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5. Parenteral Product

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Abbreviations:

LVP - Large volume Parenteral

SVP - Small volume Parenteral

P - Partition coefficient

HEPA - High- efficiency Particulate Air

LAL Test - Limulus Amoebocytes Lysate test

BET - Bacterial Endotoxin Test

IPC - In-Process Control

WFI - Water for Injection

RH - Relative Humidity

FTM - Fluid Thioglycolate Medium

SCM - Soyabean-casein digest Medium

Objectives:

This chapter provides an overview of the development of injectable (parenteral) drug products. Injectable drug products are relatively specialized and diverse, depending on both the location and type of disease to be treated in a patient.

Developing an optimized formulation around a certain type of product will determine not only whether or not the drug will be effective for its intended use, but also if it will be stable for an extended period of time.

Pre-formulation studies. are used to both determine the physical properties of a drug molecule of interest and understand the conditions where the drug is stable.

Formulation development studies achieve those optimal conditions through either the use of additives or the manner in which the drug is processed. Additionally, since the body's natural defences are bypassed when injecting this type of drug product, special care must be taken to ensure that micro-organisms and other extraneous materials are not present.

After completing this chapter, the student will be able to:

define the different types of injectable (parenteral) drug products.

understand the different specifications required for injectable drug products.

understand the process of developing an optimized formulation in a laboratory.

understand the process of transferring and scaling up the new formulation to a large- scale manufacturing environment.

5.1 Introduction to Parenteral Product:

A. Definition: Parenteral

The term Parenteral has been derived from the Greek word **Para enteron,** which means **outside the intestine.** These are unique dosage forms as they are administered by injecting directly into the body tissues through skin and mucous membranes, which form the primary protective systems of the body. Thus, parenteral preparations (par + enteral) as the name suggests are administered from other than enteral routes (i.e., oesophagus, stomach, intestines are by passed by the parenteral drugs). Parenteral products are sterile preparations containing one or more active ingredients intended for administration by injection, infusion or implantation into the body. They are packaged in either single-dose or multi dose containers.

B. Ideal properties of parenteral product:

The parenteral products should be **pure** and should not be contaminated with agents of physical, chemical, and biological origin.

To meet these requirements, the pharmaceutical industries manufacturing parenteral dosage forms should practice the **current Good Manufacturing Practices (cGMPs).**

The pharmacists and other health care professionals while dispensing parenteral dosage forms to patients should also practice **Good Aseptic Practices (GAPs).**

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.

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.

5.1.1 Types of Parenteral Products:

The types of Parenteral products are **based on Volume** and the **state of product** according to USP.

A. Based on Volume:

- **SVP** – An injection that is packed in containers labeled as containing **100 ml or less.**
- **LVP** – These are parenterally designed to provide fluid, calories and electrolytes to the body and the volume is **more than 100ml.**

B. Based on States of products:

a. Transfusion Fluids:

These are parenteral solutions administered by intravenous route.
Some examples are **sodium chloride, Ringer's solution, and dextrose.**

b. Solutions or Emulsions of Medicaments for Injections:

These are used as injections and available in single dose or multiple dose containers.
Some examples are **diclofenac sodium and dexamethasone.**

c. Powder for Injections: These are sterile solid preparations distributed in their final volume when the vial or container is shaken to form a clear particle -free solution.

d. Lyophilised Powders for Injections:

These dosage forms during administration are converted into solutions or suspensions after reconstitution.

An example is **ceftriaxone injection.**

e. Colloidal Solutions:

These are homogeneous solutions in which the particles are dispersed in the liquid phase. These are normal solutions of sodium chloride (0.9% w/v concentration, i.e., close to the concentration in blood).

An example is **iron dextran.**

f. Concentrated Solutions for Injections:

These solutions are diluted with water for injection before administering through injection or intravenous infusion**.**

g. Injectable Emulsions:

These are liquid preparations in which the drug substances are dissolved or dispersed in a suitable emulsion medium. Injectable lipid emulsions provide essential fatty acids and vitamins, thus have been used since ages as a source of energy for hospitalized patients.

Nowadays they are administered intravenously for delivering lipid-soluble therapeutic agents due to the biocompatible nature of the lipid-based delivery systems.

An example is **propofol** US.

h. Injectable Suspensions:

These are liquid preparations in which the solids are suspended in a liquid medium. They are used as sustained or controlled release parenteral dosage forms for prolonging the drug action. On subcutaneous or intramuscular administration, they provide prolonged action compared to the aqueous solutions.

An example is **methylprednisolone acetate.**

i. Oily Injections:

These are used to prepare parenteral controlled release dosage forms. The drug release in oily injections is controlled by the drug partitioning into the aqueous medium from the oil medium.

An example is **dimercaprol injection.**

j. Implants:

These are sterile solids implanted in the tissues to release the active ingredient for prolong periods. They are stored in individual sterile containers.

k. Sterile Solids:

These preparations are dry sterile solids dissolved in a solvent and then administered in the body. They are available in dry solid forms as the drugs lose their stability in solution forms.

An example is **benzylpenicillin G sodium injection.**

5.1.2 Parenteral Preparations Are Further Categorized into The Following Types as Per Their Dosing:

a. Single-Dose Preparations: These preparations can be used once. They contain sufficient quantity of the injection which permits easy drawing and administration of the volume specified on the label.

b. Multi-Dose Preparations: These preparations contain an antimicrobial preservative in appropriate concentrations; however, the formulations already exhibiting antimicrobial properties are not added with preservatives. They are meant for multiple dosing; thus, the chance of contamination increases after partial withdrawal. Therefore, the containers should be equipped adequately to ensure protection of the contents that should not exceed 30ml (as the contamination risk is high with multiple penetrations of closures).

A. Advantages of parenteral formulations:

a. On intravenous administration, an immediate physiological response is achieved, which is important in acute medical conditions,
   e.g., cardiac arrest, anaphylactic shock, asthma, hyperglycaemia, hypoglycaemia, etc.
b. They are essential for drugs with poor bioavailability or that degrade rapidly within the gastrointestinal tract.
   (e.g., insulin and other peptides).
c. They can be administered to unconscious or uncooperative patients or to the patients with nausea and vomiting.
d. They are administered by trained medical staff; thus, the dosage and frequency of administration are both controlled.
e. They may give rise to local effects.
   e.g., local anaesthesia.
f. They are also used to correct the electrolyte imbalances (using infusion solutions).
g. They may be readily formulated to offer a wide range of drug release profiles, including:
   - Rapidly acting formulations (intravenously administered drug solutions), and
   - Long-acting formulations (intramuscularly or subcutaneously administered drug suspensions or solutions in which the drug is precipitated out of solution at the injection site). Intermediate/long -acting insulin formulations and steroid injections are the examples of such formulations.

h. specially formulated solutions are infused to provide total parenteral nutrition to the patients who cannot consume food.
i. Parenteral products can by passes pre systemic or first pass metabolism and the Onset of action is quick.

j. The drugs, which cannot be administered orally, can be administered by this route. c
k. The drug action can be prolonged by modifying the formulation.
l. This route can deliver transfusion fluids containing nutritive like glucose and electrolytes such as sodium chloride.

B. Disadvantages of parenteral formulations:

Pain on injection
Difficult to reverse an administered drug's effect.
Sensitivity or allergic reaction at the site of injection.
Requires strict control of sterility & non- pyrogenicity than other formulation.
Trained person is required.
Require specialized equipment, devices, and techniques to prepare and administer drugs.
More expensive and costly to produce.

C. Limitations of **parenteral formulations**:

a. Their manufacturing process requires aseptic techniques, thus is complicated than other formulations.
b. Highly trained staff and special equipment are required for manufacturing parenteral formulations to achieve the finished product specifications.
c. The staff should be skilled to ensure adequate administration of the dosage form via proper route. For example, if a parenteral suspension (to be administered intramuscularly or subcutaneously) is administered intravenously, a pulmonary micro-capillary blockage occurs in the blood flow at that site.
d. Parenteral formulations give rise to pain at the time of administration.
e. They result in rapid and intense allergic reactions if the patient is allergic to the formulation being administered.
f. The effects of drugs administered parenterally cannot be reversed even immediately after administration.
g. Injection causes pain at the site of injection.
h. The trained persons are required to administer the drug.
i. It is difficult to save a patient when overdose is given.
j. There are chances of sensitivity reaction or allergic reaction of a drug by an individual. These reactions are sometimes fatal and lead to death.

5.2 Pre-Formulation Factors and Essential Requirements /Aspect:

Pre-formulation involves studying the physical and chemical properties of drug prior to formulation.

It is related to analytical and pharmaceutical investigations supporting the efforts of formulation development for all dosage forms.

Pre -formulation studies are performed under stressed condition s of temperature, humidity, light, and oxygen so that the reactions are accelerated, and potential reactions can be detected.

A few **physicochemical properties/ preformulation factors** that affect a drug substance are discussed below:

A. Colour: It is a property of inherent chemical structure of drug and indicates the intensity or level of unsaturation. The intensity of colour depends on the extent of conjugated unsaturation, and also on the presence of chromophores **(e.g., –CO, –NO2, and –NH2).** Some saturated compounds have minute trace s of highly unsaturated, intensely coloured impurities and/or degradation products, and thus exhibit colour. These compounds under highly stressed conditions of heat, light, and oxygen produce colour. A significant colour change in a parenteral product becomes a limiting factor to its shelf-life even before a significant change in chemical stability is noted.

B. Odour: This property of a new drug substance is examined by smelling the headspace of the drug container previously closed to allow concentration of volatiles. The presence and description of any odour is recorded.

C. Molecular Structure and Weight: These are the basic characteristics of the drug from which the potential properties and reactivities of functional groups can be determined.

D. Particle Size and Shape: These characteristics are determined by microscopic evaluation using a scanning electron microscope or an optical microscope with polarising attachments. The morphological characteristics of the drug substances should be recorded by a sketch or by a photomicrograph (as a permanent record) so that they can be compared with the future batches. A polarising microscope is used to determine whether the drug is crystalline or amorphous, as polarised lights are refracted by crystalline materials (and are thus visible when polarisation attachments in the ocular and objectives are crossed at an angle of 90 °) while the amorphous or glassy substances become invisible.

