SS INSTITUTE OF PHARMACY

UNIT-IV

PARENTERALS

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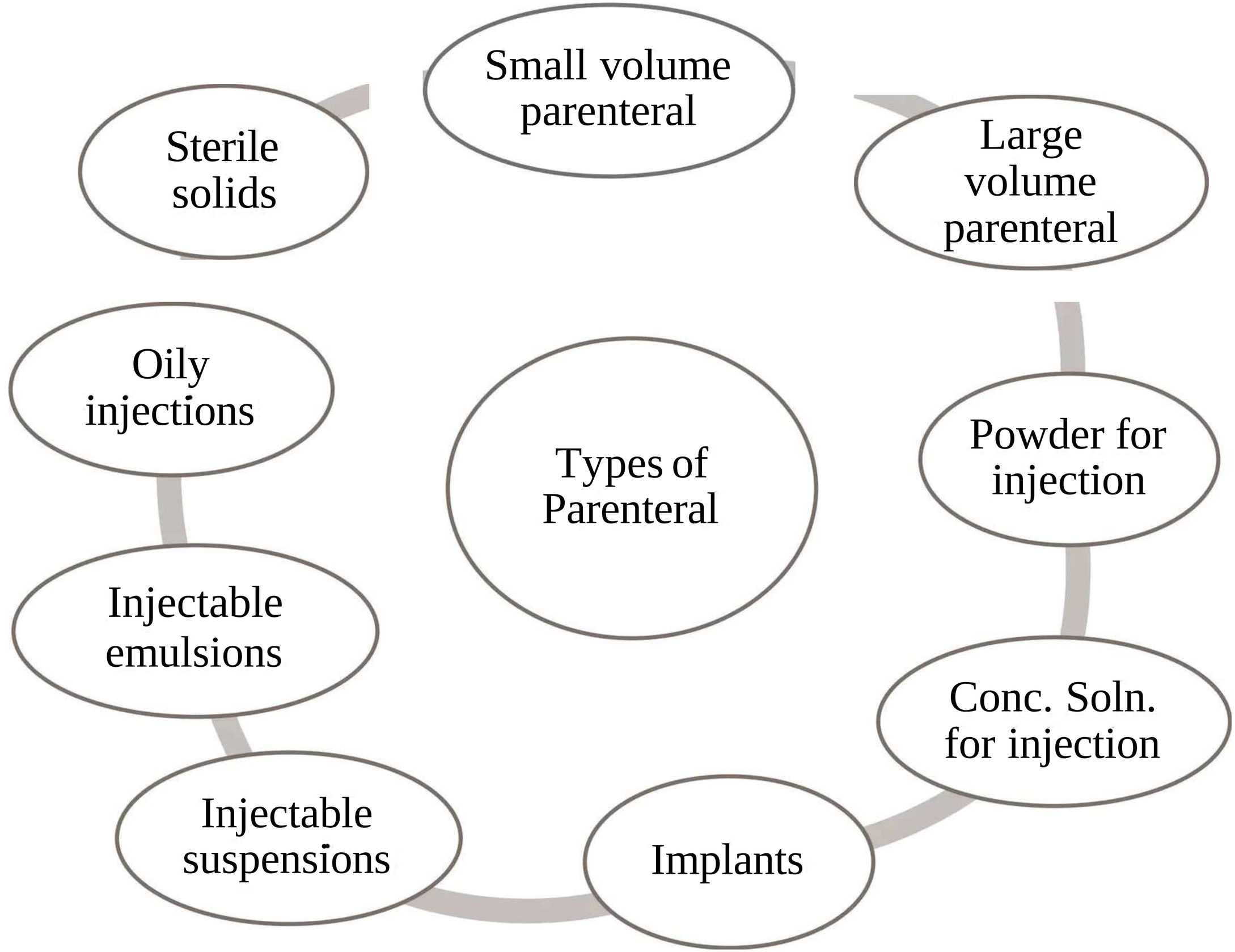
INTRODUCTION

Pharmaceutical Parenteral :- are sterile products (dosage forms of therapeutic agents that are free from viable microorganisms), that are administered directly into the body tissues rather than the oral route (via the alimentary canal).

The word parenteral is coined from a greek words “para eneteron” which means to avoid the intestines. Parenteral products are unique among dosage foms because they are injected through the skin or mucous membranes in to the inteval body compañments.

Definition :- parenteral preparations are sterile, pyrogen free liquids (solutions, suspensions, or emulsions) or solid dosage foms, containing one or more active ingredients, packaged in their single or multi dose containers. They are intended for administration by injection, infusion, or implementation in to the body, directly in to the veins, muscles, or under the skin or more specialised tissues such as spinal cord etc.

Types of Parenteral



•Small Volume Parenteral– are sterile injectable products containing a solution or suspension, prepared by dissolving the active ingredient and other substances in water for injection or other non – aqueous base or a mixture of both. They are called as injections, that are packaged in volumes up to l00ml.

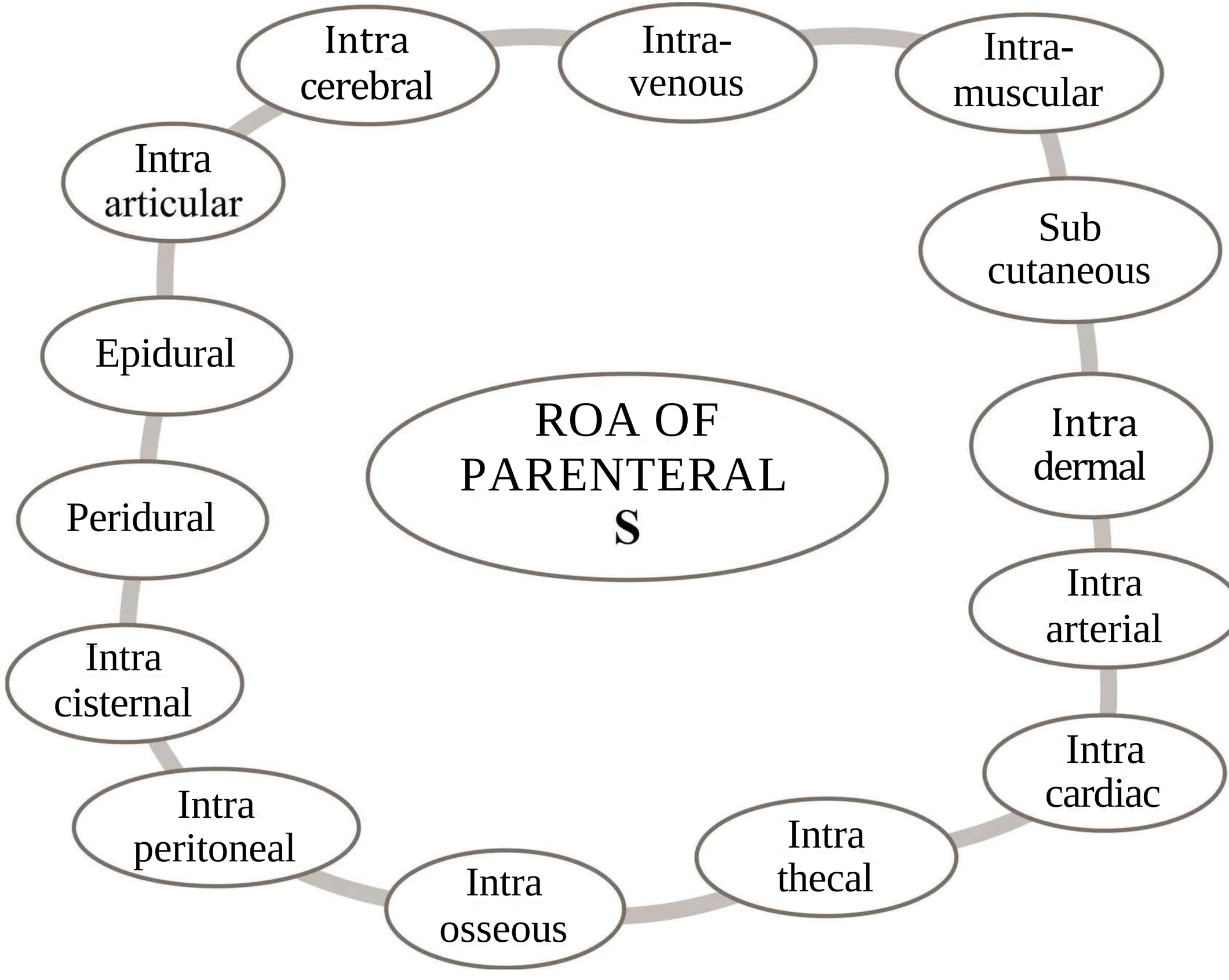
•Large Volume Parenteral – are composed of sterilised aqueous solution of the active ingredient with water as the continuous phase, packaged in a single dose container with a capacity of l00ml or more. They are also called as infusions that are free of bacterial endotoxins or pyrogens.

•Powder for Injection - are sterile solid preparations that are mixed with or reconstituted with a diluent before administration. These preparations are prefered when dmgs are not stable in solution.

•Concentrated Solutions for Injections – are diluted with water for njJectJonqbefore administering through injection or

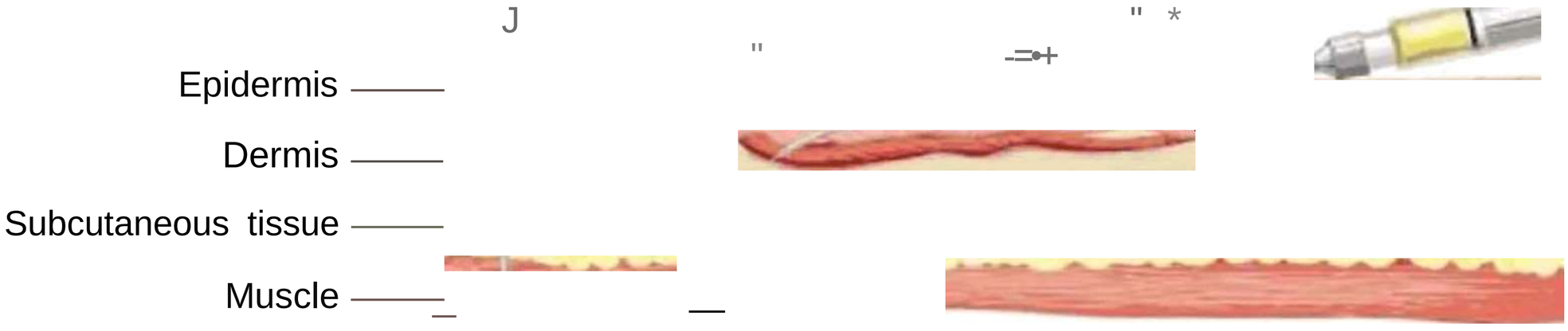
- Implants – are solid sterile preparations inserted in to the tissue to release the active ingredient for long periods. They are packed in sterile containers individually.
- Injectable Suspensions - are liquid preparations in which the solids are suspended in a liquid medium. They are used to produce sustained or controlled release parenteral dosage forms for prolonging the dvg action.
- Injectable emulsions –are liquid preparations in which the dvg substances are dissolved or dispersed in a suitable emulsion medium. They are administered intravenously for delivering lipid – soluble therapeutic agents.
- Oily Injections – are used to prepare parenteral controlled release dosage forms. The dmg release in oily injections is controlled by dmg partitioning into the aqueous medium from the oil medium.
- Sterile solids – are dry solids dissolved in a solvent and then administered in the body.

Routes of Administration of Parenteral



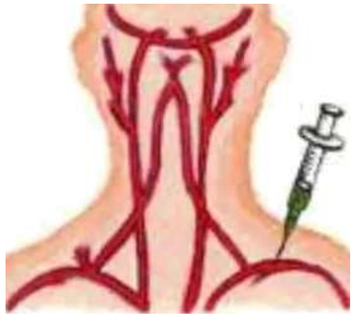
- Intravenous – directly in to patients veins.
- Intramuscular – injected deeply in to muscle tissue.
- Subcutaneous – injected under the skin in to the fatty layer but not in to the muscle.
- Intradermal – injected in to the top few layers of the skin.

