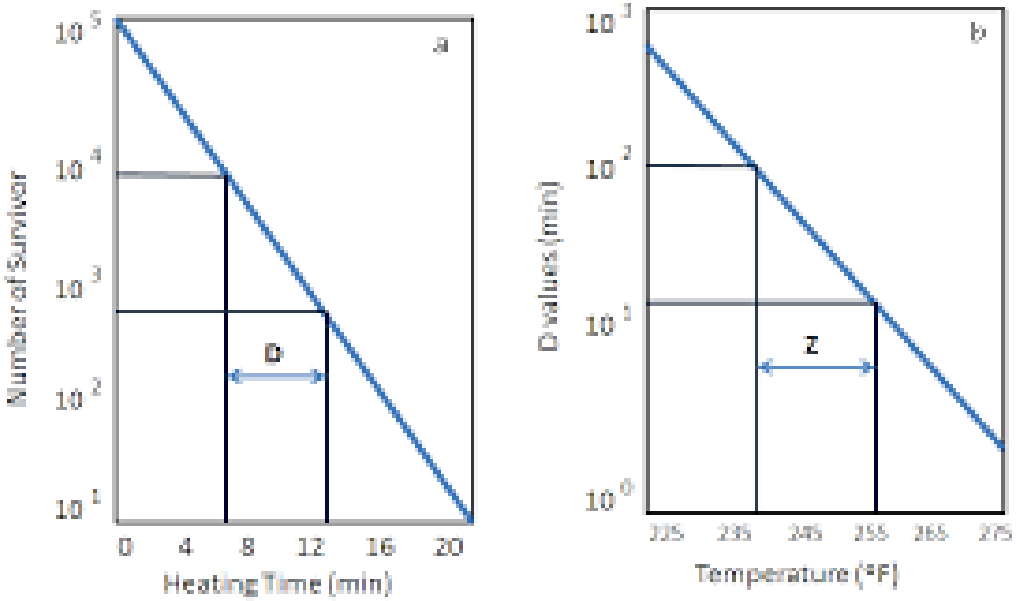


$$D\ (\text{dakika}) = t / (\log N_o - \log N_t)$$

Z-value

Z-value is the number of degrees the temperature has to be increased to achieve a tenfold (i.e. 1 log10) reduction in the D-value.

$$Z = t_1\text{-}t_2/\log D_1\text{-}\log D_2$$



Lethality Factor (F_0)

At a certain temperature, the time required to reduce the number of microorganisms to the limit of 10^{-6}.

$$F_0 = \Delta t \times 10^{(T-121/Z)}$$

T: Sterilization temperature

Δt: 1 minute

Z: 10 °C

Example: **Calculate F_0 for sterilization at 115 °C.**

$F_0 = 1 \times 10^{(115-121/10)}$

$F_0 = 1 \times 10^{(-6/10)}$

$F_0 = 1 \times 10^{(-0.6)}$

$F_0 = 3.98$ minutes

The thermal lethality of sterilization performed at 121 °C for 1 minute equals the thermal lethality of sterilization at 115 °C for 3.98 minutes.

Methods of Sterilization

The various methods of sterilization are:

1. Physical Methods

- **a. Thermal (Heat) Methods**
  - **Dry heat sterilization**
  - **Moist heat sterilization**
- **b. Radiation Method**
- **c. Filtration Method**

2. Chemical Methods

- **a. The use of Gaseous sterilizing agents**
- **b. The use of Liquid sterilizing agents**

Heat Sterilization

Heat sterilization is the most widely used and reliable method of sterilization.

The process is more effective in a hydrated state where under conditions of high humidity, hydrolysis and denaturation occur, thus lower heat input is required. Under the dry state, oxidative changes take place, and higher heat input is required.

💣This method of sterilization can be applied only to the thermostable products.

Dry Heat Sterilization

It employs higher temperatures in the range of 160-180^{0}C and requires exposures time up to 2 hours, depending upon the temperature employed.

The benefit of dry heat includes good penetrability and non-corrosive nature which makes it applicable for sterilizing glasswares and metal surgical instruments.

It is also used for sterilizing non-aqueous thermostable liquids and thermostable powders.