E. Thermal Analytical Profile: The drug samples are heated between ambient temperature and its melting point, thus are exposed to changes in temperature during synthesis and isolation which may be exhibited as a thermal profile. The samples neither absorb nor emit heat prior to its melting point, if no thermal history exists for the compound. The techniques used for studying this phenomenon is called Differential Thermal Analysis (DTA) that can detect the endothermic transitions like melting (or fusion), boiling, sublimation, and desolvation. Differential Scanning Calorimetry (DSC) is a similar process. Thermo Gravimetric Analysis (TGA) is another thermal analytical method used for detecting the existence and stability of solvated drug molecules.

F. Melting Point: It is the temperature at which the solid and liquid phases are in equilibrium. Its determination is a primary indication of purity as even the presence of small amounts of impurity can be detected by lowering and increasing the melting point range.

G. Hygroscopicity: It is the phenomenon of moisture absorption by compounds under specific conditions of moisture and humidity. A high degree of hygroscopicity can adversely affect the physical and chemical properties of a drug substance, making it pharmaceutically unfit. These studies are conducted by placing tarred containers containing correctly weighed drug samples at different conditions of humidity for up to 14 days. Any gain or loss in weight is detected at pre-determined intervals till equilibrium is reached. The drug is recommended to be stored under dry and low humidity conditions if it is determined to be very hygroscopic or unstable in the presence of moisture.

H. Solubility: This property is essential for developing solutions to be injected either intravenously or intramuscularly. Solubility is a function of chemical structure; salts of acids or bases are the drugs that can achieve the desired degree of water solubility. The analytical method used for measuring solubility can vary according to the drug moiety. If unsaturated conjugation is present in the drug structure, it absorbs visible or UV light, and can be analysed by spectrophotometry. However, the compounds that do not absorb UV or visible light can be analysed by transferring filtered aliquot solutions to previously tarred weighing pans, evaporating the solvent, and drying to a constant weight under low temperature conditions.

I. Optical Activity: It is the phenomenon in which the plane polarised light is rotated by a compound. If the beam of light is rotated to the right or in clockwise direction by an angle, the substance is dextrorotatory and if the compound rotates the beam of light to the left or in anti-clockwise direction, the substance is laevorotatory.

J. Ionisation Constant: This property is used to determine the pH-dependent solubility of a compound. Potentiometric pH titration or pH-solubility analysis is used for determining the pka value. Ionisation constant of a compound also helps in determining the ionisation degree of an acid or base.

K. Partition Coefficient (P): It is the measure of a compound's lipophilicity. It can be determined by measuring the equilibrium concentration of a drug in aqueous and oily phases in contact with each other at a constant temperature.

Partition coefficient can be expressed as: P = [Coil] / [Cwater]

5.2.1 Essential Requirement for Formulation of Parenteral Products

A. Solutes,
B. Vehicles, and
C. Additives.

A. Solutes: Active pharmaceutical ingredients and excipients should be selected such that their quality is best suited for parenteral administration. Low microbial level enhances the effectiveness of either the aseptic or terminal sterilization process used for the preparation. The non - pyrogenic ingredients in the similar manner enhance the non -pyrogenicity of the finished injectable product. It is a common GMP procedure to establish microbial and endotoxin limits on active pharmaceutical ingredients and other excipients Chemical impurities present in the active pharmaceutical ingredients used for parenteral preparations cannot be removed during the processing; thus, they should be non -existent. Even trac e amounts of these impurities may produce harmful effects to the patient or cause stability problems in the product. Therefore, the best grade of chemicals should be used and their analytical profile should be determined by the manufacturers to ensure that each chemical lot used in the formulation fulfils the required standards. Reputable chemical manufacturers follow the strict requirements for quality parenteral products and apply the GMPs to their chemical manufacturing. Examples of critical bulk manufacturing precautions are:

a. Preventing cross -contamination and transfer of impurities by using a suitable equipment or properly validated cleaning method,
b. Washing the equipment with water for injection,

c. Using closed systems for bulk manufacturing steps not followed by purification, and
d. Maintaining the standard endotoxin and bio-burden testing limits for the substance.

B. Vehicles:

Both aqueous and non -aqueous vehicles can be used in the formulation as per the requirement:

a. Aqueous Vehicles: These are of the following types:

i. Water for Injection U.S.P.

- It is the most commonly used solvent in the large -scale manufacturing of injections.
- Its purification is carried by distillation or reverse osmosis, and this water fulfils the standards same as of purified water for the presence of total solids, which is not more than 1mg/100ml of water for injection U.S.P. and may not contain added substances.
- This water if not sterile, should be free from pyrogens.
- It can be used for manufacturing injectable products terminally sterilised after preparation.
- It should be collected in sterile and pyrogen-free containers.
- It should be used within a day of collection.

represents the method by which potable water can be converted into water for injection:

ii. Sterile Water for Injection U.S.P.

- It is packed in single-dose containers of 1 litre capacity.
- It should be free from pyrogens and should have endotoxin in acceptable level, i.e., up to 0.25 U.S.P. endotoxin units per millilitre.
- It should not be present with any antimicrobial agent or other added substance.
- However, its total solids content may be slightly higher than that in water for injection, because during sterilisation of water for injection U.S.P. leaching of solids occurs from the glass-lined tanks.
- It should be used as a vehicle for already sterilised and packed injectables.
- It is used for reconstitution of antibiotics. It is aseptically added to the vial (containing drug) to prepare the desired injection. For example, a suitable injection may be prepared using the sterile dry powder ampicillin sodium U.S.P. by aseptically adding sterile water for injection.

iii. Bacteriostatic Water for Injection U.S.P.

- It is sterile water for injection containing suitable antimicrobial agents.
- It is packed in prefilled syringes or in vials containing up to 30ml of water.
- It should be labelled with the names and proportions of antimicrobial agents present in it.

- Due to the presence of antimicrobial agents, it should be used only in parenteral preparations administered in small volumes.
- It is used in small volume parenteral preparations as a sterile vehicle.
- It should be added with bacteriostatic agents in multiple -dose parenteral preparations. The added bacteriostatic agents should be chemically compatible with the medicinal agent being dissolved or suspended.
- It should be avoided in neonates.

iv. Sodium Chloride Injection U.S.P.

- It is a sterile isotonic solution of sodium chloride in water for injection.
- It has no antimicrobial agents but contains 154mEq each of sodium and chloride ions per litre.
- It is used as a sterile vehicle in solutions or suspensions of drugs intended for parenteral administration.
- It is often used as a catheter or intravenous line flush for infusing fluids and intravenous medications and for drawing blood for laboratory analysis. About 2ml is generally used to flush the line after each use or after every 8 hours if the line is not used.

v. Bacteriostatic Sodium Chloride Injection U.S.P.

- It is a sterile isotonic solution of sodium chloride in water for injection.
- It should be labelled with the names of antimicrobial agents present in it.
- Sodium chloride present in 0.9% concentration makes the solution isotonic.
- While using this isotonic solution as a vehicle, it should be made sure that the drug is compatible with the preservative and sodium chloride.
- It is also used to flush a catheter or intravenous line in order to maintain its potency.
- It should be avoided in neonates.

vi. Ringer's Injection U.S.P.

- It is a sterile solution of sodium chloride, potassium chlor ide, and calcium chloride in water for injection.
- The concentration of sodium chloride, potassium chloride, and calcium chloride is similar to those of physiologic fluids.
- This injection is either used as a vehicle for other drugs or alone as an electrolyte replenisher and plasma volume expander.
- Lactated Ringer's injection U.S.P. is a sterile solution of sodium chloride, potassium chloride, calcium chloride, and sodium lactate in water for injection.
- It is used as a fluid and electrolyte replenisher and as a systemic alkaliser.

b. Non-Aqueous Vehicles: An aqueous vehicle cannot be used for an injection, if the added drug has limited water solubility or is prone to hydrolysis. Due to these physical or chemical factors, aqueous vehicles are used limitedly, and non-aqueous vehicles are the only alternative.

The non -aqueous vehicles ideally should possess the following features:

i. They should be non-irritating.
ii. They should be non-toxic.
iii. They should be pharmacologically inert.
iv. They should fluidise over a wide range of temperature.
v. They should be non-sensitising.
vi. They should metabolise easily.
vii. They should be less viscous to allow syringability.
viii. They should have a high boiling point to permit heat sterilisation.

The examples of commonly used non -aqueous vehicles are **fixed oils or vegetable oils (like corn, olive, peanuts, soybean, cotton seed, sesame. Ethyl oleate, isopropyl myristate, benzyl benzoate, and dimethylacetamide** are some other non-aqueous vehicles used occasionally. Non-aqueous vehicles are also used for **steroidal hormones and oil - soluble vitamins.** The use of mineral oil is avoided as it cannot metabolise in the body.

c. Additives:

The following high-quality solutes should be used in the formulation of parenteral products:

- **Medicaments:** These are the active ingredients and are sterilised before adding to the formulations.
- **Additives:** The following additives are added to increase the utility and stability of parenteral products:

i. Solubilisers: These are added to maintain the solubility of slightly soluble drugs by increasing their solubility. Dimethylacetamide, ethyl alcohol, polysorbates (20, 40, and 80), lecithin, PEG 300, PEG 40, and castor oil are the examples of commonly used solubilisers.

ii. Antioxidants: Many drugs in solution degrade by oxidation reactions (addition of oxygen or removal of hydrogen) mediated by free radicals or molecular oxygen. Metal, hydrogen, and hydroxyl ions catalyse such oxidative decomposition. Drugs with a favourable oxidation potential are more susceptible to oxidation.

For example, drugs like epinephrine, morphine, ascorbic acid, menadione, etc. are formulated in their reduced form and get easily oxidised. Oxidation can be minimised by increasing the drug's oxidation potential. Salts of sulphur dioxide (such as bisulfite, metabisulfite, and sulphite) are most commonly used as antioxidants in aqueous parenteral. They keep the product stable by getting oxidised and gradually get consumed through its shelf -life. Some common examples of antioxidants are given in below.