Intramuscular Subcutaneous InPavenous Inkadermal

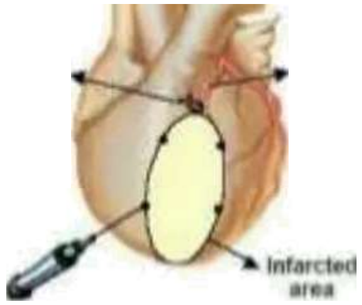


Inhamuscular Subcutaneous InPavenous Intradermal

- Intra arterial – injected in to the artery.
- Intracardiac – given in to the heart muscle or ventricle in times of emergency.
- Intrathecal – given in to the subarachnoid space that surround the spinal cord.
- Intraosseous – given directly in to the bone marrow.



Intra-Arterial Injection



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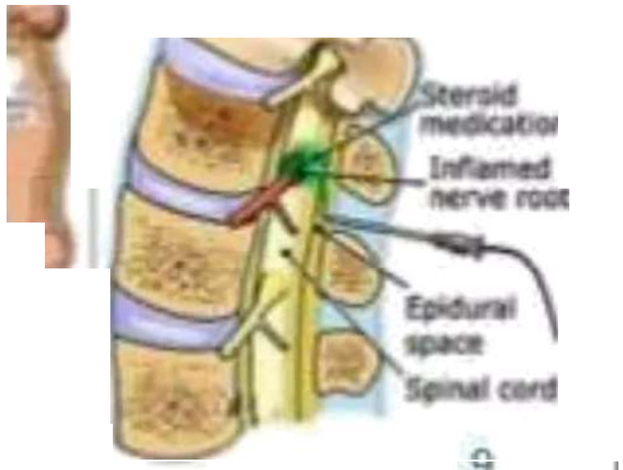
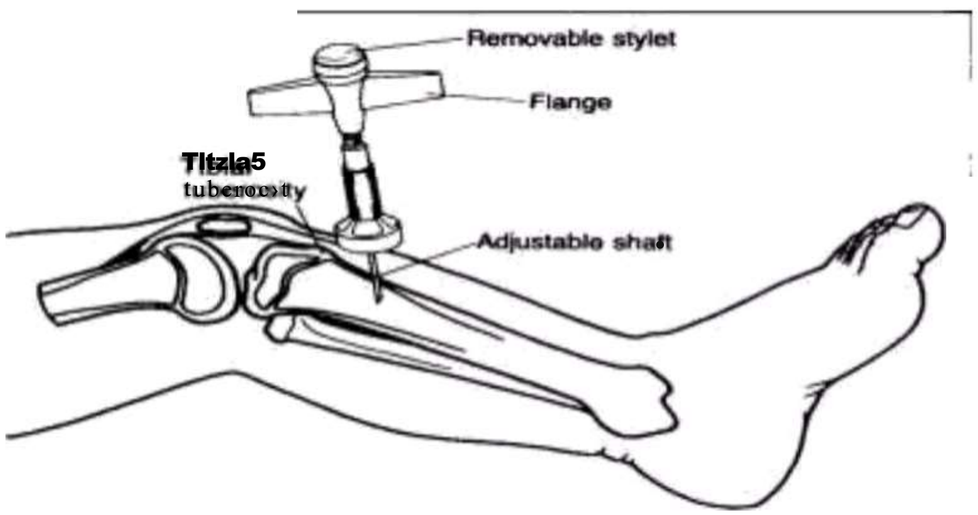


Intrathecal



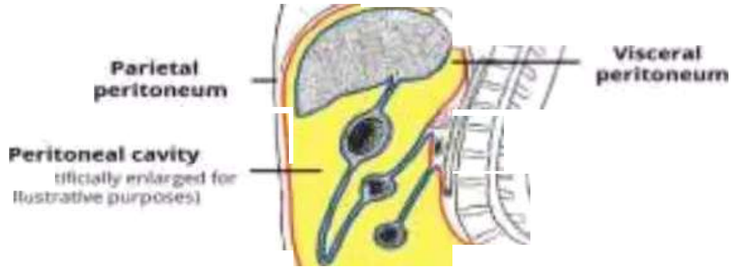
In aosseous

•Intraperitoneal – directly in to the peritoneal cavity.

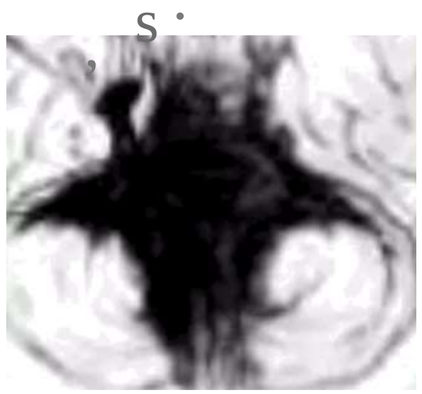
•Intracisternal – injected between first and second ccervical nerve.

•Peridurat – injected in between the dura mater and inner aspect of vertebra.

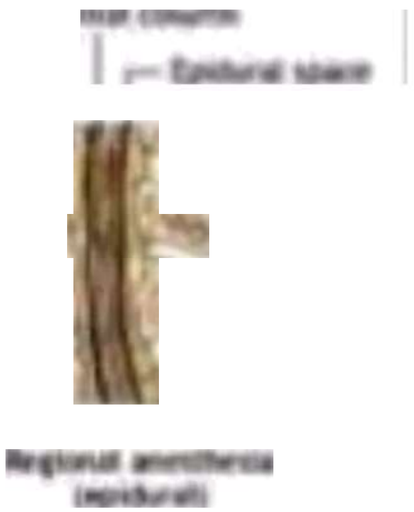
•Epidural – injected near the spinal cord such that it affects the local nerves.



Intraperitoneal



Intracisternal



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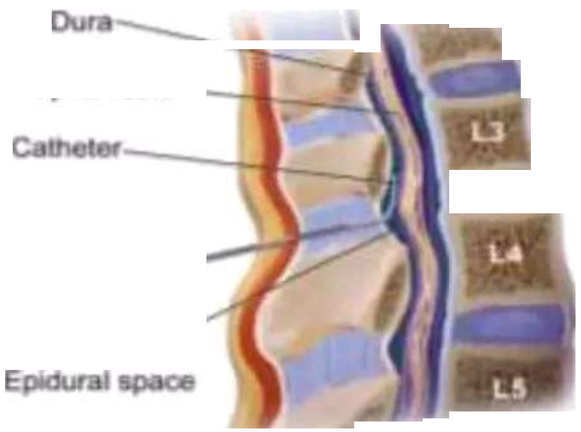
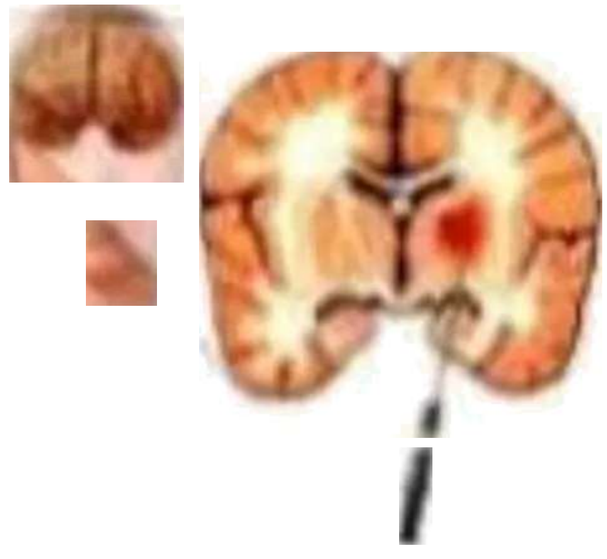


Epidu al

•Intraarticular – directly in the articulating ends of the bones in a ’oint.

•Intracerebral – injected in to the cerebrum.

Intraarticular



Intracerebral

Advantages of Parenterals

>Useful for patients who cannot take dmgs orally, or when the patient is unconscious or uncooperative.

>Rapid onset of action.

>No chance of missing a dose.

>The dmg is directly released in to the blood stream by injection so minimum dmg is needed to produce the effect as there is no wastage.

<Essential for drugs with poor bioavailability or that degrade rapidly within GIT

<Useful for emergency actions.

<Providing sustained dmg delivery.

<Avoid first pass metabolism.

<Complete bioavailability.

>Low toxicity as compared to solid dosage forms.

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

Disadvantages of Parenterals

<Manufacturing process requires aseptic techniques.

<Pain on injection.

<Need of medical help for administration. Trained person is required.

>Difficult to reverse an administered drug's effect.

>Sensitivity or allergic reaction at the site of administration.

>Requires specialised equipment, devices and techniques to prepare and administer drugs.

>More expensive and costly to produce.

>Chances of improper dosing.

>Danger of blood clot formation.

PREFORMULATION FACTORS AND ESSENTI&L REQUIREMENTS

Pharmaceutica\ Factors Affecting Parentera\ Administration:-

- Solubility of dvg & volume of injection
- Na1re of vehicle
- Type of dosage form
- Fomulation ingredients
- pH and osmolarity of injectable solutions
- Colour of the formulation.

Solubility of Drug & Volume of Injection

- Before a dvg is administered through intravenous route, the dvg should be completely solubilised in the vehicle chosen
- Volume of injection can be detemined by the extent of dvg solubility in its intended vehicle and the dose required for the desired therapeutic effect.

Nature of Vehicle

- Dvg in aqueous vehicle can be administered by any parenteral route.
- Dvg in non – aqueous vehicle are administered by intramuscular route.
- In case of mixed solvent system, intravenous route of administration is prefered, but precipitation of dvg at the infusion site should be prevented.

Type of Dosage Form

- Parenteral dosage foims mainly include solutions, suspensions, emulsions and sterile solids for reconstiNtion.
- Suspensions are administered through intramuscular or subcutaneous route.
- Dvgs administered through intravenous route should be clear and not contain any pañicles.
- Before administering, sterile solids via intravenous route, they are dissolved in reconstituting diluents.

Formulation Ingredients

- Formulations are made up of significant therapeutic ingredient and excipients.
- Antimicrobials are added to preseme sterility.
- Surfactants are added to maintain solubility of the dvg in the vehicle.
- For achieving desired duration of action, addictives like high molecular weight polymers or oily solvents are added. Formulations containing such macromolecules are administered through subcutaneous or intramuscular route, to allow the delayed release of the active ingredient.

pH and Osmolarity of Injectable Solutions

•Formulated at a pH and osmolarity similar to that of biological fluids. But this is not possible for parenterals that are unstable at neutral pH. Thus they should formulated at a pH which they are stable.

•Some formulations are hyper osmotic with biological huids. Such formulations are not be administered through intramuscular or subcutaneous route.

•Therefore such formulations should contain solute contents equal to the biological huid even if solubility and stability and stability problems arise.

