INDUSTRIAL PHARMACY-I

UNIT IV-PARENTERALS

CLASS:29

TOPIC Aseptic processing

Formulation of injections, sterile powders,

Productionprocedure-Asepticprocessing:

- The parenteral drug manufacturing (Drug Product Manufacturing) process includes compounding, mixing, filtration, filling, terminal sterilization, lyophilization, closing, and sealing, sorting, and inspection, labeling, 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 visibleparticulate 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.

1) Cleaning andwashingofcontainersandclosures
2) Preparationofsolutions
3) Sterilization
4) Filling andsealing
5) Evaluationofparenterals
6) Packagingandlabeling

1. **Cleaning of containersand closures:** - all the containers, closures and equipments which are requiredduring the preparation of parental products are thoroughly cleaned withdetergent 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.

2. **Preparationof Solution:-**The various ingredients of the formulation of parental preparationsareweighedandcollectedinthepreparationroom.therawmaterialsrequired 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 pharmacistshoulddecidetheorderofmixingandexactmethodofpreparationtobe 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 aceptic condition to avoid contamination of filtered solution, before it is finally transferred into final container and sealed
3. **Sterilization**:-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 are sterilised either by autoclaving atthetemperatureof115°Cto116°Cfor30minutesor121degreecentigradefor20minutes or in hot air oven at 160 degree centigrade for 2 hours. the thermolabile preparations are sterilized by filtration through a suitable bacteria proof filters. 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 injectionindosesexceeding15ml,thebacteriostaticagentshouldnotbeused.The sterilised product is filled into the final containers and sealed .the process of filtration,.

filling and sealing are done under aseptic conditions

4. **Filling and Sealing:-** 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 feelingsingledosewhereas,vialsareusedforfillingmultidoses.bottlesaremeantfor filling transfusion fluids . On small scale feeling is done manually by using hypodermic syringeandneedle.onthelargescalefeelingisdonebyautomaticfillingmachine.The sterile Powders are filled into containers by individual weighing or by using automatic orsemi automatic 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 belowtheneckofampoulesandthesolutionshouldnottouchtheneckofampoules.this will prevent the cracking and stanining 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 sealingmachineisusedinwhichtip ofampoule isusedtofusedtosealit.The vials and transfusion bottles are sealed by closing its opening with rubber closures .Therubber closures are held in place by crimping the aluminium caps which is done manually or by mechanical means.

5. **Evaluationof Parenterals:-**The finished parenteral products are subjected to the following test ,in order to maintain quality control.

   a) Sterility testb)claritytestc)Leakagetestd)Pyrogentest.

6. **Packagingandlabeling:-**After evaluationof the parenteral preparation,the ampoules ,vials

and transfusion bottles are properly labelled and packed. The label should state as:-

a) Nameofthepreparation

b) Quantityofthepreparation

c) Mfg.Lic.no.

d) Batchno.

e) Dateofmanufacture

f) Dateofexpiry

g) Storagecondition

h) Retailprice

i) Manufacturer'saddress

Asepticprocessing:-

The objective of aseptic processing is to maintain the sterility of a product that is assembled from components, each of which, whenever possible products intended to be sterile should be terminallysterilizedbyheatintheirfinalcontainer.Whereitisnotpossibletocarryoutterminal

sterilization by heating due to the instability of a formulation or incompatibility of a pack type (necessary to the administration of the product, e.g. plastic eye-dropper bottles), a decision shouldbe taken to use an alternative method of terminal sterilization following filtration and/or aseptic processing. Sterilization can be achieved by the use of moist or dry heat, by irradiation

withionizing radiation (noting that ultraviolet irradiation is not normally an acceptable method of sterilization), by ethylene oxide (or other suitable gaseous sterilizing agents), or by filtration with subsequent aseptic filling of sterile final containers. In order to maintain the sterility of the components and the product during aseptic processing, careful attention needs to be given to: the environment, personnel, criticalsurfaces, container/closure sterilization and transfer procedures, the maximum holding period of the product before filling into the final container and the sterilizing filter. Certain solutions and liquids that cannot be sterilized in the final container can be filtered through a sterile filter of nominalporesize0.22micron(orless),or with atleast equivalent microorganism-retaining properties, into a previously sterilized container. Such filters can remove bacteria and moulds, but notallviruses or mycoplasmas. Consideration should begiven tocomplementing the filtration process withsomedegree of heat treatment.Filtrationalone is not considered sufficient when sterilization in the final container is possible. Of the methods currently available, steam sterilization is preferred.

1. 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 stabilityby 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-dosebottles 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, withthe solidparticles accountingfor0.5-30%ofthe suspension.The vehicle may beaqueous,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 syringeability while suspending agents modify the viscosity of the formulation

Generalstepsinmanufacturing:

- Sterilizationandmillingofactiveingredient(s).
- Sterilizationofvehicle.
- Asepticwettinganddispersionoftheactiveingredient(s).
- Asepticmillingofthebulksuspension.
- Asepticfilling ofthebulksuspensioninsuitablecontainers

Formulationofsterilepowders:-

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.

Sterilepowersarepreparedbyfollowingmethods.

1. Sterilerecrystallization:
2. Lyophilization:
3. Spraydrying

1. **SterileRe-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:

   Thismethodrepresentsvariationsfrombatchtobatchandcontamination.

2. **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.

Advantage:

This method involves removal of water at low temperatures.

Disadvantage:

i) In this method, the biological molecules are damaged by the stress associated with freezing, and drying.

ii) This method is expensive and time consuming

3. **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.

Advantage:

i) This method is Simple, Economical, scalable and faster.

ii) This method involves Coating of particles during drying prolonged release.

Disadvantage

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

i) In this method,higher levels of drugs are lostin comparison to freeze-drying.

ii) This method has a limited solvent choice for a given drug.

In this method,product cannot be prepared directly in vials or plates