E.g. Sodium bisulfide, Ascorbic acid.

iii. Chelating Agents: These agents form complexes with the metal ion and dissolve in the solvent, thus preventing the metal ions from interfering in the manufacturing process. Some common examples of chelating are given below.

Eg. Disodium edetate, EDTA

iv. Buffers: These are added to maintain the formulation pH, as a change in pH results in product degradation. Either a weak base and its salt or a weak acid and its salt are used as a buffer in parenterals. Some common examples of buffers.

E.g. Citric acid, Sodium citrate

v. Stabilisers: These are added to formulations which can undergo rapid oxidation. Some common examples of stabilisers.

Eg. Sodium metabisulphite

vi. Surfactants: These are used for disposing a water-insoluble drug as a colloidal dispersion, for wetting powder, for preventing crystal growth in a suspension, for providing acceptable syring Sability, and for solubilising steroids and fat - soluble vitamins. Some common examples of surfactants.

E.g. Sodium lauryl sulphate (SLS), Polyethylene, Sorbiton

vii) Preservatives: These are included in the formulation to maintain the sterility of solution when a multiple dose package is used. Some common examples of preservatives.

E.g. Methyl Paraben, Propyl Paraben

viii. Tonicity Adjusting Agents: These are used to ease parenteral administration by reducing pain or tissue irritation. Some common examples of tonicity adjusting.

E.g. Sodium sulfate

C. Importance of Isotonicity:

Isotonicity is important for parenteral formulations because if the solution is isotonic with blood, the possibility of the product penetrating the RBCs and causing haemolysis is reduced.

Solution having less osmotic pressure than the blood plasma is hypotonic and solution having more osmotic pressure than the blood plasma is hypertonic. In hypotonic solution, water diffuses into the RBCs causing them to swell and finally burst, i.e., haemolysis. In hypertonic solution, water diffuses out of the RBCs causing them to shrink. In isotonic solution (e.g., 0.9% sodium chloride), the RBCs maintain their tonicity.

Production Procedure – Aseptic Processing The general procedure for manufacturing parenterally include planning and scheduling of equipment's, material managements, and manufacturing requirements like ingredients, drugs, etc. An overview of the manufacturing process of parenterally is shown in figure.

The parenteral drug manufacturing (Drug Product Manufacturing) process includes compounding, mixing, filtration, filling, terminal sterilization, lyophilization, closing, and sealing, sorting, and inspection, labelling, and final packaging for distribution.

The manufacturing process is complicated; requiring organization and control to ensure the product meets the quality and the specifications as shown in.

Aseptic processing requirement adds more complication but assures that all dosage forms manufactured are free from any contamination of microbial, endotoxin, and visible particulate matter. The manufacturing process initiates with the procurement of approved raw materials (drug, excipients, vehicles, etc.) and primary packaging materials (containers, closures, etc.) and ends with the sterile product sealed in its dispensing package.

5.3 Overview of Manufacturing Process of Parenterals:

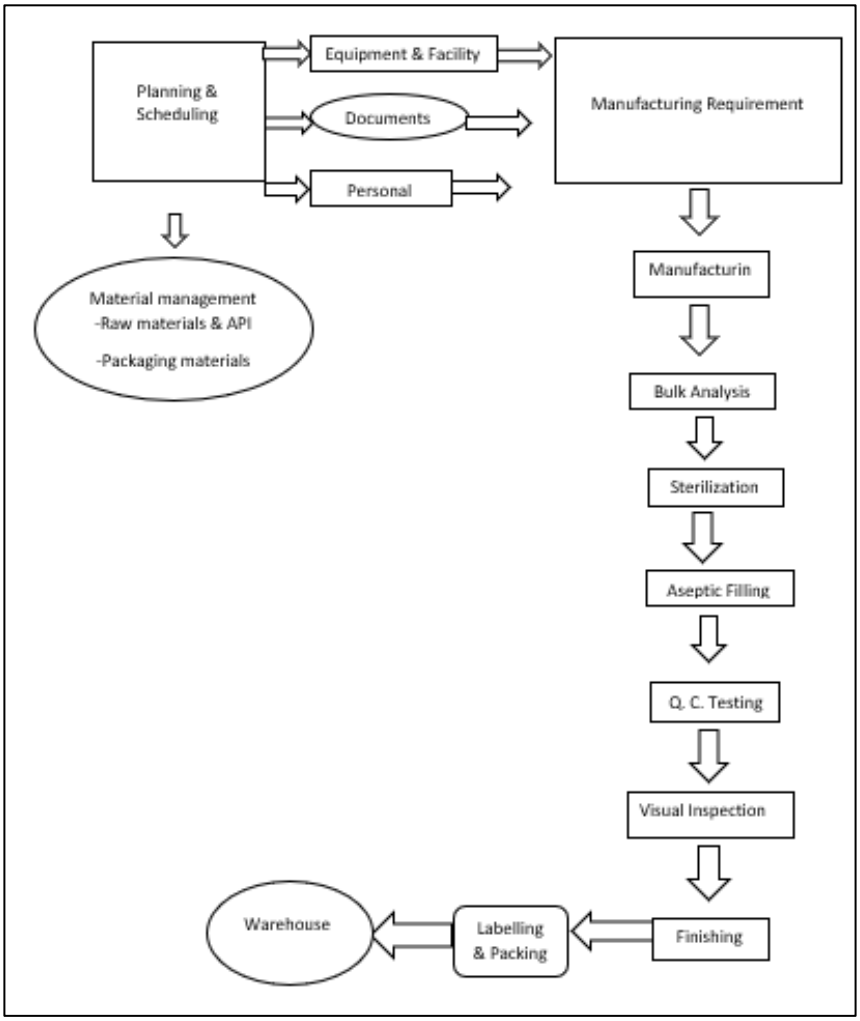

Figure 5.1: Manufacturing Process of Parenterals

The manufacturing of parenteral involves the following steps:

A. Cleaning and washing of containers and closures,
B. Preparation of solutions,
C. Sterilisation,
D. Filling and sealing, and
E. Packaging and labelling.

A. Cleaning and Washing of Containers and Closures:

The vials are soaked in detergent solution overnight. This removes any sticking particles, grease, etc. from them. Then the vials are washed three to four times with tap water to remove the soap solution. Th e vials are washed with 1.0% hydrochloric acid and then again with tap water to remove surface alkalinity. The vials are finally rinsed with de - ionised water followed with distilled water and sterilised for 4 hours at 200°C temperature. Rubber closures are boiled with 1.0% detergent solution for 30 minutes followed by washing with tap water to remove the detergent. Then they are again boiled for 30 minutes with 1.0% hydrochloric acid solution and washed with tap water. Then they are boiled with 1.0% sodium carbonate and again washed. Thereafter the closures are treated with a bacteriostatic solution, washed three to four times with pyrogen free water, and sterilised by autoclaving for 30 minutes at 115°C temperature.

All the containers, closures and equipment's which are required during the preparation of parental products are thoroughly cleaned with detergent and washing is done with tap water, followed by clean distilled water and finally rinsed with water for injection. Rubber closures are washed with hot solution of 0.5 % sodium pyrophosphate in water. The closures are then removed from the solution, washed with water followed by rinsing with filtered water for injection. on a small-scale washing is done manually but on a large-scale automatic washing machines are used.

B. Preparation of Solution:

The active pharmaceutical ingredient is completely dissolved in water for injection with constant stirring. Then the other excipients are added one at a time with stirring to make them dissolve. The desired pH is adjusted by using buffering agents like sodium hydroxide and hydrochloric acid. The volume is made up with water for injection, and the pH is re-adjusted if required.

The various ingredients of the formulation of parental preparations are weighed and collected in the preparation room. the raw materials required in the preparation of parenteral products should be pure. water for injection free from pyrogens and microorganisms are used in preparation of parenteral products. The Industrial pharmacist should decide the order of mixing and exact method of preparation to be followed before preparing the parenteral products. The parenteral preparation must be prepared under strict aseptic conditions. The ingredients are accurately weighed separately and dissolved in the vehicle as per method of preparation to be followed. The parenteral Solutions so formed is passed through bacteria proof filter, such as, filter candle, Seitz filter, membrane filter, and sintered glass filters. the

primary objective of filtration is to clarify the solution by removing foreign particles. if the parenteral preparations are required to be sterilized by means of bacteria proof filters, filtration should be done under strict aseptic condition to avoid contamination of filtered solution, before it is finally transferred into final container and sealed.

C. Sterilisation Parenteral products:

Except those containing thermolabile substances, after being filled and sealed in the final containers are sterilised, and this process is termed terminal sterilisation. so for sterilising thermolabile products, non -thermal methods are used. These methods involve filtration through bacteria -proof filters. In some thermolabile preparations (e.g., colloids, oleaginous solutions, suspensions, and emulsions), each component is sterilised separately, and the product is formulated and processed aseptically. Sterilisation by radiation is a non -thermal method. Dry solids (e.g., penicillin, streptomycin, polyvitamins, and som e hormones) are effectively sterilised by ionised radiations. Gaseous sterilisation is not preferred when a glass container or other impermeable barrier may prevent the permeation of gas into the material. Dry heat sterilisation also has limited application as the materials being sterilised should not get affected by the elevated temperatures. Another method of sterilisation is lyophilisation (also known as freeze drying). Autoclaving involves pressurised steam which is the most useful and the most effective sterilisation method for aqueous liquids or substances through which steam can easily penetrate. This method is however not effective under anhydrous conditions, e.g., a sealed ampoule containing an anhydrous oil or a dry solid. To prevent the contamination following sterilisation, materials which have been autoclaved are covered; however, this is not required in parenteral solutions as they are already sealed. The effectiveness of a sterilisation method should be verified on a routine basis using biological indicators.