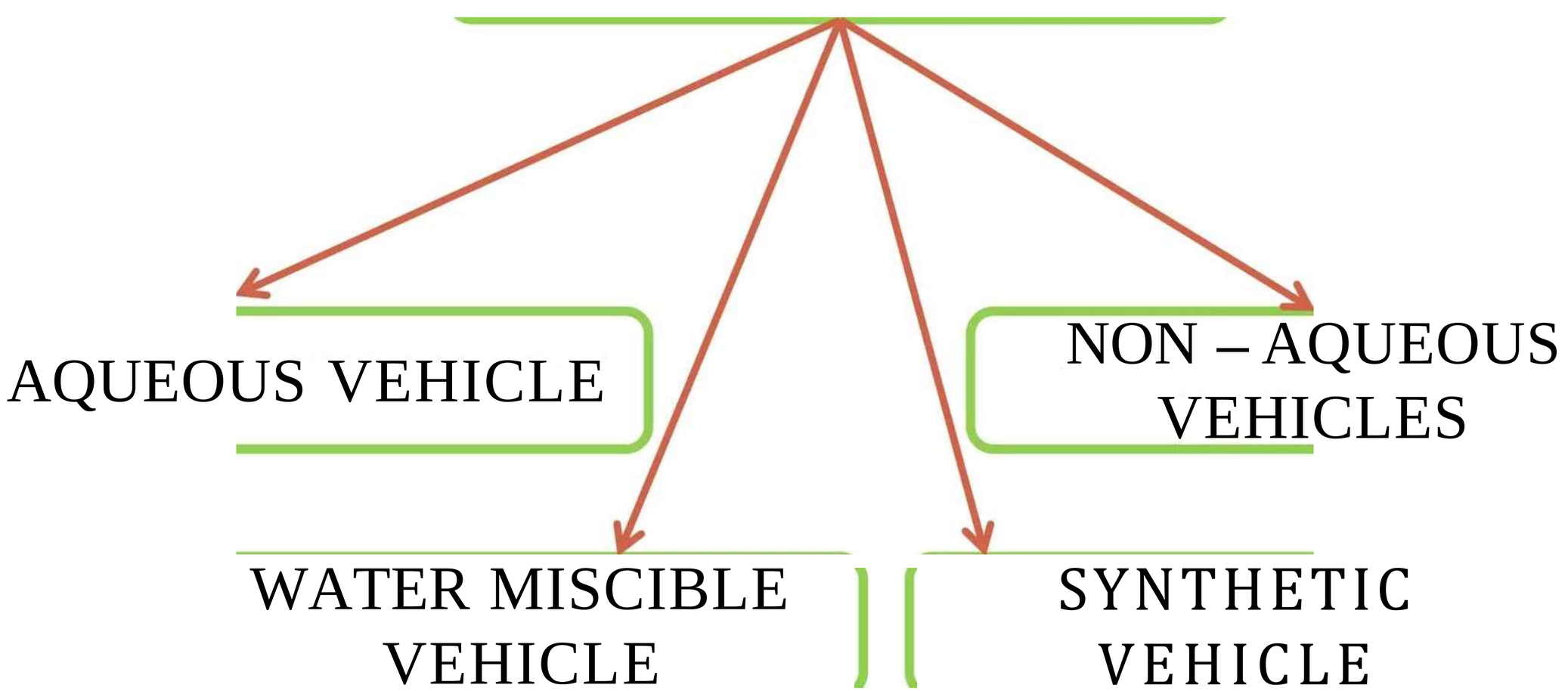
Colour of the Formulation

•Propeñy of an inherent chemical stmcture of dmg and indicates the level of unsaturation.

•A significant colour change in the parenteral product becomes a limiting factor to its shelf life even before a chemical stability is noted.

VEHICLES USED IN PARENTERAL FORMULATIONS

Vehicles or solvents are used as medium for formulation of drugs as parenterals in the form of suspensions, emulsions, solutions, etc., The vehicles used in formulations a



Aqueous Vehicle

- NaCl INJECTION USP
- BACTERIOSTATIC NaCl INJECTION USP
- RINGERS INJECTION
- WATER FOR INJECTION (WFI)
  - STERILE WFI
  - BACTERIOSTATIC WFI
  - WFI FREE FROM CO_2
  - WFI FREE FROM DISSOLVED AIR

Water for Injection

- WFI is the most commonly used solvent in the manufacture of parenterals.
- Water obtained from by either of thee two processes :- reverse osmosis and distillation.
- Does not contain any added substances and meet the standards for presence of total solids – not more than 1mg/l00ml.
- Should be used within 24 hours
- Available in 4 different types.

Sterile WFI

- Is the WFI which is sterilised and packaged in single dose container of not greater than llitre size.
- Must not contain any added substance.
- Standard limit for the presence of solids can be slightly greater than WFI.
- Mainly used for reconstitution of dry parenteral products.

WFI free from CO_2

- Is sterile WFI which is free from dissolved carbon dioxide or from which carbon dioxide is removed.
- Are used in preparations which are weakly acidic and slightly soluble in water.
- Prepared by boiling WFI for 10 minutes.

WFI *tree* from dissolved air

•WFI free from dissolved air i.e., atmospheric air.

•Used to improved the stability of the preparation which are susceptible for oxidation in presence of air.

•Done by boiling freshly distilled water for 10 minutes, and to be used immediately.

Bacteriostatic WFI

•Is sterile WFI containing suitable antimicrobial agents.

•Can be packed in prefilled syringes or vials containing not more 30ml.

•Type and proportion of antimicrobial agent used should be controlled.

•Chemical compatibility of the antimicrobial agent with the active ingredient should be checked.

•Employed as a sterile vehicle in preparation of small volume parenterals.

NaCl Injection USP

•Is a sterile isotonic solution of NaCl in WFI, containing 154 mEq each of sodium and chloride ions per litre.

Bacteriostatic NaCl Injection USP

•Is a sterile isotonic solution of NaCl in WFI, which contains an amount of antimicrobial agent.

Ringers Injection USP

•Sterile solution of NaCl, KCl, $CaCl_2$

•Either used as vehicle or as electrolyte replenishner and plasma volume expander.

•Lactated Ringers Injection USP is a sterile solution of NaCl, KCl, sodium lactate, and $CaCl_2$ in WFI

Non – Aqueous Vehicles

•When the dmg has limited water solubility or is prone to hydrolysis3 «queous solvents or vehicles are replaced by non – aqueous solvents.

•Should be non –irritating, non – toxic, pharmacologically inert, metabolise easily, have high melting point to permit sterilisation.

•E.g – fixed oils or vegetable oils like corn, olive, sesame oil.

Water Miscible Vehicles

•Used in parenterals to enhance drug solubility and act as a stabilizer.

•E.g – PEG, glycerin3dimethyl acetaminde, propylene glycol.

Synthetic Vehicles

•E.g – isopropyl alcohol, benzyl benzoate, ethyl oleate.

ADDICTIVES / EXCIPIENTS USED IN PARENTERALS

- Solubilisers
- Antioxidants
- Chelating agents
- Buffers
- Stabilizers
- Surfactants
- Presematives
- Protectants
- Tonicity adjusters

ISOTONICITY & its IMPORTANCE

An isotonic solution is one that has the same osmotic pressure of blood. Parenteral products that are administered to the patient should be osmotic. Isotonicity is impoñant for parenteral formulations because if the solution is isotonic with blood or body fluids, the possibility of the product penetrating the red blood cells and causing destvction is reduced.

Hypotonic solutions are solutions having lesser osmotic pressure than the blood plasma. When a blood cell is in a hypotonic solution, the solution passes in to the RBC, and the cell sta0s to swell, resulting in a burst out and releasing the contents of the cell. This leads to an iaeversible damage.

Kypertouic solutions are solutions having higher osmotic pressure than the blood plasma. When a blood cell is in a hypeñonic solution, the cytoplasm an the organelles moves from the cell in to the solution to attain equilibrium. This results in the shrinkage of cells and cell wall appears crenate, which is a reversible process.

In isotonic solutions, the red blood cells maintain their tonicity.

Tonicity can be maintained by the two main following methods :-

- Cryoscopic method / Freezing Point Depression method

A solution which is isotonic with blood has a freezing point of 0.52°C. Hence, the freezing point of the dvg solution must be adjusted to this value.

The weight of the adjusting substance required to maintain isotonicity is calculated by the following formula -

$$^{0}o\ w/v \text{ of adjusting substance} = (0.52 - a) / b$$

Where,

a.= freezing point of unadjusted solution

b.= freezing point of $^{0}/o$ w/v solution of adjusting solution

•Sodium Chloride Equivalent method

This method represents the number of grams of sodium chloride equivalent to lgram of drug. This is calculated by the following formula -

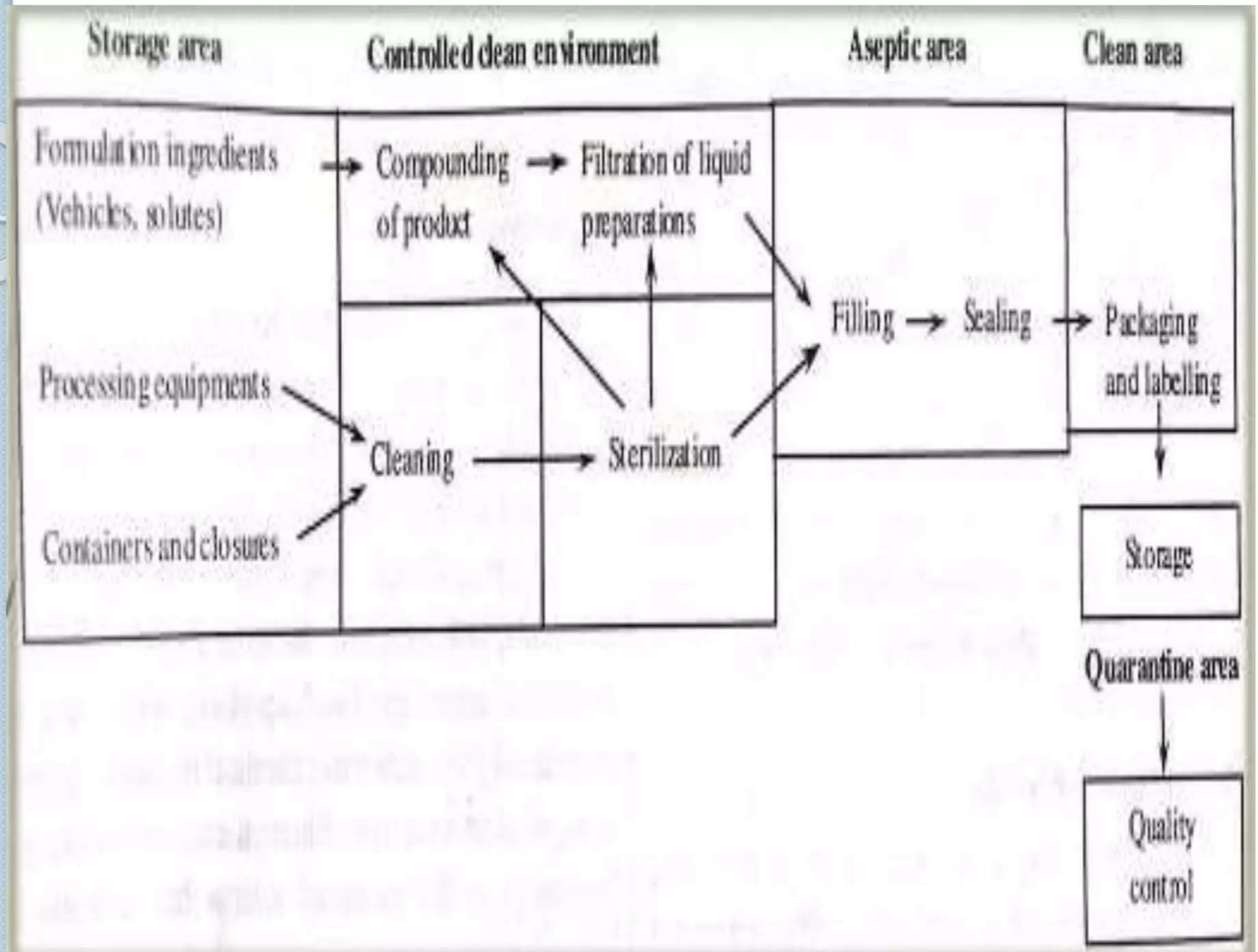
= (molecular weight of NaCl / ‘i’ factor of the NaCl) * (‘i’ factor of the drug / molecular weight of drug)