Examples of dry heat sterilization are:

1. **Incineration**
2. **Red heat**
3. **Flaming**
4. **Hot air oven**

Hot-air oven

Dry heat sterilization is usually carried out in a hot air oven, which consists of the following:

i)An insulated chamber surrounded by an outer case containing electric heaters.
ii) A fan
iii) Shelves
iv) Thermocouples
v) Temperature sensor
vi) Door locking controls.

Operation

i) Articles to be sterilized are first wrapped or enclosed in containers of cardboard, paper or aluminum.
ii) Then, the materials are arranged to ensure uninterrupted air flow.
iii) Oven may be pre-heated for materials with poor heat conductivity.
iv) The temperature is allowed to fall to 40^0C, prior to removal of sterilized material.

Moist Heat Sterilization

Moist heat may be used in three forms to achieve microbial inactivation.

1. Dry saturated steam – Autoclaving
2. Boiling water/ steam at atmospheric pressure
3. Hot water below boiling point

- **Moist heat sterilization involves the use of steam in the range of 121-134^{0}C.**
- **Steam under pressure is used to generate high temperature needed for sterilization.**
- **Saturated steam acts as an effective sterilizing agent.**
- **Steam for sterilization can be either wet saturated steam (containing entrained water droplets) or dry saturated steam (no entrained water droplets).**

Autoclaves use pressurized steam to destroy microorganisms, and are the most dependable systems available for the decontamination of laboratory waste and the sterilization of laboratory glassware, media, and reagents.

Autoclaves should be tested periodically with biological indicators like cultures of *Bacillus stearothermophilus* to ensure proper function.

This method of sterilization works well for many metal and glass items but is not acceptable for rubber, plastics, and equipment that would be damaged by high temperatures.

Autoclaves, or steam sterilizers essentially consist of following:

i) A cylindrical or rectangular chamber, with capacities ranging from 400 to 800 liters.
ii) Water heating system or steam generating system
iii) Steam outlet and inlet valves
iv) Single or double doors with locking mechanism.
v) Thermometer or temperature gauge
vi) Pressure gauges

Operation

For porous loads (dressings) sterilizers are generally operated at a minimum temperature of 134^0C, and for bottled fluid, sterilizers employing a minimum temperature of 121^0C are used.

Gaseous Sterilization

The chemically reactive gases such as formaldehyde and ethylene oxide possess biocidal activity.

Ethylene oxide is a colorless, odorless, and flammable gas.

- **The mechanism of antimicrobial action of the two gases is assumed to be through alkylations of sulphydryl, amino, hydroxyl and carboxyl groups on proteins and amino groups of nucleic acids.**

- **The concentration ranges (weight of gas per unit chamber volume) are usually in range of 800-1200 mg/L for ethylene oxide and 15-100 mg/L for formaldehyde with operating temperatures of 45-63°C and 70-75°C respectively.**

Liquid Sterilization

Hydrogen Peroxide Sterilization

This method disperses a hydrogen peroxide solution in a vacuum chamber, creating a plasma cloud. This agent sterilizes by oxidizing key cellular components, which inactivates the microorganisms.

Radiation Sterilization

Many types of radiation are used for sterilization like electromagnetic radiation (e.g. gamma rays and UV light) and particulate radiation (e.g. accelerated electrons).

The major target for these radiation is microbial DNA. Gamma rays and electrons cause ionization and free radical production while UV light causes excitation.

Radiation sterilization is generally applied to articles in the dry state; including surgical instruments, sutures, prostheses, unit dose ointments, plastic syringes and dry pharmaceutical products.

UV light, with its much lower energy, and poor penetrability finds uses in the sterilization of air, for surface sterilization of aseptic work areas, for treatment of manufacturing grade water, but is not suitable for sterilization of pharmaceutical dosage forms.

Gamma ray Sterilizer

Gamma rays for sterilization are usually derived from Cobalt-60 source.

Gamma-ray irradiation at doses of ≥15 kGy was required for effective sterilization as evidenced by complete eradication of gram positive and negative bacteria.

Ultraviolet Irradiation

The optimum wavelength for UV sterilization is 260 nm.

A mercury lamp giving peak emission at 254 nm is the suitable source of UV light in this region.