D. Filling and Sealing of Ampoules:

The steps given below are followed to fill the ampoules manually:

a. A little more than 1.1ml of the drug solution is gently drawn into the syringe to avoid large numbers of air bubbles in the liquid.
b. The syringe is inverted so that the air rises towards the needle, and then the plunger is pushed up to expel the bubble and leave 1.1ml in the barrel.
c. The needle is wiped with a cellulose film disc, unlike filter paper or a cloth, so that no fibres are left on the needle.
d. The ampoule is inverted over the needle. Since the needle surface is dry, no liquid will be put on the ampoule neck. If the ampoule is held straight and the syringe is reverted for filling, the weight of the plunger may force a drop of solution from the needle tip, thus contaminating the neck.
e. Once the ampoule is settled over the needle, both (the ampoule and the syringe) are reverted together and the liquid is gently expelled to prevent splashing into the neck.
f. Finally, the needle tip is touched against the constriction at the bottom of the neck to dislodge the last drop of liquid and then the needle is withdrawn without touching the neck. After filling the ampoules, they should be immediately sealed to prevent the contamination of contents. They are sealed by melting a portion of the glass neck.

The following two types of seals are employed:

i. Tip- or Bead -Seals:

This type of seals is made by melting glass using a high - temperature gas-oxygen flame at the tip of the ampoule neck to form a bead that closes the opening. A uniform bead can be produced if the ampoule neck is heated uniformly on all sides either by using burners on opposite sides of stationary ampoules or by rotating the ampoule over a single flame.

The flame temperature and the interval of heating to completely close the opening with a glass bead should be carefully determined. Excessive heating will lead to expansion of gases within the ampoule against the soft bead seal and formation of a bubble. If this bubble bursts, the ampoule is no more sealed; and if it does not, the wall of the bubble will be thin and fragile. On the other hand, insufficient heating will leave an open capillary through the center of the bead. An ampoule that is incompletely sealed is called a leaker.

ii. Pull-Seals:

This type of seals is made by heating the ampoule neck below the tip. By holding the tip with forceps or other mechanical devices, the ampoule is rotated over the flame from a single burner. When the glass softens, the tip is grasped firmly and pulled away from the ampoule body while rotating it continually. The small capillary tube so formed is twisted closed. Pull -sealing is a slow process than tip -sealing, but surer.

Pull-sealing is suitable for powder ampoules or other types having a wide opening. If the ampoule necks become wet during filling, they fracture at the time of sealing. Wet ampoule necks also increase the frequency of bubble formation and carbon deposition in case of organic product. Product decomposition in an ampoule can be prevented by displacing the air in the space above the product.

This is done by introducing a stream of inert gas (such as nitrogen or carbon dioxide) during or after filling. Immediately after filling the ampoule is sealed so that the gas does not diffuse out. This process should be validated to ensure adequate displacement of air by the gas in each container. The parental preparations should be immediately sterilized after sealing in its final containers. The sterilization is done by any one of the methods of sterilization, which depends on the nature of Medicaments present in the parenteral preparations.

For thermostable medicament, the parenteral product is sterilised either by autoclaving at the temperature of 115°C to 116°C for 30 minutes or 121 degrees centigrade for 20 minutes or in hot air oven at 160 degrees centigrade for 2 hours. the thermolabile preparations are sterilized by filtration through a suitable bacteria proof filter. parenteral preparations which are sterilised by filtration method may contain a suitable bacteriostatic agent to prevent the growth of microorganisms. When the solutions are used for intravenous or intrathecal injection in doses exceeding 15 ml, the bacteriostatic agent should not be used. The sterilised product is filled into the final containers and sealed. the process of filtration, filling and sealing are done under aseptic conditions.

E. Filling and Sealing of Vials:

The filling procedure for glass vials is the same as that for ampoules. In vials containing a fixed number of dose units, an excess volume is required to allow the withdrawal of specified number of doses. The vial openings are sealed with rubber closures held in place by an aluminium sealing. A hand crimper is used to put the rubber closures and aluminium sealing onto the vials. The vials are more at risk of contamination since their openings are larger than those of ampoules. Thus, the rubber closures should be sealed on the vials immediately after filling. During the critical exposure time, the open containers should be protected from contamination using a blanket of HEPA-filtered laminar airflow. The rubber closure should tightly fit the vial mouth so that its elasticity will seal rigid to slight irregularities in the vial lip and neck. However, the closure should not fit so tightly that it cannot be introduced into the vial neck. Closures are inserted mechanically via automated process, especially with high -speed processing. By halogenating or treating the closure sur faces with silicone, friction is reduced enabling the closure to slide easily through a chute and into the container opening. The closure is positioned at the insertion site and pushed mechanically into the container opening. In case of small batches, the vials are stoppered manually with forceps; however, manual process poses greater risk of contamination than automated process.

The filtered product is filled into final container such as, ampoules, vials and transfusion bottles, which are previously cleaned and dried. ampoules are used for feeling single dose whereas, vials are used for filling multidose. Bottles are meant for filling transfusion fluids. On small scale feeling is done manually by using hypodermic syringe and needle. on the large-scale feeling is done by automatic filling machine. The sterile Powders are filled into containers by individual weighing or by using automatic or semiautomatic devices. The filling operation is carried out under strict aseptic precautions. During the filling of ampoules, the care should be taken that the solution should be filled below the neck of ampoules and the solution should not touch the neck of ampoules. this will prevent the cracking and staining of the neck of ampoules at the time of Sealing. Sealing should be done immediately after filling. Ampoules are sealed manually on a small scale by rotating the neck of the ampoule in the flame of Bunsen burner but on a large-scale ampoule sealing machine is used in which tip of ampoule is used to fused to seal it. The vials and transfusion bottles are sealed by closing its opening with rubber closures. The rubber closures are held in place by crimping the aluminium caps which is done manually or by mechanical means.

Container-closure integrity testing measures the sealability between the glass or plastic container opening and the rubber closure to remain tight and fit and to resist any microbial contamination throughout the product shelf-life. Rubber closures are positioned over the vial openings with tamper -proof aluminium caps. They cover the closure and are crimped under the vial lip to hold them in place. A closure can be removed only by destroying the aluminium cap; therefore, an intact aluminium cap is a proof that the closure has not been removed intentionally or unintentionally. This confirmation ensures the integrity of the contents with respect to sterility and other aspects of quality. The outer layer of double-layered aluminium caps or the centre of single-layered caps can be removed to expose the centre of the rubber closure without disturbing the band that holds the closure in the container. Rubber closures used in intravenous administration sets have a permanent hole. In such cases, a thin rubber disk overlayed with a solid aluminium disk is placed between

the inner and outer aluminium cap, providing a seal of the hole through the closure. Single-layered aluminium caps are applied using a hand crimper, known as Fermpress. Double- or triple-layered caps are applied using heavy-duty mechanical crimpers.

5.4 Filling of Infusion Fluids:

Parenteral solutions are prepared in an asepsis room or a laminar flow cabinet to reduce the possibility of contamination with particulate matter, to reduce the number of microorganisms in the preparation, and to increase the safety factor in the sterilisation process. A 500ml infusion bottle is considered suitable for preparation of parenteral solutions. It is assumed that the bottle has been stored with a double cap protecting the mouth. The outer cap is discarded, and the inner cap is removed. After ensuring that the bottle neck is not chipped, the solution is poured in and immediately the inner cap is replaced.

Using a forceps, a plug -type closure is removed from its storage container. The cap is lifted from the bottle and the plug is pushed into the neck carefully without touching the part that goes into the bottle. A ring -type metal cap obtained from its storage tin is tightly screwed on the bottle after inspecting it to be free from deformities. The plug or liner stored in sterile water should be washed with filtered solvent prior to use because the particles may separate, cling to the closure and later contaminate the injection.

A. Evaluation of Parenterals:

The finished parenteral products are subjected to the following test, in order to maintain quality control.

a. Sterility test
b. clarity test
c. Leakage test
d. d)Pyrogen test.

B. Packaging and Labelling - Containers and Closures Selection:

Parenteral formulations are packed in containers of glass or plastic. Container systems meant for packaging of parenteral products include ampoules, vials, syringes, cartridges, bottles, and bags. Ampoules are made up of glass and bags are made up of plastic.

The other containers are either made up of glass or plastic and should have rubber materials, like rubber stoppers for vials and bottles and rubber plungers and rubber seals for syringes and cartridges.

For example, irrigation solutions are packed in glass bottles having aluminium screw caps. Glass is widely used as a container material for parenteral pro ducts. These containers are sealed or closed with rubber stoppers. Type I glass containers are used for aqueous preparations. Interaction of the product with glass surface can be prevented by the process of siliconization, in which a thin film of silicone is applied to coat the inside surface of the

vials and ampoules. The process minimises adsorption of active ingredients from homogeneous solutions, prevents adsorption of solids from suspensions, and prevents aggregation at the glass surface in colloidal preparations. Plastics used for packaging parenteral products are polyethylene or polypropylene. Use of plastic containers is limited than that of glass containers, but the former is being used increasingly for intravenous fluids. The polypropylene container can be sterilised by autoclaving. Many plastics allow selective passage of chemical molecules and are permeable to gases. Plastics are widely used for containers of administration sets, of disposable type particularly. Rubber is mainly used for closures for multiple -dose vials, intravenous fluids bottles, plugs for disposable syringes, and bulbs for ophthalmic pipettes.

Rubber closures allow the needle of a hypodermic syringe to penetrate the multiple -dose vials and resealing of the vial after withdrawing the needle. An aluminium band is used to keep the rubber closure in place. Some rubber closures are made up of many ingredients and thus its basic structure is a linear unsaturated hydrocarbon, isoprene.

Sometimes a part or the entire natural polymer is replaced with various synthetic rubber polymers. Rubber closures may also include a vulcanising agent (sulphur), an accelerator (2- mercaptobenzothiazole), an activator (zinc oxide), fillers (carbon black or limestone), antioxidants, lubricants, etc. These substances can leach into the product or undergo chemical interaction; this can be minimised by applying lacquer or plastic coating on the surface of the rubber closures in contact with product. Coring (generation of rubber particles, known as cores, from the closures when needles are inserted) is another common problem of rubber closures, which can be minimised by the proper selection and use of gauge needle. The label of an injectable preparation should include all the information necessary for the physician and users to ensure safe and proper use of the product. All the information cannot be put on the container in a readable format, so an add -on printed matter should be supplied.