PRODUCTION PROCEDURE OF PARENTERALS

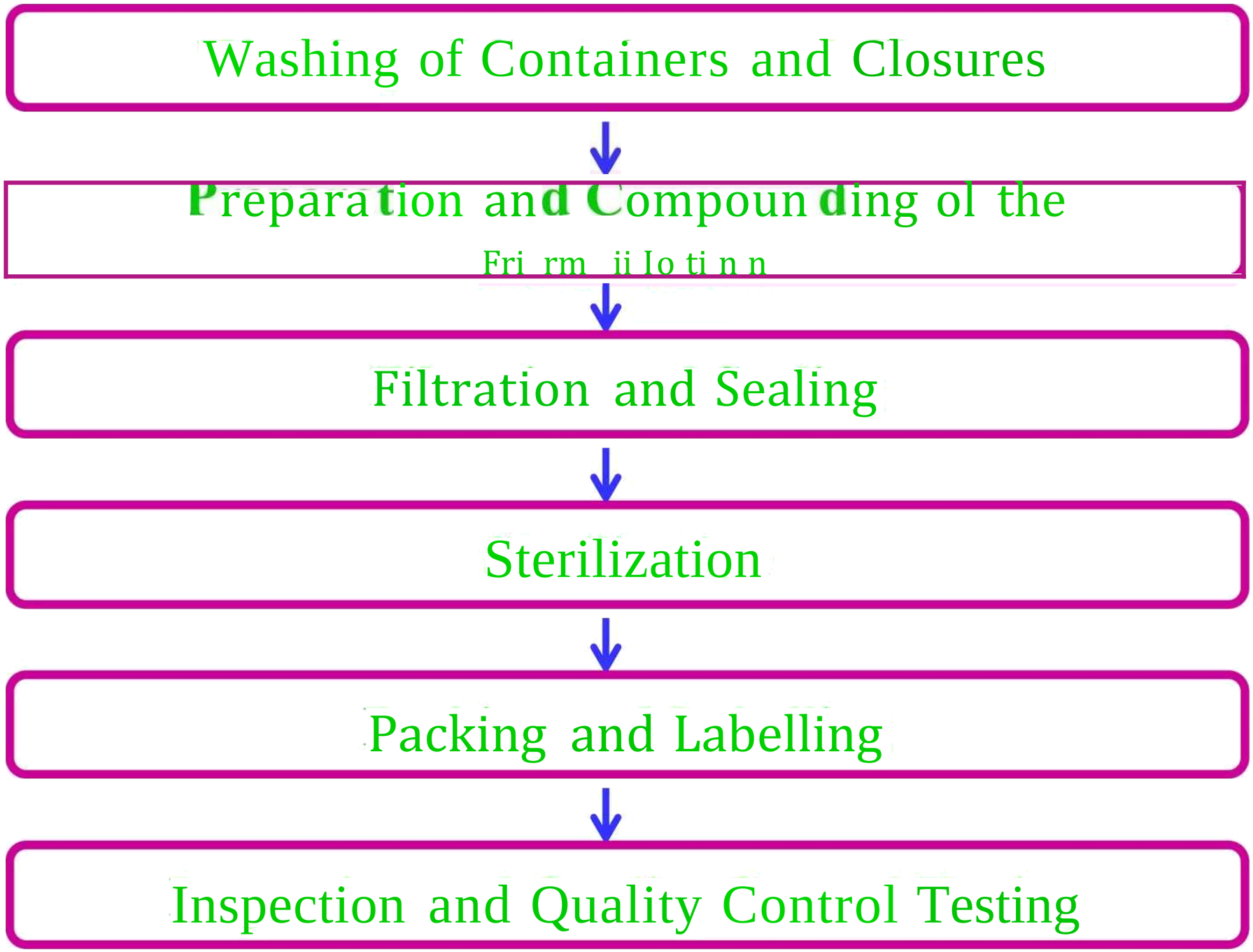
The production procedure of parenterals includes all of the steps from the accumulation, planning and scheduling of the ingredients of the fomula and equipments to the enclosing of product in the individual container for distribution. To enhance the assurance of successful manufacturing operations, all process steps must be carefully written as the standard operating procedures. The production of a quality product is a result of the continuous effoñ of the quality assurance, production and quality control personnel.

In the initial step, the ingredients, container components and processing equipments, are drawn from their respective storage areas. The ingredients are compounded according to the master formula in an environment designed to maintain a high level of cleanliness. If the product is a solution, it is filtered during transfer to the aseptic filling

Process equipment and container components are cleaned, sterilized and depyrogenated prior to use. Also, all the equipments and supplies introduced in to the aseptic filling area should be sterile. The product is sealed in a aseptic filling area, and then transpoñed to the packaging area. Packaged products are placed in quarantine storage until all the tests have been completed and in process control records have been evaluated. Then the product is released for distribution.


Storage area
Controlled clean environment
Aseptic area
Clean area
Formulation ingredients
(Vehicles, solutes)
Compounding of product
Filtration of liquid preparations
Processing equipments
Containers and closures
Cleaning
Sterilization
Filling
Sealing
Packaging and labelling
Storage
Quarantine area
Quality control

The steps involved in the manufacturing of parenterals are :-



Was in of Container and Clos res

•EquiJJmenmls a$d container must ie carefiñy cJea'ned.

•New, unused containers and equipment's are contaminated with dust, fibres, and chemical films – which usually are relatively easy to remove, by rinsing only.

•Used equipment's are scvbbed by hand immediately after use with an effective detergent that does not leave a residue on its own.

•Glass wares or metal wares are automatically conveyed, usually in an inveñed position through a series of rigorous, high pressure treatments, including hot detergent, hot tap water, and final rinses with distilled water.

•After cleaning, it is essential that the clean containers be protected from dust and other pañiculates.

Preparation & Compounding of the Formulations

- Product should be compounded under clean environmental conditions.
- Accuracy of compounding should meet the rigid standards accepted in pharmaceutical procedures.
- Products are packaged in previously sterilised containers under sterile conditions.
- In larger batches, attention must be given to achieving and maintaining homogeneity of solutions, suspensions, and mixtures, maintaining a given temperature and accelerating cooling.

Fi\tration

•Primary objective of filtration are clarification or sterilization of a solution.

•Clarification is also termed as polishing, and a highly polished solution requires the removal of particulate matter down to at least 3pm.

•Further reduction in size of the particulate matter removed to approximately 0.3pm, resulting in sterilization, the removal of viable microorganisms and spores.

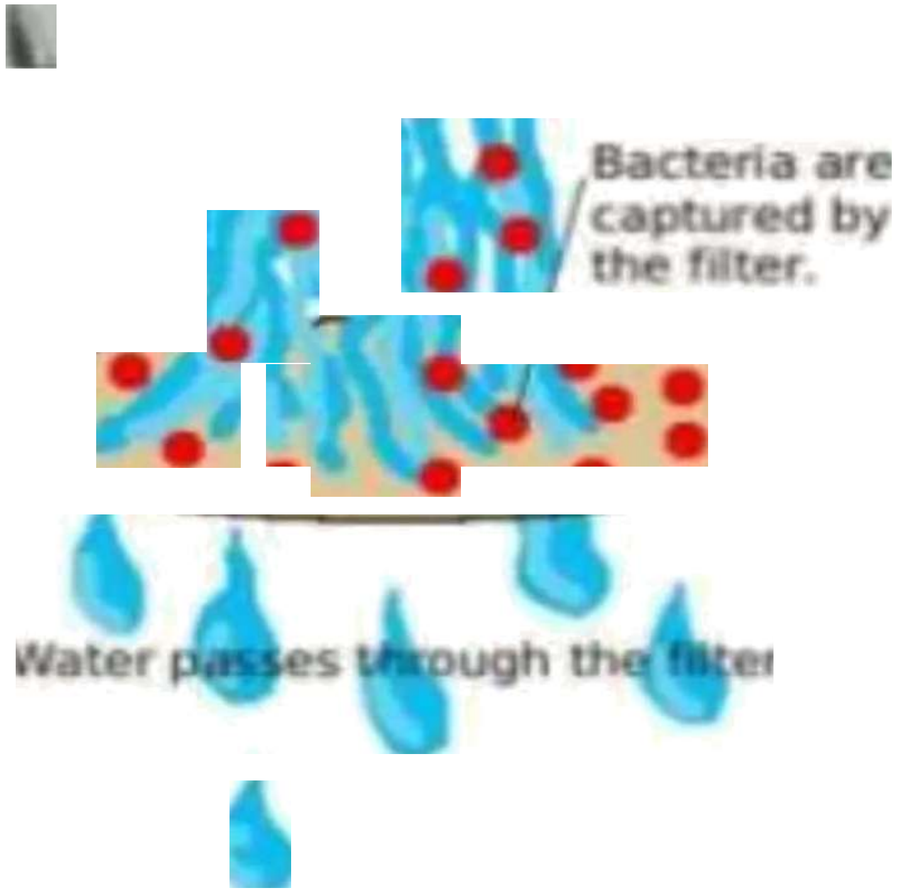
•After filtration, solution must be protected from environmental contamination until it is sealed in the final container.

•This is achieved by collecting filtrate in a container that is part of a closed system. A secondary filter is included to collect any particulate matter while the transfer process.

•The filtrate is directly fed from the collecting vessel filling machine through sterile hose connections.

•This transfer is also said as a transfer from the clean environment to aseptic environment.

- Membrane media filters are used for filtration of sterile solutions as accepted by the standards of USP and USFDA. They are made up of cellulose, PVP, and other cellulose derivatives.
- Membranes with porosity ranges from 0.2 – 0.45pm are usually specified for sterile filtrations.
- The FDA allows the use of 0.45pm filters only when colloidal solutions are filtered, as when filters of 0.2pm are used, membranes are clogged rapidly.



STERILIZATION

Sterilization is the process when the absolute condition of total destruction or elimination of all living microorganisms to produce a sterile state is achieved.

Sterilization of parenteral products are achieved by different methods. $

STERILIZ

Mois hea

Dry heat

Throughb e''a proof e

Che cal method

Rad ia ion **sterilization**

Moist Heat Sterilization

- This technique is where hot water vapour is used under high pressure as a sterilizing agent to generate high temperature for sterilization
- Autoclaves are mainly used for sterilizing at a temperature of 121^{o}C for 15 minutes.
- Bacterial death by moist heat is due to denalration and coagulation of essential proteins and cell constituents.

Dry Heat Sterilization

- Sterilization is done by the use of heat, requires higher temperature than moist heat and no longer exposure time.
- Entire content of container is maintained in the oven for a minimum of 180°C for not less than 30 minutes.
- Vital constilents of cells are denatured by oxidation.

Sterilization by Filtration

- Employed by passing the parenteral product through sterile bacteria retaining filters.
- E.g. membrane filters. Membranes of not more than 0.2pm nominal pore size should be used.

Sterilization by Radiation

•Sterilization by radiation like EM Rays, pañiculate radiation etc. by targeting the microbial DNA has proven to be a useful method.

•Gamma radiation is commonly used for sterilization, which is usually derived from Cobalt 60 source.

•Ultraviolet and X-Rays are also used for sterilization, but gamma rays have more penetrating power.

Gaseous or Chemical Sterilization

- Chemically reactive gases such as formaldehyde, methanol, and ethylene oxide possess biocidal activity.
- Mechanism of antimicrobial action of such gases is assumed to be through alkylations of sulphadryl, amino, hydroxyl and carboxyl groups of nucleic acids.
- Commonly used gases – combination of ethylene oxide and carbon dioxide. Carbon dioxide is added to minimize the chances of an explosion.
- Ozone gas is also used which oxidize most organic matter.

FILLING

- Product is subdivided from bulk containers to individual dose containers more easily and uniformly.
- Subdivision of low density liquid can be achieved with light duty machinery.
- Viscous, sticky or high density liquids require more mgged machines, to withstand the pressure required to dispense them.
- Sterile solids are difficult to subdivide accurately and precisely in to individual dose containers than are liquids.
- Rate of how of solid materials tends to be slow and iaegular. Containers with relatively large opening must be used, and the sterile solids are subdivided in to containers by individual weighing.