The word labelling is used to indicate all labels and other written, printed, or graphic matter on an immediate container or on any package or cover in which the product is enclosed. The label should not be put on the outer shipping container.

5.5 Label Comprises of The Following Details:

a. Name of the preparation,
b. Percentage content of the drug in a liquid preparation,
c. Quantity of active ingredient in a dry preparation,
d. Volume of liquid need to be added for preparing an injection or suspension from a dry preparation,
e. Route of administration,
f. Storage conditions,
g. Expiry date,
h. Name of the vehicle and the proportions of each constituent if the product is a mixture,
i. Names and proportions of all substances added for increasing the product stability, and
j. Name of the manufacturer or distributor and an identifying lot number which provides the complete manufacturing history of the package.

The label should be arranged such that adequate area of the container remains uncovered for its full length or circumference for allowing proper examination of the product. The labels prepared for dialysis, haemofiltration, or irrigation solutions should fulfil the requirements for injections, other than those relating to volume. They should also mention that they are not meant for intravenous injection. The injections for veterinary use should also be labelled.

After evaluation of the parenteral preparation, the ampoules, vials and transfusion bottles are properly labelled and packed.

5.5.1 The Label Should State As:

a. Name of the preparation
b. Quantity of the preparation
c. Mfg.Lic .no.
d. Batch no.
e. Date of manufacture
f. Date of expiry
g. Storage condition
h. Retail price
i. Manufacturer's address.

A. Production Facilities and Controls:

The facilities for manufacturing sterile products should be designed to maintain desired cleanliness for each step. Almost perfect cleanliness should be maintained in aseptic filling rooms. The surrounding areas should provide a buffer area with the cleanliness standards slightly lower than those for the aseptic rooms. Prevention of contamination should be the prime aim in the design of these facilities. Such exceptional design and construction standards can be obtained by combining the knowledge of the purpose of the facility with the utilisation of best construction materials. Ceiling, walls, and floors should be constructed with easily cleanable and non - porous materials, so that accumulation of debris and moisture can be prevented. One of the best finishes for rigid surfaces is the spray-on-tile, which is a ceramic epoxy finish applied on the ceiling and walls by spraying or painting to form a continuous, smooth, seal coating. Although, this epoxy finish can degrade, wear or peel due to the rigorous effects of continuous washing with detergents and disinfectants. Flooring is done with ceramic-plastic cement applied as a thick coat over the rigid floor to form a continuous, sealed surface. Another flooring material which is in use in areas of less heavy traffic is sheet vinyl with heat -welded seams, covered to the side walls and applied by adhesives on underlying surfaces. Movable metal partitions are also used to provide flexibility of room arrangement, but they have seams and joints sealed with much difficult.

Glass is used in partitions to facilitate supervisory view of the operation, and also to provide pleasant, better light ed, and less confining surroundings for the personnel. Lighting fixtures should be recessed and presence of exposed piping or other dirt - collecting surfaces should be avoided. Furniture should be of non -porous, hard-surfaced materials, especially of stainless steel. The walls should have suspended counters.

The equipment which cannot be sterilised or are sterilised with difficulty are kept out of the aseptic areas. If they are to be used in the aseptic area, they should not be taken out and should be expos ed to disinfecting processes continuously. The operating machinery parts when not in use should be enclosed in stainless steel housing. The electrical, gas, water, air ventilation, and other utilities lying in these areas, need proper mechanical servicing. This can be effectively done by providing a floor above, space underneath, or corridor along with the side of production area where all service connections are made available and are properly maintained. This prevents any kind of disruption in production and also contamination of the production area by regulating the operations and personnel. HEPA-filtered laminar airflow is added to the basic design and construction of aseptic area. Commonly, laminar airflow is added to a clean room for better environmental control in a local area, like in workbench enclosure or over a filling line.

B. Personnel:

The personnel working in the production and manufacturing unit of parenteral products should be neat, orderly, and reliable. Their health condition should be good, and they should not have any dermatological infections which might increase the microbial load. If the personnel are suffering from influenza, allergies, or similar illness, their entry should be restricted in the aseptic area until their complete recovery. But healthy personnel with adequate personal hygiene will also shed a large number of viable and non -viable particles from their body surface. This results in continuous problems even when the personnel are present in clean rooms. Proper training and gowning of the personnel can only reduce (and not eliminate) the problem of particle shedding. The operators in an aseptic area should be provided with proper formal training in the principles of aseptic processing and techniques to be used. Also, the acquired knowledge and skills of the personnel should be evaluated to make sure that the training has been effective before they are allowed to involve in the preparation process. Retraining should be given on a regular schedule to enhance the maintenance of the required level of expertise. An effort should be made to make the operators realise their essential role in determining the reliability and safety of the final sterile product. This is especially required for supervisors, who not only understand the r equirements of aseptic procedures but also regulate the full involvement of other employees to fulfil the aseptic requirements.

The uniforms of personnel should be designed such that they restrict the shedding of particles from their body; this prevents he entry of these contaminants into the production environment. The uniforms of personnel working in aseptic areas should be sterile. Whenever the personnel return to the aseptic area or after every break period, fresh, sterile uniforms should be used. In plants where the product is to be sterilised in its final container, this is not required. 180 Industrial Pharmacy-I.Uniforms consist of coveralls, hoods for covering hair, face masks, and Dacron or plastic boots for both men and women. Sterile rubber or latex -free gloves are also worn during aseptic operations, after scrubbing the hands thoroughly with a disinfectant soap. Two pairs of gloves are worn; one at the beginning of the gowning procedure and the other after all other apparel has been put on. Goggles are worn to complete the coverage of all skin areas. Uniforms are mainly of Dacron or Tyvek and are effective barriers to the viable and non -viable particles shedding from the personnel ’s body. The uniforms are lint-free and comfortable. Air showers are sometimes recommended to the personnel before entering the processing area to blow away the loose

lint from the uniforms. Gowning rooms should be designed to improve pre -gowning and gowning procedures by the trained personnel. This ensures continued sterility of the exterior surfaces of the sterile gowning components. A separate exit room should be used for de-gowning.

C. Functional Areas:

There are many functional production areas such as warehousing or procurement, compounding or formulation, material (containers, closures, and equipment) preparation, filtration and sterile receiving, aseptic filling, stoppering, lyophilisation, and packaging, labelling and quarantine. These areas are involved for attaining the aim of manufacturing a sterile product of high quality. Some additional requirements for the aseptic area are designed to provide an uncontaminated environment to which a sterile fluid may be exposed for a short -term while transferring a portion of it from the bulk container to individual -dose containers. Dust, lint, other particles, and microorganisms are found floating in the air, lying on counters or other surfaces, on clothing and body surfaces of personnel, in the respired air of personnel, and accumulated on the floor. Therefore, for reducing the presence of these contaminants, the aseptic area is designed and controlled in such a manner that they are no longer hazardous for the aseptic filling of preparations. For the effective flow of components, the aseptic area should be just adjacent to the support areas. Also, barriers (like sealed walls, manual or automatic doors, airlock, pass - through, ports of various types, or plastic curtains) should be provided to reduce the entry of contaminants in the aseptic area.

D. Flow Plan:

a. Firstly, the flow of parenteral components after release is either from the warehouse to the compounding area (as for the formula ingredients) or to materials support area (as for the containers and equipment).
b. After proper processing in these areas, the components flow into the aseptic area for filling the product in a suitable container.
c. Then, the product passes into the quarantine and packaging area for performing all the required tests.
d. In case the product is to be sterilised in the final container, its flow is interrupted after it leaves the aseptic area for performing sterilisation.
e. After obtaining the tests report, the batch records are reviewed to ensure that the product fulfils the release specifications.
f. Then the product is passed to the finishing area for final release for shipment.
g. Sometimes, changes are observed in this flow plan for fulfilling the needs of an individual product or to follow the existing facilities.
h. The automated operations have larger capacity and can transport the components from one area to another with slight or no handling by operators.

E. Layout of Sterile Products Area:

The sterile product area should be free from microbial contamination. Particles of size not more than 0.5 μm should be present in this area. The particle count should not exceed a total of 100 particles/f t 3. This complete area is divided into clean -up area, preparation area,

aseptic area, quarantine area, and the finishing and packaging area. These areas should be constructed and designed such that they can be effectively cleaned, operations can be carried out efficiently, and also the personnel feel comfortable in the environment. The clean-up area should withstand moisture, steam, and detergents. Inward air leaks and dirt collecting crevices, corners, and projections should not be present in the area so that accumulation of dust and microbes can be prevented. Ceiling and walls should be coated with epoxy and vinyl polymeric continuous film coating materials.

In the preparation area, the formulation is compounded and preparations for filling operations are done (such as assembling equipment). Thus, the controls maintained for this area should be stricter in co mparison to those for clean -up area. Cabinets and counters should be made up of stainless steel and should not have any catch area where dirt can accumulate. The area should also have a sink and a counter space. Ceiling, walls, and floors should be sealed. The aseptic area should have maximum security as it is the major part of processing the sterile products. An ultra -clean environment should be maintained in this area. The ceiling, walls, and floors should be painted with germicidal paint (e.g., Fungi Check). The walls should have glass panels built on it to facilitate visibility and super vision from a non-sterile area. All the fixtures should be buried in the ceiling walls to eliminate ledges, joints, and other locations where dust and dirt may accumulate.

All the counters should be made up of stainless steel and should be hung from walls. All the operating parts of mechanical equipment should be completely sealed within a stainless-steel cabinet. Small-scale operations should be carried out under an aseptic hood. The personnel should enter the aseptic area through an airlock. The personnel should wear sterile dresses, masks, caps, foot -covers, etc. Minimum movement should be undergone in the aseptic area. The air in the aseptic area should be made free from fibres, dust, and microbes by fitting High Efficiency Particulate Air (HEPA) filters. These filters can efficiently remove 99.97% or more of particles up to 0.3μm size. HEPA filters are used in laminar air flow benches in which air moves with uniform velocity along parallel lines with minimum eddies. The air flow is either horizontal or vertical. The minimum effective air velocity is 100±10 ft/minute. Air being the greatest sources of contamination should be clean in sterile product area. It should be made to pass through a pre -filter (of glass wool, cloth, or shredded plastics) to remove large particles. Then it should be passed through an electrostatic precipitator to remove the particles in air (on which an electrical charge is induced), which attract to the oppositely charged plates. This treated air is finally passed through HEPA filters. UV lamps are also installed to produce a disinfectant action on directly irradiated surfaces between the antibacterial UV rays. The aseptic area should be maintained carefully, and the total viable count of bacteria should be routinely determined in sterile product area to make sure the area is free from microbial contaminants.