Filling of Ampoules

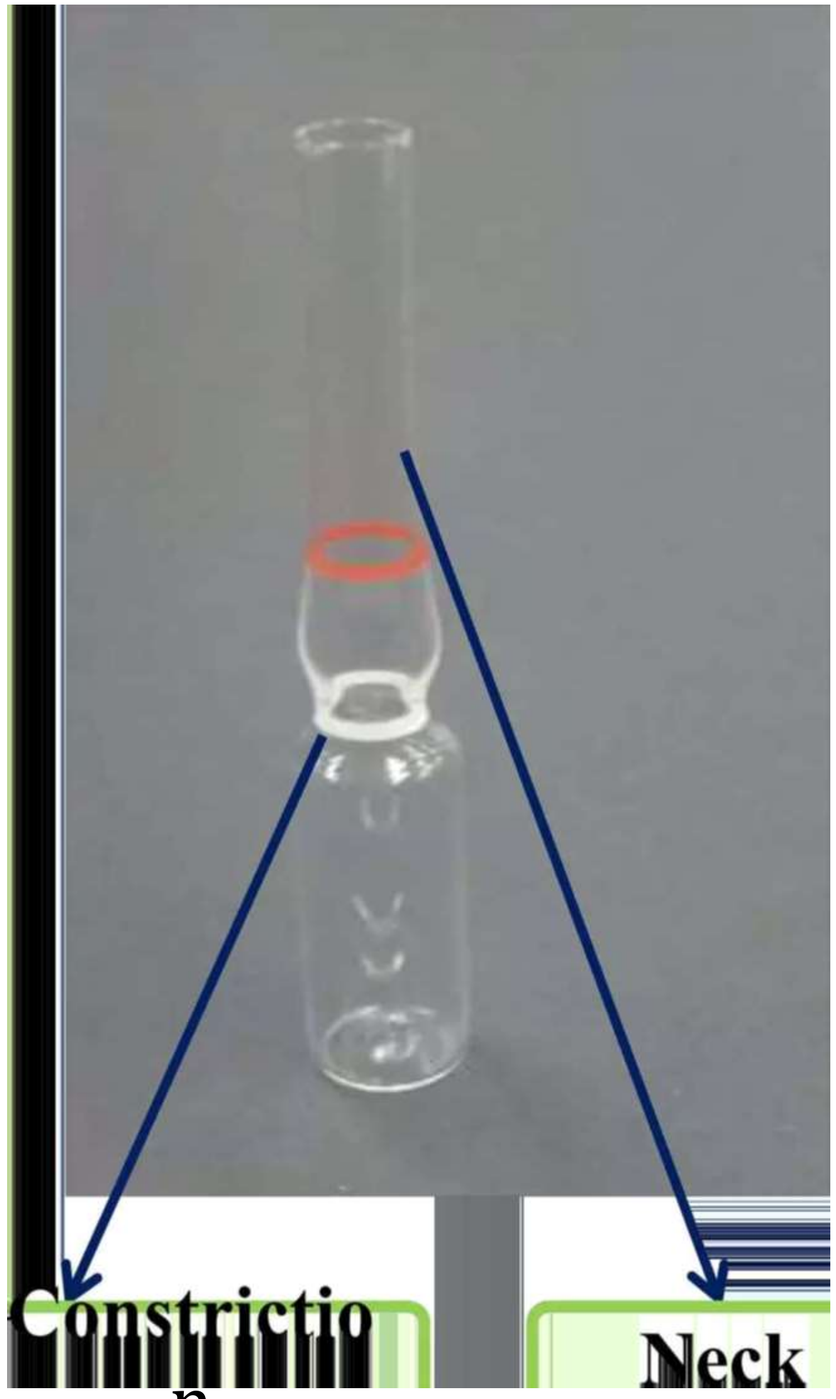
•Drug solution is gently drawn in to a syringe to avoid air bubbles in the liquid.

•Syringe is inverted, so that the air entrapped is expelled when the plunger is pushed.

•Needle is wiped with a cellulose film disc.

•Ampoule is inverted over the needle. Once the ampoule is settled over the needle, both the ampoule and syringe are returned together, and the liquid is gently expelled.

•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 removed without touching the neck of the ampoule.



On a large scale basis,

- Ampoules are filled using modem and sophisticated machines
- Sterilised ampoule tray is directly loaded in to slant hopper of the unit.
- Wheel delivers ampoules one by one on moving eccentric ampoule rack.
- A series of process like pre-gassing and post-gassing of ampoules with nitrogen and filling of liquids is achieved during the procedure.

Filling of Vials

- Filling procedure of glass vials is same as that for ampoules.
- In glass vials, containing a fixed number of dose units, an excess volume is required to allow the withdrawal of specified number of doses.
- Sterilized dry vial are fed below the filling unit.
- The filling unit consists of a filling head, syringes, and nozzles. Vials have to washed, depyrogenated and sterilized and filling has to be carried out in a strictly controlled environment.

Filling of Infusion Fluids

- Solutions are prepared in an aseptic room or laminar flow cabinet, to reduce contamination from microorganisms.
- An infusion bottle is considered for preparation of parenteral products
- Bottle is protected with double cap
- Outer cap is discarded, and the inner cap is removed.
- After ensuring, that bottle or packet neck is not damaged, the solution is poured in and immediately the inner cap is replaced.

SEALING

- Containers should be sealed in the aseptic area immediately adjacent to the filling machine.

Sealing of container assures:-

- Retaining of contents of a sterile product in the container
- Assures the consumer that the container has not been opened and the product is sterile
- If opened, the product is no longer sterile.

Sealing of Ampoules

After filling of ampoules, they should be immediately, sealed to prevent the contamination of contents by melting a poñion of the neck of the ampoule to form either of the two types of seals :- tip or bead seal aud pu\l sea\.

- Tip or Bead Seal :- made by melting glass using high temperature gas – oxygen flame at the tip of the ampoule neck to form a bead that closes the opening. The flame temperature and internal of heating to completely close the opening should be carefully determined.
- Pull seal :- made by heating the neck of rotating ampoule below the tip, then pulling the tip away to form small, twisted capillary just before to being melted closed.
- Pull sealing is slower than tip sealing, but the seals formed pull sealing are more reliable.

- Excessive heating of air and gases in the neck of the ampoule, causes expansion against soft glass with the formation of fragile bubbles at the point of seal.
- Fracture of the neck of the ampoules occurs during sealing if wetting had occuaed at the time of filling.

Open a ou e

Tip seal

Pull seal

Sealing of Vials

Vial openings are sealed with rubber closures held in place by an aluminium sealing. Open containers should be protected from contamination using a blanket of High Efficiency Particulate Air – filtered laminar air

- A hand crimper is used to put the rubber closures and aluminium sealing on to the vials.
- When closures are to be inserted by machines, the surface of the closure is usually halogenated or coated with silicone to reduce the friction.
- This make it easy for the closure to pass from the rotating drum of the machine to the bottom of the chute, where it is positioned over a

Sealing of Infusion Fluids

- The cap of the infusion bottle or package is lifted, using a forceps, a plug type closure is selected and the plug is pushed in to the neck carefully without touching the part that goes in to the bottle.

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- Plug should be stored in sterile water and washed with filtered solvent prior to use, to prevent contamination from particles attached to the closure.
- Finally, a ring type metal cap is tightly screwed on the bottle after inspecting for deformities.

CONTAINER AND CLOSURE SELECTION

CONTAINERS

Containers are in intimate contact with the parenteral product. No container available is totally non – reactive. Both the chemical and physical characteristics affect the stability and the sterility of the product.

In total, when a container is selected,

- It should maintain the integrity of the product
- Product should be sterile, pyrogen – free, high purity preparation till used.
- Should be attractive and strong
- Allow easy withdrawal of contents
- Should not interact with the product.

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

Container Selection Considerations

Containers for parenteral products are either single dose containers and multiple dose containers.

- Size of the single dose containers is limited to l000ml by the USP. Single dose containers are intended to provide sufficient dvg for just one dose. Single dose containers may range from litre bottle of IV solutions to 1ml or smaller ca0ridges. For avoiding the risk of contamination and increased control of administration of drugs, led to the development of single dose disposable administration units.
- Size of the multiple dose containers is limited to 30ml, as it is done to limit the number of entries for withdrawing a poñion of the contents of the container to avoid the risk of contamination of microorganisms.

Plastic Containers

The principal ingredient of various plastic materials used for containers is the thermoplastic polymer, for e.g., polystyrene, polyamide, polyvinyl chloride etc.

Plastic materials used in medical field may contain a substantial amount of plasticizers, fillers, antistatic agents, antioxidants, antimicrobial agents etc. for special purposes.

Advantages:-

- Light weight
- Low in additives, low toxicity, and low reactivity with products.
- Flexible and resistant to breakage.

Disadvantages:-

- May interact with the product
- Not clear and transparent as glass.

Types of Plastics

- Thermosetting plastic :- *Mown* as thermoset, is polymer material that irreversibly cures. The cure may be done through heat generally above 20o ^{oq} thermosets are hard and have a very tight meshed, branched structure.
- Thermoplastics :- known as thermosoftening plastic, is polymer that turns to a liquid when heated and freezes to glassy state when cooled sufficiently. They are high molecular weight polymers, and can be remelted and remoulded.

A new group of plastics – polyolefins are mainly used as the container material for parenteral products. E.g., polypropylene. It is a linear polymer, highly crystalline, has a high melting point of l65°C, and low permeability of gases and water.

Plastic has certain properties that should be considered :-

- Sorption – is a process in which the drug product interacts with plastic and leads to the loss of drug material and decrease in therapeutic activity.
- Permeation - gas or vapour may permeate through the plastic to interact with the product in the container, leading to chemical reactions like oxidation or hydrolysis etc.
- Photo –degradation –occurs when the formulation reacts with UV light leading to change in physical or chemical property of the plastic.
- Chemical reactivity –occurs when certain ingredients of the plastic material react with the dmg leading to modification of the drug or plastic.
- Leaching –occurs when the contents of the plastic material migrates from the plastic in to the drug formulation.

Quality control tests of the selected plastic should be done to evaluate the level of toxicity.

Glass Containers

Glass is the preferred material for containers for injectable products. Glass is mainly composed principally of the silicon dioxide tetrahedron, modified physicochemically by oxides of sodium, potassium, calcium, magnesium etc.

Glass containers are coated internally with silicone fluid to produce a hydrophobic surface. Then, this glass I baked at a temperature of 150 ^{o}C

Generally, glass are of 4 types •-

Type I :- Borosilicate Glass

- Highly resistant and least reactive glass containing 10% boric acid, 80% silica and small quantities of aluminium oxide and sodium oxide.
- Has a high melting point and can withstand high temperature.
- Prepared by adding boron to the traditional mixture of silicate sand, soda, and ground lime.
- Suitable for packaging of parenteral preparations and alkali sensitive materials.
- Expensive.
- Most ampoules and vials are made of Type 1 glass.

Type II :- Treated Soda Lime Glass

- Containers made of commercial soda lime glass that has been dealkalised or treated to remove surface alkali. This process of dealkalising is Lown as sulphur treatment.
- Prepared from soda lime glass by treating its surface with moist sulphur dioxide at a temperature above 500 °C. the acidic gases neutralises the surface alkali to produce a layer of sodium sulphate which can be easily removed by washing.
- This type of glass is used for alkali sensitive products and parenteral products.
- Cheaper than Type I.
- Used to store infusion fluids, blood and plasma.

Tvee III :- Soda Lime Glass

- Type 3 glass is a regular soda lime glass in which the containers are untreated and have an average chemical resistance.
- Alkaline glass having high percent of lime and soda and no boric oxide.
- Contains 75% silica, 15% NaOH, 10% CaO, MgO, K_2O
- Prepared by melting raw materials, such as sodium carbonate (soda), lime, dolomite, silica, AlO, and small quantities of fining agents (sodium sulfate, NaCl) in a glass furnance at atemperature up to 1s5 ^{o}
- Cheapest glass.
- For storage of oily injections and non – aqueous parenteral products

Type IV / Type NP :- General Purpose Soda Lime Glass

- Made up of plain soda lime and not used for parenteral preparations.
- Low hydrolytic resistance.
- Not used for products that should be autoclaved as it increases the erosion rate of the glass container.
- Intended for oral or topical use.

Other Types

- Neutral glass :- intermediate between Type I and Type III
- Coloured glass :- generally used for drugs which are sensitive to light.

Quality control tests of the selected glass should be done to evaluate the level of hydrolytic and chemical resistance, light transmission, or any presence of particulates.