F. Clean Room Classified Area:

The clean or buffer room is the secondary engineering control. It houses the primary engineering controls (the LAFH, BSC, or CAI) where the aseptic compounding is actually performed. The clean room is a specially constructed enclosed area, which contains one or more clean zones, where the concentration of air borne, particles is controlled using HEPA filters, continuous air circulation, and a physical barrier to non - filtered (or outside) air.

Clean rooms establish appropriate environmental levels for airborne particulates, temperature, humidity, air pressure, and airflow patterns. Clean rooms are categorised by their constant air quality or class. Lower the classification number, cleaner is the air. Clean rooms are divided into different classes.

a. In order to reach the air grades B, C, and D, the number of air changes should be related to the room size, and the equipment and personnel in the room. The air system should be provided with HEPA filters for grades A, B, and C.
b. After 15 -20 minutes of clean -up period, an unmanned state (no manual activity) should be received.
c. Appropriate inert and action limits should be fixed for particulate and microbiological monitoring results. A corrective action in the operating procedures should be taken in case these limits are exceeded. The need for other parameters (like temperature, relative humidity, etc.) depends on the nature of product and manufacturing procedure. These parameters do not have any relation with the purifying classes.

Most products should be prepared in grade.The components after washing should be handled i n grade D environment. The sterile starting material should be handled in grade A environment with grade B background. Solutions to be sterile filtered should be prepared in grade C environment; while if not filtered, the preparation should be done in grad e A environment with grade B background. The aseptically prepared products should be handled and filled in grade A environment with grade B background. The sterile ointments, creams, suspensions, and emulsions should be prepared and filled in grade A environment with grade B background, when the product is exposed and is not subsequently filtered.

i. Individual settle plates are exposed for 4 hours or less; cfu: colony-forming unit. Warning limitation and action for contamination by particles and microbes depend on the controlling results. Also, corrective action should be provided in case of exceeding the above limits.

G. Air Control:

The air should be exchanged at recurrent intervals in areas engaged by personnel. Fresh outside or recycled air should be filtered first for eliminating the gross particulate matter by using a spun glass, cloth, or shredded polyethylene filter. To provide a gradation of particle size removal from highly contaminated air, a series of prefilter is used, in which the first is of larger pore size and the next is of smaller. HEPA filter made up of glass fibres and fillers or electrostatic precipitators is used for removing at least 99.97% particles of 0.3 μm size and larger. Air passing through HEPA filters is made free of foreign matter. Another air cleaning system is used to wash the air with a disinfectant and control humidity simultaneously. Blowers should be installed upstream to the filters in the air ventilation system so that all dirt-producing devices are ahead of the filters. The clean air is disseminated to the specific areas through stainless steel ducts. It is not possible to keep these ducts clean all the time; thus, a HEPA filter is installed at the point from where clean air enters the controlled room. Another alternative is to replace the ducts with a room (a plenum) above the production area into which the clean air is blown and then distributed to all the controlled rooms through the provided openings. Through this, the whole plenum remains clean and aseptic.

The clean, aseptic air flows into the maximum-security rooms at the greatest volume flow rate, and in these areas, a positive pressure is formed. Due to this pressure, the unclean air is prohibited from entering the aseptic area through cracks, temporarily opened doors, or other openings.

H. Environmental Control:

The level of effective physical and biological environmental control somewhat depends on the facility type. The standards for environmental control vary from plant to plant, and also depend on the topographic location, the area involved (clean -up, packaging, compounding, or filling), and the type of product being prepared. Therefore, the standards should be flexible, and seasonal condit ions should also be considered. The area used for manufacturing aseptic products not requiring terminal sterilisation should be maintained under rigid biological control. On the contrary, the compounding and filling areas should be under less rigid biological control if the products are to be terminally sterilised. The standards of cleanliness and daily disinfection for the clean -up and packaging areas should be rigid.

I. Traffic Control:

An effective environmental control can be easily maintained if the personnel and supplies are not moved from one place to another. Therefore, the aseptic areas should be designed in a manner to control and limit traffic. Only the personnel's washrooms, the non -sterile manufacturing area, and the packaging area should have a direct access from the outside. The personnel's access to the aseptic corridor should be through an airlock. Passthrough openings and double-ended sterilisers should be provided for controlled passage of supplies from non-septic to aseptic areas. Personnel should enter the aseptic areas after following rigidly prescribed protocol that includes washing their hands, and removing their street clothing, donning gowns, hats, shoes, facemasks, gloves and other prescribed attire. On entering the aseptic area, the personnel should not move in and out of the area without re - dressing. Personnel assigned for cleaning and packaging should not enter these areas. Unofficial personnel should not enter the aseptic area.

J. Laminar Flow Benches:

The aseptic area environment can be controlled bsssssy using laminar airflow originating from HEPA filter, which occupies one side of the limited space completely. Hence, the total space is rinsed with very clean air to remove all the contaminants. The orientation of the airflow direction can be horizontal (figure 7.5) or vertical (figure 7.6) and occupy either a limited area (like a workbench) or an entire room.

At the present time, this is the only way by which a Class 100 clean room (in which the particle count in the air is not more than 100 per cubic foot of 0.5 μm and larger in size) can be attained. The air coming from HEPA filter is uniformly blown out of the entire back or top of a workbench, or entire side or ceiling of a room. The airflow should have a uniform velocity (100 ± 20ft/min) and direction throughout the given cross -sectional area. Contamination is controlled because it is brushed away with the airflow.

Contaminants entering downstream from the filter can get transferred to working areas beyond the downstream by improper setting of supplies, handling of personnel, or discharge from equipment. The risk of contamination through these situations is less when the air flows vertically from the ceiling-mounted HEPA filters. Thus, vertical flow is often employed to protect critical sections of processing lines and similar actions. Horizontal flow is often used for workbenches for providing protection to the processing lines.

K. Materials Support Area:

Materials support area is a Class 100,000 clean room, designed to resist moisture, steam, and detergents. The ceiling, walls, and floor should be of impermeable materials so that they do not retain moisture. Coating of vinyl or epoxy-sealing provides a continuous surface with no holes or crevices. These surfaces can be washed thoroughly at regular time intervals. These areas are exhausted sufficiently for removing the heat and humidity which provide comfort to personnel. Due to high humidity and heat, microbial growth may occur which should be prevented. Precautions should be taken to prevent dust accumulation. Material support area is utilised for filling operations, like cleaning and assembling of equipment. There should be sink and counter space in the area. This area should be cleanable and microbial load should be checked and controlled routinely. There should be no deposition of dust or other contaminants on clean containers and equipment. To prevent dust accumulation, the containers should be packed in boxes or wrapped preliminary for sterilisation and dehydrogenation process.

L. Compounding Area:

This area as the name suggests is used for compounding formulation. The steps taken to control microorganisms and particulate matter in this area should be morefirm than for the materials support area. Required measures should be taken to regulate dust generated from weighing and compounding operations. Stainless steel should be used for the construction of cabinets and counters, which should be fitted well to the walls and other furniture. This prevents the accumulation of dirt. The ceiling, walls, and floor should be same as in the materials support area. Back or top of a workbench, or entire side or ceiling of a room. The airflow should have a uniform velocity (100 ± 20ft/min) and direction throughout the given cross -sectional area. Contamination is controlled because it is brushed away with the airflow. Contaminants entering downstream from the filter can get transferred to working areas beyond the downstream by improper setting of supplies, handling of pe rsonnel, or discharge from equipment. The risk of contamination through these situations is less when the air flows vertically from the ceiling-mounted HEPA filters. Thus, vertical flow is often employed to protect critical sections of processing lines and similar actions. The ceiling, walls, and floor should be of impermeable materials so that they do not retain moisture. Coating of vinyl or epoxy-sealing provides a continuous surface with no holes or crevices. These surfaces can be washed thoroughly at regular time intervals. These areas are exhausted sufficiently for removing the heat and humidity which provide comfort to personnel. Due to high humidity and heat, microbial growth may occur which should be prevented. Precautions should be taken to prevent dust accumulation. Material support area is utilised for filling operations, like cleaning and assembling of equipment. There should be sink and counter space in the area.

This area should be cleanable and microbial load should be checked and controlled routinely. There should be no deposition of dust or other contaminants on clean containers and equipment. Compounding Area This area as the name suggests is used for compounding formulation. The steps taken to control microorganisms and particulate matter in this area should be firmer than for the materials support area. Required measures should be taken to regulate dust generated from weighing and compounding operations. Stainless steel should be used for the construction of cabinets and counters, which should be fitted well to the walls and other furniture. This prevents the accumulation of dirt. The ceiling, walls, and floor should be same as in the materials support area.

M. Aseptic Area:

Aseptic area should be designed in such a manner that it controls the growth of microbes and particulate matter. The ceiling, walls, and floor should be sealed so that they can be easily washed and sanitised with a disinfectant. Stainless steel should be used for constructing the counters and they should have no legs (and need to be hung from the wall) so that dirt cannot collect in the areas where they are placed on the floors. The light fixtures, utility service lines, and ventilation fixtures should be fitted in the walls or ceiling to prevent the accumulation of dust and dirt in ledges, joints, and other locations. Tanks with the compounded product should remain outside the aseptic filling area and the product is fed into the area through hose lines. If the tanks are moved in, proper sanitisation is needed. Large mechanical equipment in the aseptic area should be stored inside a stainless-steel cabinet to seal their operating parts and dirt -forming tendencies from the aseptic environment. All these equipment parts should be kept below the filling line. Mechanical parts that will be in contact with the parenteral product should be demountable for cleaning and sterilisation.