PACKAGE TYPE	TYPE OF FORMULATION CAN BE PACKED	MINIMUM QUALITY OF GLASS THAT CAN BE USED
AnnpoUe	Aqueous Injectables Of Any pH	Type I
	Aqueous Injectables Of pH Less Than 7	Type II
	Non-Aqueous Injectables	Tyç>o III
Vial	Aqueous Injectables Of Any pH	Type I
	Aqueous Injectables Of pH Less Than 7	Type II
	Non-Aqueous Injectables	Tyj>a III
	Dry Powders For Parenteral Use irdceecs Tu Bæ Ro<x›no1‹s«t••<s Œotoro Usa	Type IV
Bottles ard Jars	Tablets, Capsules, Oral Solids & Other Solids For Raœnssituto‹i	TyçælV
	O‹aï Lqu•æ i Soklions. Suspt›nsæns Emu uorisî	Typa IV
	Nasai& Ear EXops	Typa IV
	Conain Typos 0 f Exlomoi S•m soëds i R‹ä>oficiants, Lacai i ‹tantst	Type IV
	&ood ü Re\atod Products	Type I

CLOSURES

A closure is a device which seals the container to exclude oxygen, carbon dioxide, moisture, and prevents the loss of volatile substance. It is also used to close and open the mouth of container, and prevents the leakage of the medicament during transportation. Closures prevents deterioration of the product from the effect of microorganisms and environment. Various types of materials are used for making closures, such as, plastic, metal, rubber, glass etc.

Requirements of Closure :-

- Must be compatible with the product.
- Should not absorb medicament.
- Should not become sticky upon storage.
- Should not become hard on exposure to air, atmosphere, and light.
- Should not allow permeation of air and water vapour.

Rubber Closures

Rubber closures are used to seal the openings of cartridges, vials, and bottles, providing a material soft and elastic enough to permit entry and withdrawal of a hypodermic needle without the loss of the integrity of the sealed container.

Advantages of Rubber Closures:-

- Self sealability
- Adequate protection from microbial contamination , and withstand high temperature and pressure of autoclaving.
- Available in variety of composition, colours, and design.

Disadvantages of Rubber Closure:-

- Additives used in manufacture of rubber closures may leach out in to the product and cause deterioration.
- Good quality rubber closures are expensive.
- Certain mbber closures may show problem with aging.

WPES OF RUBBER CLOSURE

i Commonflangedclosure

2 SlbFedorfrwzedried product

. CaFlage andDisposable syringe

● *^*MONFLANGEDO#URE

eMost commonly used in closing of vials andlbo1les.

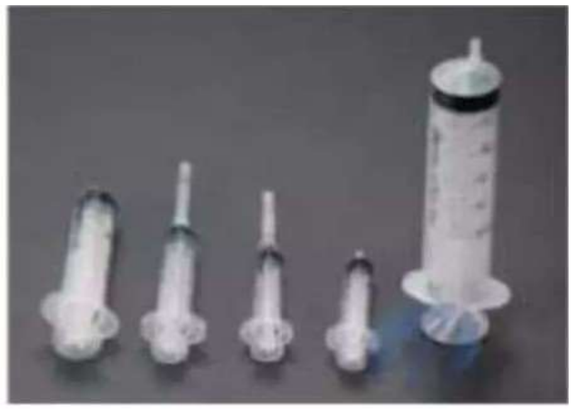
2. SLOWED OR F A M E DRED PRODUCT CLO#URE

+These closures has a slot or pathway for the ice sublimation

mUsed to seal the freeze dried productsor lyophilized products.

*• CA&TILAGEANDD\&POSABLE SYRNGECLOSURE

+ Cartilage is made of glass, one end of which is sealed w•th the mbber piston and the other end with aluminium over seal and mbber septum.



Composition

Rubber closures are compounded of natural mbber, a vulcanizing agent such as sulphur, an accelerator such as 2-mercaptobenzothiazole, an activator such as zinc oxide, fillers such as limestone, etc.

- Ingredients are combined by kneading them into a homogenous plastic mass on a roller mill. Homogenous mass is rendered fluid and then vulcanized in to desired shape under high temperature and pressure.

Quality control tests such as permeability, self sealability, sterility etc should be conducted with the rubber closures.

PRODUCTION – FACILITIES & CONTROL

PERSONNEL

The people who produce sterile products should be assisted by professional training.

- All employees should be in good health and subjected to periodic physical examinations.
- Personnel entering aseptic area should follow a procedure which includes removing outside clothes, scrubbing hands and arms thoroughly with a disinfectant soap and putting the uniform gown prescribed.
- A full body water and soap shower would be essential both when entering and leaving the manufacturing area to control contamination in both directions.
- An air shower for the fully attired worker is also necessary to blow away any loose lint.
- Personnel shall be restricted from carrying mobile, wearing nail polish, false fingernails, jewellery, cosmetics, hair spray, perfumes etc.
- Gowning area should be provided for pregowning, gowning and degowning.

- The uniform gown consists of mainly the face mask, gloves, hood, coverall, and booties.
- Firstly a pair of gloves is put on and then wear clean and sterilized hood, then put on cleaned, sterilized protective coverall avoiding any touch on the floor. The hood shall be tucked inside the neck of the coverall. Sit on a step and put on protective booties one by one without touching the floor.
- The booties shall be put on over the shoes enclosing the feet and bottom of the coverall tucked inside the booties.
- Lastly remove the gloves, disinfect with 70% iso propyl alcohol solution, put on another fresh gloves and disinfect again.
- Añer use, the uniform gown is discarded.

FACILITIES

The facilities for the manufacture of sterile products should be designed for control of cleanliness appropriate for each step. The prevention of contamination must be the primary objective in the design of these facilities.

The production area is normally divided in to :-

i Clean up area

2. Compounding area

Aseptic area

». Quarantine area

s Packaging and labelling area

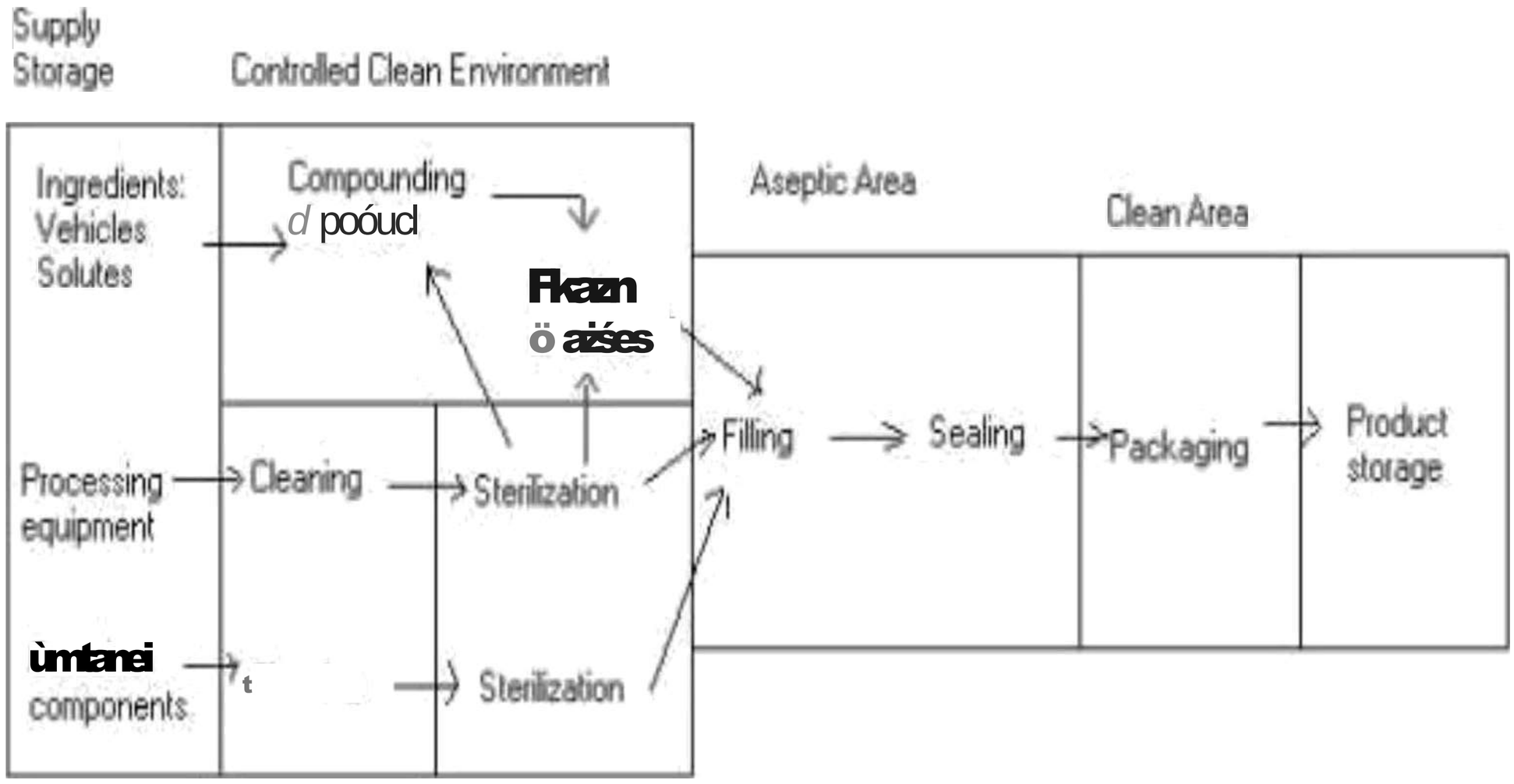


Diagram through the production department

Clean Up Area

- In clean areas, all exposed surfaces, inward air leaks and dirt collecting crevices3 corners, and projections should be smooth, impenetrable and unbroken to minimize the shedding or accumulation of particles or microorganisms and to permit the repeated application of cleaning agents and disinfectants, where used.
- The cleaning area has ceiling and walls should be coated with epoxy and vinyl polymeric continuous film coating materials.
- Air inside the clean area should be free from dust and microorganisms. This is ensured through high efficiency filters.
- Should withstand moisture, steam, and detergents.

Compounding 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 comparison 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 ñoors should be sealed, easy to clean and non-porous. Glass is used as partitions to permit supervisory view of the operations

Aseptic Area

The aseptic area should have maximum security as it is the major pañ of processing the sterile products. An ultra– clean environment should be maintained in this area.

- The ceilings, walls, and hoors should be painted with germicidal paint. The walls should have glass panels built on it to facilitate visibility and supervision from a non – sterile area.
- All the fixtures should be buried in the ceiling walls to eliminate ledges, joints and other locations where dust or 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.

- Furniture should be *ot* non-porous, hard surfaced materials, preferably stainless steel.
- Gas cylinders should be excluded and all gases should be piped *tvom* outside the area. Sinks and drains must be excluded *teom* the areas where aseptic procedures are performed.

Small scale operations should be carried out under an aseptic *hood*. The personnel should enter the aseptic area through an air – lock, wearing all the necessary accessories. Xlinimum movement should only be allowed while working in an aseptic area.

Quarantine Area

Quarantine area consists of a store where the in – process batches as well as approved batches are stored sejiarately. This area has limited access and is under the control of a responsible person. Without, the consent of the in-charge, other personnel cannot enter in to this particular area.

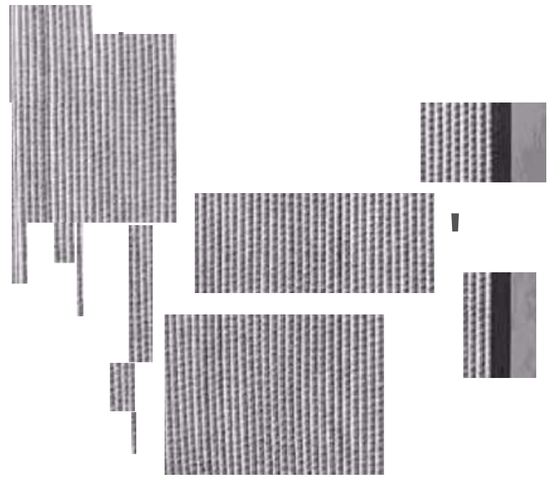
Packing and Labelling Area

In this area, the batches are packed and labelled. Packing is camied out by packaging machines, while labels are obtained by over printing devices. At, a time only one product labels are printed.

Parenteral packing plays a vital role in the production of sterile preparations. Packing should be camied out in such a manner that the sterility of the product is maintained.

,;/RKgNTR$/TION CONTROL

Air being the greatest sources of contamination should be clean in sterile product area. It should be made *to* pass through a pre—fi1ter (glass wool, cloth etc) *Io* remove large particles. Then it should be passed through electrostatic precipitator *!o* remove the particles in air.



The treated air should be then passed through High Efficiency Particulate Air (HEPA) Filters. These filters can efficiently remove 99.97% *ov move of* particles up *to* 0.3pm size. HEPA filters are used in laminar air *Aow* benches in which air moves with uniform velocity along parallel lines. The air flow is either horizontal *oe* vertical, and the minimum effective air velocity is 100 +l0ft/mint.

l ' o installed to produce a disin fecta nt a eioJ

Clean Room Classified Area

The Clean Room is a specially constructed enclosed area, which contains one *ov* 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 air.

Clean Room establishes appropriate environment levels *lov* airborne particulates, temperature, humidity, air pressure, and airflow patterns.

- Air cleanliness is classified into 4 types :- Grade A, Grade B, Grade C, Grade D. Grade D has the largest number *of* airborne particles whe

Clean Room	Properties
Class 10,000	10,000 or less particles of 0.5gm and larger size exist in a given cubic foot of air.
Class 1,000	1,000 or less particles of 0.5gm and larger size exist in a given cubic foot of air.
Class 100	100 or less particles of 0.5gm and larger size exist in a given cubic foot of air.

ENVIRONN!LI4I!AL CONTROL

Environmental control is essential *to* the manufacture of a quality product. The level *of* effective physical and biological environmental control depends on the characteristics *of* the facility.

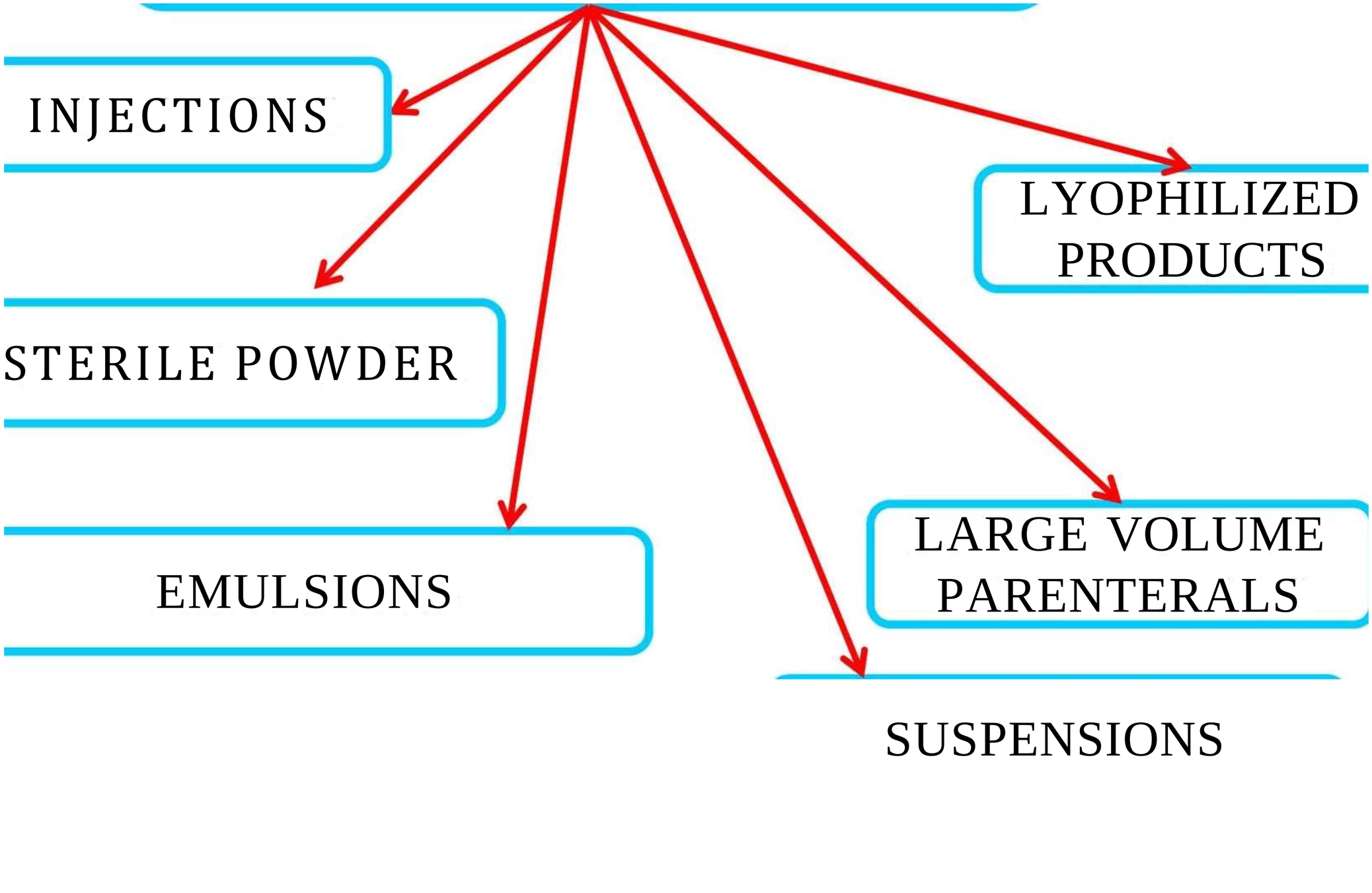
- The standards *wœ* environmental control vary *leom* plant to plant, and also depend on the topographic (physical features of an area) location, the area involved (clean-up, packaging, compounding, *oe* filling), and the type *of* product being prepared. Therefore, the standards should be flexible, and seasonal conditions should also be considered. Standard Operating Procedures (SOP'S) *foe* implementing any standards should be established and the implementation outcome should be recorded.
- The area used *foe* 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 sterilized.
- The standards *ot* cleanliness and daily disinfection for the clean-up and packaging areas should be rigid.

i?xcel1ence in environment control would be relatively easy to achieve were it not for the necessity *ot* personnel and supplies *!o* move *teom* one area *to* another. Therefore, a carefully designed arrangement *to* control and minimize traffic, particularly in and out *of* the aseptic area, is essential.

- The only access directly from the outside is *!o* the personnel wash *vooms*, the equipment wash *vooms*, the non– sterile manufacturing area, and the packaging area.
- Access by personnel to the aseptic *covvidov* and aseptic compounding and filling *vooms* is only through an air lock.
- Passthrough openings and double ended sterilizers are provided to permit controlled passage *of* supplies *from* non-aseptic to aseptic areas.
- Personnel should be permitted to enter aseptic area only after following rigidly prescribed procedures *lov* removing their clothing, washing their hands, and donning gowns, hats, shoes, facemasks, and gloves, Once entering the aseptic area, they should not be allowed to move in and out without regowning. Unauthorized personnel should never be allowed to enter the aseptic area.

PARENTERAL FORMULATIONS

PARENTERAL FORMULATION PRODUCTS



Formulating Injections

Injections are sterile, pyrogen free solutions or dispersions (emulsions or suspensions) of one or more active ingredients in a suitable vehicle.

- Injections are prepared using an aqueous vehicle. If necessary suitable non – aqueous solvents as indicated in the individual monographs.
- Injections that are dispersions should remain sufficiently stable so that, after shaking a homogenous dose can be withdrawn.
- Injections can be prepared mainly in two types :-

> Single-does injections :- are injections meant for use in a single patient for single case, or procedure. They should not contain any antimicrobial preservatives.

< Multiple-dose injections :- are injections that contains more than one dose of medication. Multidose preparations contain a suitable antJmpcrobial prservative spin appropriate

Formulating Large Volume Parenterals

- Large volume parenterals are sterile aqueous solutions or emulsions, which are free from particulate matter having water for injection as its main component.
- They are formulated as single-dose injections administered by inYavenous infusion, packed, terminally heat sterilized and administered in large volumes. The large volume parenterals are mostly clear aqueous solutions, except for the oil-in-water emulsions.
- Before administration, sometimes additional dmgs are added to them by either injecting small volume parenterals to the adminisYation sets or by the piggyback method (smaller volume infusion of an additional drug is added to the inYavenous delivery system).
- To meet iv nutritional requirements, one or more ofthe following are added:-

< Proteinsubstrates

< Carbohydrate substrates - dexoose, sucrose, and dextran

> Electrolytes – saline, ringem solution

< Vitaminsandtrace elements

Production of Large Volume Parenterals

The manufacture and filling *of* LYP into containers are carried out in a high standard clean *voom* environment. High standards are required *to* prevent these products *tvom* getting contaminated. The quality *of* products can be ensured by strictly following the quality assurance procedures.

In commercial manufacturing faciliäes, large volumes *of* fluids are used in the production *ot a* product batch. The fiuids *teom* a bulk container are filled into the product container using high-speed filling machines. Before filling the ßuid into the container, it is passed through an in-line membrane filter *to vemove* the particulate matter.

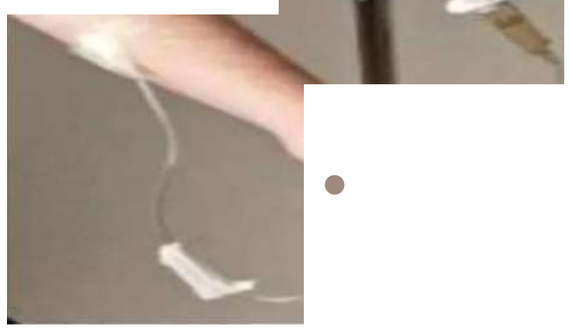
Aßer fißing, the neck *ot* each glass bottle is immediately sealed with a ti;§ht- 5tting rubber closure held in place with a crimped aluminum cap. The outer cap is also of aluminum and an outer tamper - evident closure is used.

In case plasäc bags are used, the pre-formed plasäc bags are asepäcatly filled and heat sealed immediately. A blow-fitl-seal System can also be used thatinvolves melting the plasäc, forming the bag and filling and sealing in a high-quality clean *eoom* environment. Blow-fill-seal system minimises the problems with product handliiig, cleaning and particulate contaminaäon. Aßer the product is filled *into* containers, they are checked for particulate matter and the integrity *of* container closures is established. Rastic containers should be sterilised with an over-pressure during the sterilisation cycle so that

Types of tnrge Volume Parenterals

« Cmiânumis infusion .- typical consists *ot* a base mutton with additives. Also called as maintenance infusion, *oe* replacement infusion.

Dxip :- used *to* deliver an N medication *to* treat a specific medical condition.



The most common LYPs are IY solutions compounded from a standard solution such as 0.9% sodium chloride (also known as NS), dextrose 5°/oin water (DSW), dextrose S°/oin normal saline (DSNS), and LR solution.

The most common volumes for LYPs are 250 ml, 500 ml, and 1000 ml.

Formulating Parenteral Suspension

A Pharmaceutical suspension is a coarse dispersion in which internal phase (therapeutically active ingredient)is dispersed uniformly throughout the external phase. Parenteral suspensions provide prolonged duration of action by forming a depot.

- Solid content of parenteral suspensions usually ranges between 0.5 – 5% and up to 30% in case of antibiotic preparations.
- Amount of solid and nature of solvent determines the viscosity and syringeability (facility of passing of product in and out of a syringe) of the product.
- Most important requirement of parenteral suspensions is a small and uniform size particle which can be achieved by various size reduction techniques.
- Small, uniform particle size gives slow, uniform rates of sedimentation and predictable rates of dissolution and drug release. Also, uniform particle size reduces crystal growth during storage.

A parenteral suspension may have stabilization problems between the period *of* manufacture and consumption.