Entering of personnel in the aseptic area should be done by an airlock. They should wear sterile coveralls with sterile hats, masks, goggles, and foot covers. Movement inside the aseptic room should be negligible and in -and-out movement should be restricted during a filling process. If th e product is to be sterilised terminally in a sealed container, the necessities of room preparation and the personnel can be fairly relaxed. However, a single standard procedure is required for fulfilling all the desired standards.

N. Isolation Barrier Technology:

Isolation barrier technology is used for isolating aseptic operations from personnel and the neighbouring environment. Using this technology in sterility testing has given positive results. In European circles, favourable results have also been reported from use in hospital IV admixture programs. Because of such results, experimental efforts in adapting automated, large -scale, aseptic filling operations to isolators have gained momentum. The operations are performed in windowed, sealed walls with operators working through glove ports. The sealed enclosures are pre -sterilised using peracetic acid, hydrogen peroxide vapour, or steam. Sterile supplies are introduced from sterilisable movable modules through specially designed transfer ports or directly from attached sterilisers, including autoclaves and hot -air sterilising tunnels. The results obtained are very promising and provides enhanced control over aseptic environment.

5.6 Quality Control Tests of Parenteral Products:

Parenteral products should undergo the most stringent quality control tests as they are meant to be used within the body. These products are monitored for sterility and pyrogens to make sure that they possess the required features. The tests performed for the quality control of parenteral products are:

A. Leaker testing,
B. Clarity testing,
C. Pyrogen test,
D. Sterility testing, and
E. Particulate matter monitoring.

A. Leaker Testing:

Ampoules are sealed by tip sealing and pull sealing methods. Due to imp roper handling, there are chances that the ampoules are incompletely sealed, and cracks may appear around the seal or at the base during the process of sealing. Therefore, the leak test is used for identifying improper filling and sealing of ampoules, and i f found any they are rejected. In this test, sample ampoules are immersed in a deeply coloured dye solution (0.5 -1.0% methylene blue) and negative pressure of 27 inches Hg or more is applied in a vacuum chamber for 30 minutes.

After this period, vacuum is released and the dye under the influence of atmospheric pressure penetrates the ampoules t hrough any opening present. The ampoules are then washed externally and visually observed to check any change in the product colour due to the penetrated dye. The l eak test can be carried out during the cycles of autoclaving by immersing the ampoules in a dye bath. This method achieves two objectives, firstly it evaluates the presence of any leakage and secondly it sterilises the product. The leak test is not suitable for vials and bottles because they have rubber closures which are not rigid.

B. Clarity Testing:

Clarity test is required for preventing the distribution and use of parenteral products having particulate matter. Clarity is a factor that needs to be consider ed seriously in parenteral preparations. Clarity testing is mainly performed through human visual inspection of the containers in a direct light against a black and a white background.

As a result, the transparent particles are visible against black backgr ound and the coloured particles are visible against the white background. The method of visual inspection has some limitations. Due to this reason, the particulate matter can also be identified by passing the solution through a filter and then examining the filter under a microscope. Many automatic image analysis devices are developed (such as Quantimat 720 system 20), which focus image of particles on a TV screen and concurrently a permanent record is also formed. There are some other devices available for identifying the particulate contamination; such devices are based on light absorption, light scattering, or change in electrical resistance. Coulter counter method is also used for detecting particulate matter.

C. Pyrogen Test:

Pyrogens are endotoxin metabo lites of microorganisms that increase the body temperature when parenteral preparations contaminated with them are administered.

The pyrogen test is carried out as flows:

a. Rabbit Test: For this test, healthy rabbits maintained under suitable environment and diet before the test, are used. Normal or control temperatures are selected for each animal and are used as the base for easily determining any increase in temperature when the test solution is injected. Three rabbits whose temperature differs from each other by not more than 1 °C and whose body temperatures are also normal are selected. The test solution (obtained from the product to be tested) is warmed up to 37±2°C and injected in the marginal ear vein of each rabbit, completing each injection within 10 minutes of the start of administration. The temperature should be monitored at intervals of 30 minutes for 1 -3 hours after the injection. The product is considered to fulfil the requirements for the absence of pyrogens if no rabbits show a rise in temperature of 0.5°C or more; on the other hand, if any of the three rabbits show a rise in temperature of 0.5 °C or more, the test is continued using five more rabbits. Now if not more than three out of the eight rabbits show a rise in temperature, the product is considered to meet the requirements for the absence of pyrogens.
b. Limulus Amebocyte Lysate (LAL) Test: This in vitro test method for detecting pyrogens in the product utilises the gelling property of the lysate of the amebocyte of Limulus polyphemus (the horseshoe crab). If the pyrogenic endotoxins from gram - negative bacteria are present in the product, a firm gel is formed within 60 minutes on incubating the product at 37 °C. The LAL test is 5 -10 times more sensitive than the rabbit test; and with the use ofserial dilutions, it is assumed to be semi-quantitative.

D. Sterility Testing:

Sterility test is a confirmatory test for sterilisation process. Parenteral preparations such as injectables, ophthalmic products, and absorbent cotton are tested by this test, which is performed aseptically to avoid product contamination during the test.

a. Principle:

Sterility test works on the principle that on supplying microorganisms with nutrient medium and incubating them under favourable temperature, they start growing and multiplying, and their presence can be detected by the appearance of turbidity in the clear medium.

b. Preparation of Culture Media:

The culture media used for sterility testing should stimulate the growth of various aerobic and anaerobic microorganisms such as bacteria and fungi.

Two types of culture media that can be used are:

i. Fluid Thioglycollate Medium: This medium supports anaerobic as well as aerobic bacterial growth. Table 1. enlists the ingredients and their quantities used for preparing this medium:

Table 5.1: Composition of Fluid Thioglycollate Medium

Ingredient	Quantity (for100ml)
L- Cysteine	0.5gm
Sodium chloride	2.5gm
Dextrose	5.5gm
Agar	0.75gm
Yeast extract	5.0gm
Pancreatic digest of casein	15.0gm
Sodium thioglycolate	0.5gm
Resazurin (0.1% fresh solution)	1.0gm
Distilled water (q. s)	1000ml

ii. Soybean-Casein Digest Medium: This medium supports aerobic bacterial growth and fungal growth.

Table 5.2.: enlists the ingredients and their quantities used for preparing this medium.

Ingredients	Quantity (for100ml)
Pancreatic digest of casein	17.0gm
Peptics digest of soyabean meal	3.0gm
Sodium chloride	5.0gm
Dibasic potassium phosphate(K2HPO4)	2.5gm
Dextrose	2.5gm
Distilled water (q. s)	1000ml

iii. Sampling (Selection of the Sample Sizes) The sample itself and their number should be procured from the given batch of sterile product. The material should be thoroughly mixed if the sample is to be obtained from the bulk. The sample is withdrawn randomly from the batch of final containers.

5.6.1 Test Methods:

A. Membrane Filtration Method: This method is used when the test substance is:

- An oily preparation,
- An ointment that can be placed in the solution,
- A soluble powder or a liquid with antimicrobial properties,

- A solid with no antimicrobial properties and not readily soluble in the culture media, and
- A liquid product whose volume in a container is 100ml or more.

a. Procedure:

Sterility tests utilise s membrane filters having pore size not greater than 0.45μm and diameter 47mm. These filters should retain microbes. The filtration system and the membrane should be sterilised and the substances are membrane filtered under aseptic conditions. The membrane is washed thrice with 100ml of sterile solvent if the substances have antimicrobial properties. Then the membrane is aseptically cut into two equal halves. One half is immersed in soybean -casein digest medium (100ml) and incubated at 20 - 25°C. The other half is immersed in fluid thioglycol late medium (100 ml) and incubated at 30-35°C for a week.

B. Direct Inoculation Method: The test substance to be used in each culture medium is directly transferred or inoculated into the culture media aseptically. This inoculated liquid is mixed with the medium. If the test substance contains antimicrobial properties, it is neutralised with the addition of inactivating substances (e.g., penicillinase in case of penicillin) to the medium. The inoculated medium is incubated at 20 -25°C with soybean - casein digest medium and at 30 -35°C with fluid thioglycolate medium for a week.

C. Positive Control Test:

This test is performed to make sure that the prepared culture media and the environment conditions maintained during the test period support the microbial growth. The culture media is streaked under aseptic conditions with the causative test microorganism and then the method discussed above is adopted. On completion of the test growth or multiplication, the microbial load should be observed.

D. Negative Control Test:

This test is performed to make sure that proper sterile conditions have been maintained in the test area. The sterilised culture media is exposed to the test area and incubated. At the end of the study, there should not be any growth in the culture media, thereby proving the sterility and absence of microorganisms in the working area; an example is the laminar airflow unit.

E. Observation and Interpretation of Results:

At intervals during the incubation period and on its completion, the media are examined for the presence of growth of microorganisms. If the material under test makes the medium turbid, detection of microbial growth by visual inspection becomes difficult. Two weeks after the beginning of incubation, 1ml portions of each medium are transferred to fresh vessels contain ing the same medium. Then, the original and transfer vessels are incubated for 4 days. If no microbial growth occurs, the preparation is considered to pass the sterility test, while if microbial growth is observed, the preparation fails the test.

The sterility test is not repeated unless it can be proved that the test was invalid for reasons unrelated to the preparation being tested. If the test is declared to be invalid, it is repeated using the same number of units as in the original test. If no microbial growth is observed in the repeat test, the preparation passes the sterility test, while if microbial growth is observed which is even confirmed microscopically, the preparation fails the test.

5.6.2 Particulate Matter Monitoring:

The presence of particulate m atter in a solution to be administered intravenously is considered harmful. Till now limited data has been procured related to the extent of damage caused by particulate matter, although Garvan and Gunner have shown in 1964 that particles of rubber, insoluble chemical, lint, and other foreign chemicals can produce emboli in the vital organs of animal and man. Particulate matter in infusion fluids causes infusion phlebitis. Erythrocytes have a diameter of 4.5 μm, thus particles of more than 5μm size should form the basis of evaluation. By using Tyndall effect for analysis, particles of 10μm size can be viewed.