- Solids in the suspension gradually settle and cake, causing difficulty in redispersion prior *!o* use. Surface active agents ,ay aid in the preparation and stabilization of a suspension, by reducing the interfacial tension between particles.
- Fg., *ot* surface active agents include, polysorbate 80, pluronic F – 68 etc.
- Addition of hydrocolloids are also done *to* improve the effect *of* surface active agents and cause loss of surface charge, and reduce the tendency *to* agglomerate.
- Fg., *ot* hydrocolloids include : sodium carboxymethylcellulose, acacia, gelatin, methylcellulose etc.

Formulating Parenteral Emulsions

A pharmaceutical emulsion is a heterogenous mixture containing wo immiscible liquids that are made miscible using an emulsifying agent.

- Emulsifiers like, lecithin, gelatin, methylcellulose etc., have been used for the preparation.
- Administered through intravenous or intramuscular route.
- Principal problem in formulating a parenteral emulsion is the attainment and maintenance of uniform droplets of 1– 5 pm in size. Particle size control is rigidly required to control the formation of emboli in blood vessels.
- This is achieved with the limited choice of emulsifiers and stabilizers, an preservation of oil phase from rancidity
- Due to the difference in the density between oil and water being very low in case of emulsions, the problem of phase separation does not occur.
- Emulsions tend to produce coalescence of the dispersed phase when exposed to elevated temperature.
- Excess ve shaking of parenteral emulsions cause acceleration of rate

FOPmulating Sterile Poiwders

$)ry sterile powrier 1s ascetically added to a sterile vial and then send for final packaging. Sterile dry powder is reconstituted with a sterile vehicle before use. Powders for injection are solid substances , which when shaken with the prescribed volume of the sterile solvent, rapidly form clear, particle free solutions or uniform suspensions.

Sterile drug powder is manufactured using the following procedures -

- Lyophilization :- water or the solvent used is removed from the frozen state of the product, by sublimation, i e., direct change of water from solid in to vapour without conversion to a liquid phase. The drying of the product is achieved by subjecting the material to temperature and pressure below the triple point.
- Sterile Recrystattisation

In this method, the drug is dissolved in a solvent, then the solution is sterilised by passing through a 0.22pm membrane filter, and finally a sterile anti-solvent is added to crystallise the dmg particles, which are filtered and dried aseptically. This method is flexible and economic, but represents variation in contamination.

- Spray drying :- In this method, the drug solution is sprayed into a dry chamber where it *comes* in contact with a hot steam *ot* a sterile gas at 80[a] [Jgm]perature.

r Advantages

i) This method is simple, economic, scalable, and faster.

ii) This method involves coating *ot* particles during drying prolonged release.

r Disadvantages

i) In this method, the high processing temperatures and high shear forces can damage the drugs.

ii) In this method, higher levels *of* drug are lost in comparison *to* freeze drying.

iii) This method has a limited solvent choice *toy* a given drug.

iv) In this *metho6*, product cannot be prepared directly in vials *or* plates.

Formulating Lyophilized Products

Lyophilized or freeze dried products are prepared by freeze drying, and this process is known as tyophilization or cryodessication.

- In freeze drying, water or the solvent used is removed from the frozen state of the product, by sublimation, i.e., direct change of water from solid in to vapour without conversion to a liquid phase.
- The drying of the product is achieved by subjecting the material to temperature and pressure below the triple point.

The working of freeze drying is divided into the following steps *:-*

1. Pre-treatment
2. Freezing
3. Primary drying
4. Secondary drying

1. Pre-treatment

The solution is pre - concentrated under normal vacuum tray drying, or the formulation is revised (adding new components to increase stability, preseme product appearance, decrease vapour pressure of high vapour pressure solvents etc). This reduces the actual drying time by 8-10 times.

2. Freezing

Vials, ampoules or bottles in which the aqueous solution is packed are frozen in cold shelves (about -50^{o}C). The material is cooled below its triple point so that the product does not melt but sublime in the subsequent steps.

3. Primary Drying

Here, the pressure is lowered and heat is applied to the product so that the water sublimes. 95% of water in the product sublimes in the initial drying phase. This phase is slow, because on adding excessive heat the structure of the product gets altered. A cold condenser chamber is provided, a surface on which the water vapour resolidifies.

4. Setondary Drying

During this stage, traces of moisture is removed. The temperature of the solid is raised to as high as 50-60 ^{o}C to break any physicochemical interactions between water and frozen material, but vacuum is lowered below than that used in primary drying.

After vacuum is replaced with by ineñ gas, the bottles and vials are sealed. In the final product, the residual water content is extremely low (around 1-4%).

QUALITY CONTROL OF PARENTERALS

QUALITY CONTROL TESTS OF PARENTERALS

- LEAK TEST
- CLARITY TEST
- PARTICULATE MATTER TEST
- CONTENT UNIFORMITY TESTS
- PYROGEN TEST
  - LAL TEST
  - SHAM TEST
- STERILITY TEST
  - MEMBRANE FILTRATION
  - DIRECT INOCULATION

Leakage Test

Leakage occurs when- discontinuity exists in the wall of a package -that can allow the passage of gas-through walls. A hermetically sealed container , results in completely barring the interchange between the contents in the container and its environment. Presence of capillary pores or tiny cracks can cause microbes or contaminants to enter the container.

- Leak tests are 4 types
    a) visual inspection
    b) bubble test
    c) dye test
    d) vacuum ionization test

a) Visual fnspection

Traditional visual inspection is conducted using a viewing apparatus that comprises of

- a matt black panel.
- a non – glare white panel held next to the black panel in a veñical position.
- an adjustable lampholder.

Remove any adherent labels from the container, and obseme for about 5 seconds in front of the white panel. Repeat the procedure in front of the black panel. Record the presence of any pañicles.

X-Ray based technology uses X-ray detectors to detect defects such as cracks, foreign pañicles, or functional defects.

b) Bubble Test

The test package is submerged in to a liquid. The product under test is pressurized to about 3psig and immersed in a bath containing water or water and surfactant (e.g., polysorbate 80).

- Any leakage is evident after the application of differential pressure as the generation of foaming in the immersion liquid.
- Obsemation of bubbles can be optimized by using a surfactant immersion huid with dark background and high intensity lighting.

c) Dye Test

Detection of leakers is more effective when the ampoules are immersed in a bath of dye (0.5-1% methylene blue), and a negative pressure is applied in a vacuum chamber for 30 minutes.

- After this period, vacuum is released, and the dye under the inhuence of the pressure, penetrates the ampoules through any opening present.
- The ampoules are then washed extevally and visually obsemed to check any change in the product colour due to the dye.

d) Vacuum Ionisation Test

Vacuum ionisation test is useful for testing leakage in the vials or bottled sealed vacuum.

- This test is used under testing of the lyophilized products. High voltage, high frequency field is applied to vials which cause any residual gas, if present to glow.
- Glow intensity is the function of vacuum level.
- The blue glow is the indicative of vacuum while the purple glow indicative of no vacuum.

Clarity Test

Clarity is a factor that needs to be considered seriously in parenteral preparations, and is mainly performed through •-

- I3uman visual inspection of the containers in direct light against white and black background. As a result, transparent particles are visible against black background and the coloured particles are visible against the white background.
- Instrumental methods of evaluation for particulate matter in liquids utilizing the principles of light scattering, light absorption, and electrical resistance have been used to obtain particle counts, and size distribution,

Particulate Matter Test

The presence of particulate matter in a solution to be administered intravenously is considered harmful. The methods of particulate matter monitoring are :-

- Visual inspection
- Microscopic method
- Shadow cast method
- Electronic particle counter
- Thermocouple conductivity method

a) Microscopic method

In this method, a measured volume of sample solution is filtered through 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.

b) Shadow cast method

Particle size is measured by mode of shadow cast by the particles, as it passes through a high intensity light beam. The size limit are not more than 10000 particles/container of size ≥10pm and not more than 1000 particles/container of size ≥25pm.

c) Electronic particle counter

This method uses the principle of light scattering for counting particles in a liquid sample.

d) Thermocouple conductivity method

Instruments like coulter counter, are used to counting and sizing particles by measuring the resistance effect between two electrodes when the particle passes between them.

Content Uniformity Test

The test for uniformity of content of the parenteral products is based on the assay of the individual contents of active substances of 10 dosage units taken at random. This is done to determine whether the individual contents are within limits set with reference.

- The preparation complies with the test if each individual contents is between 85 – 115% of the average content.
- If one individual content is outside the limit but within 75-125%, determine the individual contents of another 20 dosage units taken at random.
- The preparation complies with the test if not more than one of the individual contents of the 30 units is outside 85 – 115% of the average content and none is outside the limits of 75-125% of the average content.

Pyrogen Test

Pyrogen is a substance produced by the bacterium, which produces fever when introduced or released in to the blood.

Pyrogen test are done in two ways -

1.Rabbit Test

The presence of pyrogenic substances in parenteral preparations is determined by a qualitative biological test based on the fever response of rabbits. Rabbits are used as the test animal because they show the same physiological response as that of human beings. If a pyrogenic substance is injected in to the marginal ear vein of a rabbit, an elevation of temperature occurs within a period of 3hr.

The temperature is monitored at intervals of 30minutes for 1-3hr. The product is considered to fulfil the requirements for the absence of pyrogen if no rabbits show a rise of 0.5^{o} or more. If more than 3 rabbits show a rise of temperature of $0.^{top}$ or more, the test is continued using 5 more rabbits.

2. Limulus Amebocyte Lysate (LAL) Test

LAL test is an in vitro test method developed utilizing the gelling prope3y of the lysate of the amebocytes of *Limulus polyphemus* (horseshoe crab).

In the presence of pyrogenic endotoxins from gram negative bacteria, a firm gel is formed withing 60minutes when incubated at 37‘C. Only endotoxins from gram negative bacteria constitute the majority and most potent contaminating pyrogens.

The LAL test has been found to be 5-10 times more sensitive than the Rabbit test. This test is called as the Bacterial Endotoxin Test.

Sterility Test

Since all the parenteral preparations are required to be sterile, parenteral products should be tested for sterility and must comply with the oTicial test of sterility as per USP. The test for sterility is intended for detecting the presence of viable (physiologically active) form microbes in the preparation.

Sterility test of products is carried out either by the two methods mentioned in the USP :-

I. Membrane Filtration Test (Method A)

A suitable unit consists of a closed reservoir and a receptacle between which a membrane of appropriate porosity is placed. A membrane (e.g cellulose acetate or nitrate filters) suitable for sterility test has nominal pore size not greater than 0.45pm. Before start of sterility test, membrane is rinsed with diluting or rinsing fluid which is sterile solution (e.g lgm peptic digest of animal tissue in llitre of water of pH 7.1). A9er rinsing, the contents of the container to be tested is transferred to the membrane. After filtration of the contents, the membrane is aseptically cut into two equal parts, and each half is transferred to the culture medium. This medium is incubated at 32.5 + 2.5 °C for not less than 14 days. The media is examined for macroscopic evidence of microbial growth at intervals during the incubation period and its conclusion. If no evidence of microbial growth is found, the product complies with the test for sterility. If evidence of microbial growth is found in the form of bacterial colonies, the product does

2. Direct Inoculation Test (Nfethod B)

Direct inoculation method is not only used *toy* testing of sterility *of* oily solutions, creams, ointments but also particularly *toe* surgical devices, sterile devices, surgical dressings and sutures etc.

In this test, the preparation *ov* product is transferred directly in *to* culture medium (fluid thioglycolate medium *oe* soybean – casein medium) in the inoculation tube. The inoculated media is then incubated *toy* not less than 14 days. Observe the culture several during the incubation per‘iod.

If the product being tested renders the medium turbid so that the presence *or* absence *ot* microbial growth cannot be readily by visual examination, 14 days after the beginning of incubation, transfer portions of the medium to fresh vessels of the same medium, and then incubate the original *toe* not less than 4 days. The media is examined *toy* macroscopic evidence *of* microbial growth at intervals during the incubation period and its conclusion. If no evidence *of* microbial growth is found, the product complies with the test for sterility. If evidence *of* microbial growth is found in the *lovm of* bacterial colonies, the product does not comply with the test *toy* sterility.


thank
you