The **methods** employed for particulate matter monitoring are as follows:

A. Visual Inspection: The U.S.P. has specified that each final container of an injection should be visually inspected and those having visible particles should be discarded. Thus, all the products from the production line undergo separate inspection under good light and against black and white background. Visual inspection however has some drawbacks like particle size limitation (that can be seen with naked eyes), the visual opinion may vary from inspector to inspector as their emotional state, eyes strains, fatigue and other personal factors may affect the evaluation.

B. Microscopic Method: Particles of size smaller than 50 μm cannot be detected by visual inspection. Thus, a microscopic method has been developed by the U.S.P. for detecting large volumes of intravenous solutions. This method has a limit of not more than 50 particles/ml of size 10μm and large and not more than 5 particles/ml of size 25 μm and large. In this method, a measured volume of sample solution is filtered through a membrane filter under aseptic conditions and then the particles on the surface of the filter are counted microscopically using oblique light at 40x and 100x magnification.

C. Shadow Cast Method: The U.S.P. has established standards for small -volume parenterals meant for intravenous administration, using an electronic instrument which measures particle size by mode of a shadow cast by the particles, as it passes through high -intensity light beams. The prescribed limits are not more than 10 ,000 particles/container of size ≥ 10μm and not more than 1000 particles/container of size ≥ 25μm. These specifications were laid on the assumption that five products can be added to a 1L bottle of a large -volume parenteral and they should not contribute to more than the overall limits of particles prescribed for large-volume parenteral.

D. Electronic Particle Counter: Some other method s is also available for determining the presence of particulate matter. Many electronic particle counters are available, which utilise the principle of light scattering for counting particles in a liquid sample.

E. Thermocouple Conductivity Method: Some instruments, e.g., the Coulter Counter, are available for counting and sizing particles by measuring the resistance effect between two electrodes when the particle passes between them. All of these methods require aseptic preparation techniques to achieve accuracy in counting and sizing the practices present in solution, and not those introduced accidentally during sample preparation or testing procedure. These procedures are also quite destructive and can be performed using only those samples withdrawn from a production lot.

5.7 Aseptic Processing:

A. 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 aseptic processing 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 syringe ability while suspending agents modify the viscosity of the formulation.

B. 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.

5.7.1 Sterile Powers Are Prepared by Following Methods:

A. Sterile recrystallization:
B. Lyophilization:
C. Spray drying

A. 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.

B. 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.

a. Advantage:

This method involves removal of water at low temperatures.

b. Disadvantage:

- In this method, the biological molecules are damaged by the stress associated with freezing and drying.
- This method is expensive and time consuming.

C. 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.

a. Advantage:

- This method is Simple, Economical, scalable and faster.
- ii)This method involves Coating of particles during drying prolonged release.

b. Disadvantage:

- In this method, the high processing temperatures and high shear forces can easily damage drugs.
- In this method, higher levels of drugs are lost in comparison to freeze-drying.

- This method has a limited solvent choice for a given drug.
- In this method, product cannot be prepared directly in vials or plates.

D. Formulation of Sterile Powders:

The processing and filling of sterile powders is a difficult task in the conduct of simulation as the equipment used cannot easily accommodate the liquid media generally used for the simulation. In most of the cases in the simulation process, sterile liquid media and a sterile powder placebo are added to the container. The order of addition and the extent to which the powder filling process is adap ted to accommodate the liquid fill can make this a difficult simulation. As liquid filling on a powder line is a rare event, some firms fill a number of liquid containers along with the powder fill to establish that this activity is not the cause of any contamination. The sterilising filtration for sterile powders is conducted in a separate facility (or by a separate firm), therefore simulation concerns at the filling site are restricted to the activities performed there, including milling and blending.

5.7.2 Methods of Preparing a Sterile Drug Powder:

A. Sterile Re -Crystallisation: In this method, the drug is dissolved in a solvent, the solution obtained is sterilised by passing through a 0.22 μm membrane filter, and finally a sterile anti -solvent is added to crystallise the drug particles, which are filtered and dried aseptically.

a. Advantages: This method is flexible and economic.

b. Disadvantage: This method represents variations from batch to batch and contamination.

B. Lyophilisation:

In this method, a solid substance i s 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 then aseptically loaded into a freeze dryer. The solution is then frozen at –50°C and then dried by vacuum to separate the drug powder.

a. Advantage: This method involves removal of water at low temperatures.

b. Disadvantages:

- In this method, the biological molecules are damaged by the stress associated with freezing and drying.
- This method is expensive and time consuming.

C. Spray Drying:

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

a. Advantages:

- This method is simple, economic, scalable, and faster.
- This method involves coating of particles during drying prolonged release.

b. Disadvantages:

- In this method, the high processing temperatures and high shear forces can damage the drugs.
- In this method, higher levels of drug are lost in comparison to freeze drying.
- This method has a limited solvent choice for a given drug.
- In this method, product cannot be prepared directly in vials or plates.

5.8 Formulation of Large Volume Parenterals:

Large volume parenterals are sterile aqueous solutions or emulsions having water for injection as its main component. They are formulated as single -dose injections administered by intravenous infusion. They are packed and administered in large volumes. They should be free of particles. Before administration, sometimes additional drugs are added to them by either injecting small volume parenterals to the administration sets or by the piggyback method (smaller volume infusion of an additional drug is added to the intravenous delivery system).

Large-volume parenteral products include:

- Infusion fluids,
- Total Parenteral Nutrition (TPN) solutions,
- Intravenous antibiotics,
- Patient-controlled analgesia,
- Dialysis fluids, and
- Irrigation solutions.

Large volume parenterals should be terminally heat sterilised . 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 emulsions (containing vegetable or semi -synthetic oil), electrolytes (e.g., sodium chloride), and polyols, including glycerol, sorbitol and mannitol. The large volume parenterals are mostly clear aqueous solutions, except for the oil -in water emulsions. The emulsions for infusion are produced by highly specialised method as they are destabilised by heat. This result s in many difficulties during production, thus the size of oil droplets should be controlled during heat sterilisation.

A. Production of Large-Volume Parenterals: The manufacturing and filling of large volume parenteral 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. The quality of products can

be ensured by strictly following the quality assurance procedures. In commercial manufacturing facilities, large volumes of fluids are used in the production of a product batch. The fluids from a bulk container are filled into the product container using high-speed filling machines. Before filling the fluid into the container, it is passed through an in -line membrane filter to remove the particulate matter. After filling, the neck of each glass bottle is immediately sealed with a tight -fitting rubber closure held in place with a crimped aluminium cap. The outer cap is also of alumin ium and an outer tamper-evident closure is used. In case plastic bags are used, the pre -formed plastic bags are aseptically filled and heat sealed immediately. A blow-fill-seal system can also be used that involves melting the plastic, forming the bag, and filling and sealing in a high -quality clean room environment. Blow-fill-seal system minimises the problems with product handling, clean -ing and particulate contamination. After the product is filled into containers, they are checked for particulate matter and the integrity of container closures is established. The large volume parenteral products, including irrigation solutions and dialysis fluids, should be moist heat sterilised immediately after the containers are filled. Plastic containers should be sterilised with an over -pressure during the sterilisation cycle so that they do not burst.

B. Formulation of Lyophilized Products Lyophilised or freeze-dried products are prepared by freeze drying, and this process is known as lyophilisation or cryodesiccation. It is a dehydration process used for preserving a perishable material or making the material more convenient for transport. Freeze -drying works by freezing the material and then reducing the surrounding pressure so that the frozen water in the material directly sublimes from the solid phase to the gas phase.

C. The four stages involved in the freeze-drying process are:

a. Pre-Treatment: In this stage, the product prior to freezing is either concentrated, the formulation is revised (i.e., adding new components to increase the stability and/or improve the processing), a high vapour pressure solvent is decreased, or the surface area is increased. In many cases, pre -treatment is based on the theoretical knowledge of freeze -drying and its requirements or is demanded by cycle time or product quality considerations. The methods of pre-treatment are: i) Freeze concentration, ii) Solution phase concentration, iii) Formulation to preserve product appearance, iv) Formulation to stabilise reactive products, v) Formulation to increase the surface area, and vi) Decreasing high vapour pressure solvents.

b. Freezing: On a smaller scale in this stage, the material is placed in a freeze -drying flask that is r otated in a bath (called a shell freezer) cooled by mechanical refrigeration, dry ice and methanol, or liquid nitrogen. On a larger scale, a freeze - drying machine is used for freezing. The material is cooled below its triple point (the lowest temperature at which the solid and liquid phases of the material can coexist) to ensure that the material will not melt but sublime in the subsequent steps. Larger crystals can be easily freeze dried; thus, larger crystals should be produced by freezing the product slowly or by annealing (cycling the product up and down in temperature).

c. Primary Drying: In this stage, the pressure is lowered (up to a few millibars) and heat is supplied to the material so that the water sublimes. The amount of heat required is determined by using the latent heat of sublimation of sublimating molecules. 95% of the water in the material sublimes in this initial drying phase. This phase is slow because on adding excessive heat the material's structure gets altered. The pressure in this phase

is controlled by applying partial vacuum that speeds up sublimation. A cold condenser chamber and/or condenser plates (ma intained at −50 °C temperature) provide a surface on which the water vapour re -solidifies. This condenser has no role in keeping the material frozen; but it prevents water vapour from reaching the vacuum pump, or else the pump's performance will be degraded.

d. Secondary Drying: In this stage, the unfrozen water molecules are removed, since the ice was removed during primary drying. This stage of freeze -drying is governed by the material's adsorption isotherms. In secondary drying, the temperature is increased more than in the primary drying phase, and can even be above 0°C, to break any physicochemical interactions between the water molecules and the frozen material. The pressure is also lowered (in the range of microbars or fractions of a Pascal) to facilitate desorption. However, some products are benefitted from increased pressure. After completing the freeze -drying process, the vacuum is broken with an inert gas (such as nitrogen) and the material is sealed. In the final product, the residual water content is extremely low (around 1-4%).

5.9 References:

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